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A Photo Collage

THE JOURNEY OF THE STEM CELLS



Photos by Elizabeth Read

Stem Cell Processing Team: (from the top) Virginia David-Ocampo, medical technologist, CC Department of Transfusion Medicine, receives a shipment of two cord-blood grafts; Hanh Khuu, assistant medical director, examines the grafts, packed in a liquid-nitrogen dewar, and immediately places them in her lab's freezer at -174 °C; every action is documented

the journey continues on page 10

**NIH-NMDP AGREEMENT LAUNCHES NEW PROGRAM
UNRELATED-DONOR BLOOD STEM-CELL TRANSPLANTS
MAKE THEIR DEBUT AT THE CLINICAL CENTER**

by Christopher Wanjek

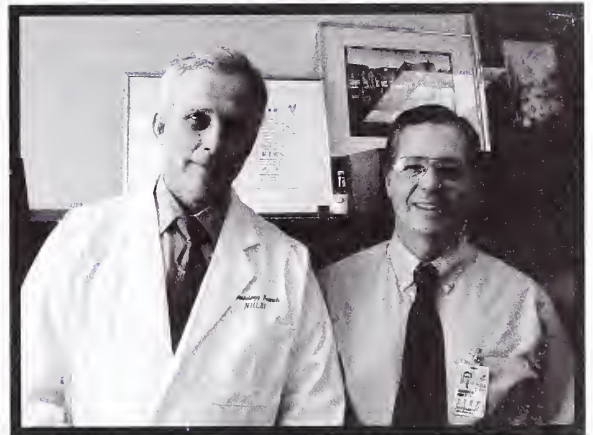
Harry Malech often fielded the question from patients and colleagues: Why wasn't NIH doing unrelated-donor hematopoietic transplants?

The NIH Clinical Center had built a reputation over the previous 15 years as a leading facility for patients receiving transplants from family members, mostly siblings, to cure cancers, marrow-failure syndromes, immune-deficiency diseases, and other blood disorders. But, unlike most transplant centers in the United States, it was not also accommodating unrelated-donor transplants.

Upwards of 70 percent of patients needing a hematopoietic transplant do not have a compatible donor in their family. NIH could only help these patients find treatment elsewhere.

The reason why was complicated, said Malech, an expert in inherited immune-deficiency diseases and a senior investigator and chief of NIAID's Laboratory of Host Defenses. But the bottom line was that there was a seemingly less-than-perfect fit between the modus operandi of NIH and the National Marrow Donor Program (NMDP), the organization that coordinates access to the unrelated-donor pool that facilitates transplants.

In 2003, Malech and his colleagues set out to change that. Like many bold initiatives at NIH, this one started with musings over a cup of coffee. Casual conversations with his friend Steven Pavletic, a transplant expert at NCI, soon stretched into extended discussions first with Elizabeth Kang, a NIAID clinician whom Malech describes as a "card-carrying transplanter," and with Susan Leitman and Charles Bolan, blood stem-



Christopher Wanjek

Matchmakers: (left) NHLBI's Charles Bolan, medical director of the new Matched Unrelated Donor Program, and NIAID's Harry Malech, program initiator, crusader, and negotiator

cell collection experts in the CC Department of Transfusion Medicine (DTM). Critical additional support was provided by NCI's Ron Gress, chief of the Experimental Transplant Immunology Branch (ETIB).

After four years of hustling and strategizing, their work paid off. This March, NIH signed an agreement with the NMDP to begin matched unrelated hematopoietic transplants at the CC.

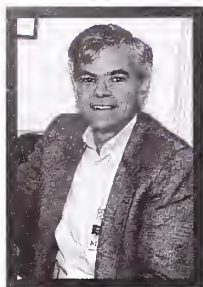
There was a surprising lack of fanfare over the signing, aside from exclamation points in e-mail messages circulating among those who had nurtured the

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TURNING MEDICAL STUDENTS INTO PHYSICIAN-SCIENTISTS



Michael Gottesman

On Saturday, March 24, NIH co-hosted a 10th reunion for members of the Clinical Research Training Program (CRTP). The CRTP was established at the recommendation of the NIH Director's Clinical Research Panel in 1996 to address concerns that medical students were not being exposed to clinical research opportunities or classroom training in the discipline of clinical research as part of their medical school curriculum.

I am pleased to report on the progress of this and other programs at NIH, including the long-standing Howard Hughes Medical Institute (HHMI)-NIH partnership, that provide medical students with the research experiences that may inspire a career as a physician-scientist.

The Seeds of Success

Clinical research training has been championed by NIH directors throughout most of NIH's history, and NIH has a proven track record of turning physicians into outstanding scientists. Approximately half of the winners of the Nobel Prize in Medicine or Physiology in the past 25 years who have M.D. degrees got their primary research training at NIH. By any measure, this is a spectacular record for a single institution.

The talent that led to this success came to NIH largely as a stream of physicians during the period encompassing the Korean and Vietnam wars. Many at NIH, including our former Director Donald Fredrickson, became concerned as this torrent turned into a trickle in the 1980s.

So Fredrickson, when he became director of the HHMI, set as a high priority the establishment of a residential program at NIH for medical students after their second year of medical school to spend a year in NIH laboratories.

This HHMI-NIH Research Scholars program, now in its 21st year, has enrolled 863 students, the majority of whom have careers in academic medicine and biomedical research. Many have returned to NIH and some are part of our faculty.

The CRTP was intended to fill a similar gap for physicians-in-training who were interested in clinical research. To date, 190 students have been enrolled, and 109 participated in the reunion activities.

The morning program offered inspiring and

informative lectures from six institute directors; the afternoon discussion by some of the more senior graduates recounted the joys and tribulations of pursuing clinical research careers.

Aims: To Achieve Balance And to Segue Gracefully

The most senior of these students are entering the chasm that lies between a completed clinical fellowship and a faculty position. A few are back at NIH, but most are dealing with the tug of clinical practice vs. their academic and research interests.

It is a delicate balance, and many institutions are reluctant to provide the necessary protected time needed to develop research projects for trained physicians who could be earning their keep by practicing medicine and surgery.

Another product of the 1996 Clinical Research Panel was the development of K awards (especially the K23) to support clinical research activities and supplement the existing K08 award for mentored laboratory research. Recently, HHMI has added a competitive start-up grant for which former HHMI research scholars may apply.

These are the mainstay of support for physician-scientists in the extramural world making the transition to independence. In the intramural program, this gap between training and independence for clinical researchers remains to be filled.

In response to recommendations of a blue ribbon panel on clinical research in 2005 and enthusiastic support from the Advisory Board for Clinical Research, NIH as a whole, and several of our institutes, are developing transition positions, such as the associate clinical investigator, to support independent clinical research as a bridge to a tenure-track position.

The reunion highlighted the enormous success of the CRTP in training medical students for clinical research careers, but it also made us think more about how to ease the transition from training to full independence as a faculty member at NIH or at an academic medical center. Creating meaningful and effective career tracks for clinical investigators must be a continuing priority for NIH.

—Michael Gottesman
Deputy Director for Intramural Research

ON TRACK

With this issue of *The NIH Catalyst*, we launch a new feature profiling the work of NIH intramural researchers newly arrived to the tenure track.

Catharine Bosio has joined NIAID's Laboratory of Intracellular Parasites at the Rocky Mountain Laboratories in Hamilton, Mont., where she will study the pulmonary pathogen *Francisella tularensis*, a continuation of the research she conducted slightly lower down on the mountain chain when she was an assistant professor at Colorado State University in Fort Collins.



Catharine Bosio

Although rare, this bacterium produces flu-like symptoms with a 60–80 percent mortality rate. It can be ingested, inhaled, or absorbed through the skin. Tularmia infections are seen in such diverse groups as landscapers on Martha's Vineyard and hunters in the Western states.

Bosio's goals are twofold: to identify better treatment options (currently either streptomycin or gentamicin) and also to use this virulent bacterium as a model to study pulmonary infections.

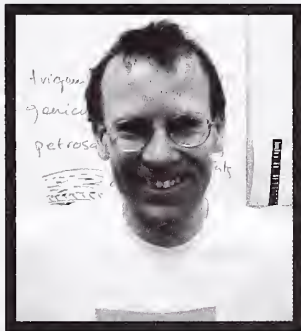
She and her colleagues have found that *F. tularensis* infection elicits production of TGF- β , a potent immunosuppressive cytokine. And *F. tularensis* actively suppresses the ability of dendritic cells to alert the host to the invading pathogen.

The big picture, she says, is that *F. tularensis* may not be unique among pathogens in its ability to "selectively uncouple antigen-presenting functions from proinflammatory cytokine secretion by critical antigen-presenting cells in the lungs, which may serve to create a relatively immunosuppressive environment favorable to replication and dissemination of the organism."

Bosio has also worked on Ebola and Marburg viruses and pneumonic plague.

Mark Hoon of NIDCR came to NIH in the early 1990s as a postdoc and had considerable success in Nick Ryba's lab in the Taste and Smell Unit in identifying taste receptors. Now in the Laboratory of Sensory Biology, he is getting a feel for somatosensory research.

Surprisingly little is known, he says, about how we sense pain, temperature, the position of our arms, or the nature of an object by touch. Hoon hopes to do



Christopher Wanjek

Mark Hoon

the same for the sense of touch that he and his colleagues have done for taste.

Key to this effort is identifying the receptors for touch, found in specialized neural endings just below the skin. The cells have been characterized, and different classes of neurons—such as fast- and slow-adapting—have been identified.

Humans have millions of sensory receptors, concentrated in the fingertips, lips, and tongue. Just as human taste buds are selective for different tastes (such as bitter or sweet), so, too, are touch receptors primed for different "flavors" of touch, such as vibration or pressure. Sensory information is carried from these touch receptors to the sensory cortex in the brain. Current knowledge of just how this transmission is accomplished is relatively crude, Hoon observes.

Using a mouse model, he plans to start to map the touch neural pathway "from the molecule up."

He will conduct a systematic search for the receptor and signaling molecules in mice using a variety of molecular screening techniques. In mice, he notes, it is the whiskers that are most sensitive to touch.

Xiaoling Li, leader of the mammalian aging group in the Laboratory of Signal Transduction at NIEHS, hopes to bring the exciting research on aging and Sir2 to the next level—that is, the mouse.

Sir2 is the famed protein found to extend the lifespan of yeast, worms, and fruit flies; it seems to be activated through caloric restriction.

Li's research, a continuation of her recent postdoc work at MIT, focuses on the NAD⁺-dependent protein deacetylase Sir2 and corresponding post-translational modification of nuclear receptors in aging and age-associated diseases.

The problem with mice, however, is that they don't age as quickly as yeast and flies, and it is therefore more difficult to study aging effects. Li's approach is to use the onset of age-related disease, such as cardiovascular disease, as a marker for aging. These changes, albeit slight, can be detected month by month.

Her group has so far shown that SIRT1, the mammalian orthologue of Sir2, removes an acetyl group from liver X receptors, members of a nuclear receptor superfamily, and regulates their transcriptional activity and corresponding cholesterol homeostasis.

—Christopher Wanjek



Xiaoling Li

MATCHED UNRELATED-DONOR PROGRAM

continued from page 1



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Transplant Experts: (left to right) NIAID's Harry Malech, whose four-year effort culminated in the new program; NIAID colleague Elizabeth Kang, whose unrelated-donor protocol opens in April; and NCI's Ron Gress, transplant immunologist and early champion of the new program

negotiations. But the deal, officially called the Matched Unrelated Donor Program, signals the dawn of a new era of research at NIH.

"The doors are now open," said Richard Childs, a principal investigator in NHLBI's Hematology Branch who performed the first matched unrelated hematopoietic transplant at NIH last year on a compassionate basis before the formal agreement was signed.

"You're going to see some real innovative stuff. These are high-risk transplants for patients who do not have other treatment options. If we can improve outcomes, it will radically change the field. . . . There's a tremendous amount of translational research here."

Childs added that this program was more than just an opportunity for NIH to stay competitive with other transplant centers. Unrelated hematopoietic transplants are inherently associated with more cases of graft-vs.-host disease (GvHD); and more so than other facilities, the CC has the range of expertise to confront and eradicate this roadblock to successful transplantation.

Making It Work

The first hurdle in implementing a successful agreement was to avoid rejection in the match between NIH and NMDP.

NIH needed the NMDP, with its immense registry of more than 10 million donors. Chances are extremely slim that a patient can find a perfect HLA blood match outside of the family. HLA matching follows Mendelian genetics, in which there is a 25 percent chance one's sibling will be a perfect match. Family members who are not a full brother or sister rarely match, and strangers have

less than a one-in-10,000 chance of matching. Like other centers, NIH did not have the resources to find matches between unrelated individuals on its own.

For its part, the NMPD was eager to involve intramural NIH investigators, whose expertise could expand and advance the field of unrelated-donor hematopoietic stem-cell transplantation. But the NMDP, as gatekeeper, set strict rules for managing and accrediting access to the donor pool.

For example, the NMDP requires an infrastructure comprising a medical director and transplant coordinators, as well as reporting requirements on transplant outcomes and procedures. Sounds simple enough, but with 27 institutes and centers, NIH was not the single entity that NMDP was used to working with.

Malech's challenge was to somehow create a central mechanism at NIH to enable anyone here to work with the NMDP—from the initial donor search through the essential coordination of the required yearly reporting process for all matched unrelated-donor transplants conducted at NIH regardless of institute.

"The initial response from many colleagues was, 'well, you can't do that,'" said Malech. "NIH is a wonderful place for spontaneous research collaborations between individual investigators, but there are a thousand reasons why you can't do something at NIH that requires multi-institute administrative coordination."

There was also worry of "stealing" away resources from the very successful sibling transplant programs already ongoing at NIH. "The NIH transplant community consists of multiple programs," Malech said. "They all do won-

derful things. They all care about their patients." There was concern, he said, that any additional costs incurred for this new program might siphon resources from the others.

Malech focused on the groups most likely to benefit from the new program: NCI, NIAID, NHLBI, and the Clinical Center. He received enthusiastic support from Gress and Pavletic, who had already established a multidisciplinary team to study chronic GvHD. Building on this inroad, Malech secured early and critical seed funding from

NIAID, NCI, and the CC that carried the project to the successful establishment of an administrative infrastructure that now derives its support from the participation of team member personnel from these entities plus NHLBI.

A key person from outside NIH who from early on facilitated the development of essential programmatic features of the NIH-NMDP agreement was Robert Hartzman, director of the C.W. Bill Young Department of Defense Marrow Donor Program, Naval Medical Research Center. And Elaine Ayres, CAPT USPHS in the CC director's office, was instrumental throughout the negotiations.

Accommodating Costs

The next hurdle was the cost. Sibling donations cost zero dollars to an investigator's individual lab budget allocation; the true cost of the collection of bone marrow or blood stem cells from family donors is hidden in the CC and institute budgets. In contrast, a matched, unrelated-donor graft could cost more than \$25,000 to procure. This includes detailed preliminary testing of blood cells from potential donors and the ultimate donor's medication and hospital expenses. Umbilical cord-blood units may cost even more. Such fees would quickly eat into an investigator's working research budget, discouraging protocols.

And it's hard to cut corners. NIH investigators could not simply reduce costs by bringing the donor to the Clinical Center. NMDP has guidelines for maintaining donor anonymity and minimizing the donor's time and travel burden.

"The NMDP is an incredibly donor-focused group," said NCI's Jennifer Wilder, a clinical nurse in the ETIB recruited from the University of Califor-

nia, San Diego, in 2005 to serve in the position of primary NIH-NMDP transplant coordinator.

This focus isn't a bad thing, Wilder said, for clearly the group is good at what it does. Forged from the Organ Transplants Amendment Act of 1988 and the National Bone Marrow Donor Registry, the NMDP has blossomed into a hub for a worldwide network of transplant facilities, with six million of its own waiting potential donors, four million more potential international

donors, and more than 50,000 cord-blood units available on NMDP participating registries. The NMDP now facilitates hundreds of unrelated-donor transplants each month and has assisted in more than 25,000 since its formation.

In the end, NIH and NMDP developed a new set of rules to guide the relationship between the two unique organizations. Malech worked through Hartzman to foster an arrangement with the NMDP to offset costs for procurement of donor products for NIH protocols.

Confronting GvHD

Unrelated-donor transplants are not new. The first unrelated-bone marrow transplant, at Memorial Sloan-Kettering Cancer Center in New York, was in 1973. A child with severe combined immunodeficiency syndrome received multiple infusions from a donor from Denmark. Decades later, however, these transplants still carry a high risk of GvHD.

The rate of acute or chronic GvHD for unrelated-donor hematopoietic transplants is about 30 to 40 percent and higher; they are also associated with a higher incidence of graft rejection and post-transplant immune complications.

Childs performed the first unrelated-donor transplant at NIH in May 2006. This was a complicated adult dual cord-blood transplant to treat aplastic anemia, a disease focus of the Hematology Branch and of Childs' transplant approach with related donors.

Cord-blood grafts are immunologically unique and permit a greater degree of HLA mismatching between donor and host without a corresponding increase in transplant complications such as GvHD. However, cord-blood units are miniscule, containing 30 to 40 cc of



Christopher Wanjek

On Deck: (left to right) NHLBI's Richard Childs, an NIH pioneer in hematopoietic transplantation; NCI's Jennifer Wilder, a clinical nurse who serves as the primary NIH-NMDP transplant coordinator; and NHLBI's Charles Bolan, medical director of the new transplant program

blood and a much smaller stem-cell dose than adult marrow or blood stem-cell grafts. A single cord-blood graft is usually only enough to treat a small child, and so cord-blood transplants have largely been the domain of pediatric medicine.

Childs, familiar with the pioneering work at the University of Minnesota on dual-cord transplants for adult patients with leukemia, saw a possibility in treating a long-term, but gravely ill, Clinical Center patient. This was a high-risk, last-ditch effort to save the man's life and was performed on a compassionate basis approved by the NMDP. Within about three weeks there were signs that the grafts were working; sadly, however, the patient succumbed to meningitis due to a chronic, extremely antibiotic-resistant infection.

New Protocols

The NIAID IRB has already approved one new unrelated-donor transplant protocol for congenital immunodeficiencies, led by Kang (#07-I-0075). This study involves transplants of bone marrow, cord blood, or peripheral-blood stem cells. The first transplant is planned for April.

For unrelated donors, precise matching is essential, Kang said, particularly for patients with severe inherited immune deficiencies. Kang's protocol requires matching at 10 of 10 HLA proteins. This entails a careful search for donors by Wilder and the NIH-NMDP transplant team, including David Stroncek, Sharon Adams, and other members of the HLA laboratory section in the DTM.

Two more protocols are well along in the IRB process, said Bolan, medical

director of the new program. One involves peripheral-blood stem cells to treat blood cancers such as leukemia and lymphoma, a study led by NCI's Michael Bishop, and another involves donor blood lymphocytes to treat a specific form of relapsed leukemia, led by Alan Wayne of NCI's Pediatric Oncology Branch.

Childs leads another developing protocol involving a dual cord-blood transplant for aplastic anemia, and other investigators from NCI, NIDDK, and other institutes have planned protocols or initiated searches for unrelated donor transplants.

Hanh Khuu and members of the DTM Cell Processing Section, working closely with Childs' group, have already overcome major obstacles in handling cord transplants, while Leitman and Phyllis Byrne, with the NIH-NMDP donor center, have provided valuable support in procedures involving unrelated donors.

"Matched unrelated-donor transplants, without question, will be more common in the future," said Malech. "If we want a robust portfolio of [transplant] programs at NIH, we need access to unrelated adult donors and cord-blood products. . . . These transplants will in essence be the standard," as the NMDP registry gets bigger and the relative percent of transplants using matched unrelated-adult donors or cord-blood increases. ■

For More Info . . .

The CC hosts a web site—
<http://intranet.cc.nih.gov/bmt/>
 —detailing the science of blood and bone-marrow transplants and subsequent treatment, as well as the intricacies of working with the NMDP.

Discoveries that add to the body of knowledge about normal and abnormal biological functions and behavior:

Identification of disease genes

- Finding that autoreactive B-cell responses to RNA-related antigens in mice are due to *TLR7* gene duplication, reflecting the importance of minor genetic mutations in autoimmunity and suggesting TLR7 as another potential target for lupus therapies (NIAID, NCI)
- Identification of the *K55R* polymorphism variant allele in association with increased risk of coronary heart disease in Caucasians in a community-based study of atherosclerosis risk, implicating *EPHX2* as a potential cardiovascular disease-susceptibility gene (NIEHS)
- Variants in *MC1R*, the gene encoding the melanocortin-1 receptor, found to confer a higher risk of mutations in the *BRAF* oncogene and in melanoma not associated with chronic sun-induced damage (NCI)
- Mutations in the gene coding for glucocerebrosidase found on autopsy in 23 percent of patients with dementia with Lewy bodies, a neurodegenerative disease with some symptoms of both Alzheimer's and Parkinson's diseases; mutations may interfere with the clearance of α -synuclein or promote its aggregation (NHGRI)
- Single mutations in the human master regulator p53 found to dramatically alter cellular response to environmental stress, potentially exerting an effect on tumor development and therapeutic efficacy (NIEHS)

Important new animal models

- Scrapie-infected transgenic mice expressing prion protein lacking the GPI membrane anchor: a model to study heart amyloidosis, develop a blood-based diagnostic test to identify brain-wasting diseases, and explore ways to rid blood of infectious prion disease agents (NIAID)
- Development of a transgenic mouse model of glaucoma, with mouse lines containing bacterial artificial chromosome with a point mutation in the human or mouse myocilin gene, with the demonstration of pathological changes in the eye similar to those seen in human glaucoma patients (NEI, NCI)
- Development of a mouse model for primary intraocular lymphoma and the demonstration that direct injection into the eye of a B-cell-specific immunotoxin (CD22-Pseudomonas exotoxin construct) can clear the tumor, suggesting a therapeutic strategy in the human disease (NEI, NCI)
- Development of a mouse-activity moni-

toring system that quantifies the activity of caged mice, enabling the analysis of the behavioral effects of experimental cancer treatments or genetic manipulations (NCI, CIT)

■ Mast cell findings in a mouse model of Smith-Lemli-Opitz syndrome (SLOS) present the first evidence of lipid raft dysfunction in SLOS and help explain the observed association of allergy with the syndrome (NIAMS, NICHD)

■ Finding in a mouse model that natural killer cells ameliorate liver fibrosis through killing activated stellate cells, elucidating the role of innate immunity in this condition (NIAAA)

■ Demonstration that mutant mice lacking the M_3 muscarinic acetylcholine receptor subtype in pancreatic β -cells display impaired glucose tolerance and greatly reduced insulin release; conversely, overexpression confers resistance to diet-induced hyperglycemia, suggesting that enhanced signaling through β -cell muscarinic receptors may represent a new avenue of type 2 diabetes treatment (NIDDK)

■ Demonstration in a mouse model of mitochondrial dysfunction that disruption of the gene for mitochondrial transcription factor A in dopamine (DA) neurons creates respiratory chain deficiency in mid-brain DA neurons and a parkinsonism phenotype (NIDA)

■ Finding that a corticotropin-releasing factor 1 receptor antagonist—antalarmin—can block stress-induced reinstatement of food-seeking behavior in a rat relapse model, suggesting that CRF1 receptor antagonists be considered in the treatment of maladaptive eating habits (NIDA, NIDDK)

■ Finding that drugs that inhibit γ -secretase, the enzyme that activates Notch protein, reduce brain cell damage and improve functional outcome in a focal ischemic stroke mouse model, suggesting that Notch signaling is a novel therapeutic target for the treatment of stroke (NIA)

Basic discoveries in cell, molecular, and structural biology with implications for the treatment of human disease

■ Discovery of a novel bacterium associated with necrotizing lymphadenitis in a patient with chronic granulomatous disease, with additional cases subsequently identified, demonstrating the application of Koch's postulates to a modern infectious disease (NIAID, CC, NCI)

■ Finding of an adaptive response by *Yersinia pestis* to extracellular effectors of innate immunity—antimicrobial reactive nitrogen molecules induced by plague

infection—during bubonic plague (NIAID)

■ First evidence, via expression profiling of human mast cells during ingestion of *Escherichia coli*, that mast cells encountering bacteria reprogram their responses to improve their innate immune function (NIAID)

■ Discovery of Kaposi's sarcoma-associated herpesvirus fusion-entry receptor—cystine transporter xCT—with implications for the study of genetic and environmental factors in xCT expression among different groups of people and the development of new treatment strategies (NIAID)

■ Identification of a cellular receptor for the varicella-zoster virus and for cell-to-cell spread of virus, with evidence that molecules that block the interaction of the receptor with the virus glycoprotein might be used to inhibit varicella-zoster infection in people (NIAID)

■ Demonstration of immune correlates of vaccine efficacy in monkeys immunized with plasmid DNA and replication-defective adenoviral vectors encoding SIV proteins and then challenged with pathogenic SIV (VRC)

■ Finding that T-cell-based vaccines can protect against the destruction of the CD4 memory compartment following acute SIV infection, and that this protection correlates directly with longer lifespan of infected animals (VRC, NIAID)

■ Finding that preferential infection reduces the lifespan of HIV-specific CD4+ T cells in vivo and thereby compromises the generation of effective immune responses to the virus itself—and that this central feature in the pathophysiology of HIV infection can be influenced by the cross-reactivity of responding CD4+ T cells (VRC)

■ Finding that Toll-like receptor agonists influence the magnitude and quality of memory T-cell responses after prime-boost immunization in nonhuman primates, thus providing significant insights for designing prime-boost immunization regimens that optimize Th1 and CD8+ T cell responses (VRC)

■ Discovery of a novel mechanism by which cytokines and inflammatory mediators can promote vascular permeability, with implications for the treatment of acute and chronic inflammation, tissue damage following stroke and myocardial infarction, diabetic retinopathy, macular degeneration, and tumor-induced angiogenesis (NIDCR)

■ Discovery of an essential role for the Akt-mTOR pathway in the action of an oncogenic Kaposi's sarcoma virus gene to induce sarcomagenesis, providing a rationale for the clinical evaluation of mTOR

inhibitors in the treatment of Kaposi's sarcoma (NIDCR)

■ Discovery that IFN- α mediates CD4+ T cell anti-HIV activity by increasing expression of the cellular APOBEC cytidine deaminase and that bolstering APOBEC can inhibit HIV infection, which may lead to new therapeutic strategies targeting host molecules rather than viral molecules (NIDCR)

■ Discovery that enzyme Cdk5 regulates pain sensation through direct phosphorylation of a pain receptor (TRPV1), identifying it as a potential drug target for developing analgesics to treat pain (NIDCR, NINDS)

■ Analysis of the role of members of the PBC family of homeodomain proteins—extrodenticle and homothorax—in *Drosophila* muscle development, with implications for the current models of how translocational activity of extrodenticle causes cancer (NICHD, NCI, CBER-FDA)

■ Analysis of acoustic wave propagation showing that the graded spiral curvature of the cochlea enhances its sensitivity to lower auditory frequencies, a finding that could lead to improved design of cochlear implants (NIDCD, DBEPS)

■ Functional and morphological recovery of dystrophic muscles in mice treated with deacetylase inhibitors, pointing to the use of such agents in the treatment of muscular dystrophy in humans (NIAMS)

■ Discovery of novel biological actions of the nutritional supplement DHEA in stimulating the production of nitric oxide and endothelin-1 from the lining of blood vessels, elucidating why DHEA supplementation may be helpful for metabolic health in some diseases and circumstances, but not in others (NCCAM)

■ Discovery of a new molecular mechanism for thyroid hormone action, providing new insight into the role of thyroid hormone in human brain, heart, lipid, and neuronal matters and underscoring concerns about agricultural chemicals that interfere with thyroid hormone activities and such public-health problems as learning disorders, cardiovascular disease, obesity, and depression (NIEHS)

■ Demonstration that *SHPRH*, a putative tumor-suppressor gene, is the human orthologue of the yeast Rad5, the most significant factor in yeast DNA repair and the prevention of genomic instability during replication, providing a new mechanism for understanding and potentially treating several types of cancers (NHGRI)

■ Demonstration in mice that an impaired epidermal barrier can promote an inflammatory response, suggesting that the most effective treatments for inflammatory skin

disorders might concomitantly suppress the immune response and enhance epidermal differentiation to restore the barrier (NHGRI, NEI, NICHD)

■ Discovery of a novel endogenous lipid, *N*-arachidonoyl-L-serine, and its vasodilator activity at a novel endothelial receptor, with implications for the dynamics of an endogenous vascular protective agent (NIAAA)

■ Demonstration that dopamine-related disorders, such as Parkinson's disease, may not stem from changes in the overall levels of cortical activity, but from dysfunctional coordination of corticostriatal circuitries (NIAAA)

■ Discovery of the pathway in the brain that may underlie human stable visual perception in spite of continual shifts in the retinal image resulting from rapid eye movements (NEI)

■ Demonstration in mice of key roles for sphingosine-1-phosphate signaling in immunity (NIAMS, NIDDK, NIAID)

■ Design and synthesis of new nucleotide derivatives that interact with P2 nucleotide receptors that induce cardioprotection in an ischemic heart model, with potential value in preventing platelet aggregation and reducing cardiomyopathy (NIDDK)

■ Identification of novel isoforms of protocadherin-15 as components of the tip-link complex of hair cell stereocilia, further elucidating the mechanism of transduction in sensory cells of the inner ear (NIDCD, NHGRI)

■ Elucidation of the role of p53 in mitochondrial respiration and the ascendancy of the glycolytic pathway as the energy source for cancer cells (NHLBI, NIDDK)

■ Discovery that the behavior of oxidatively modified RNA may, in part, explain age-related changes in protein modification and thermostability and the accumulation of protein aggregates in neurodegenerative diseases (NHLBI)

■ Discovery that resveratrol induces in obese mice on a high-fat diet a variety of metabolic and physiologic effects associated with caloric restriction and extended lifespan, raising the possibility that longevity in humans may be pharmacologically enhanced without severe dietary restriction (NIA)

■ Identification of a link between circulating endothelial microparticles and ischemic stroke with regard to severity, lesion volume, and outcome (NINDS, CBER-FDA)

■ Identification of the neutralization epitope responsible for the hepatitis B virus subtype-specific protection in chimpanzees (CC, CBER-FDA)

■ Quantification of hepatitis B virus ge-

nomes and infectivity in human sera (NIAID, CBER-FDA)

■ Finding that natural regulatory T lymphocytes (T-regs) can be activated through their innate immunity receptors to prevent autoimmune uveitis in a mouse model and that T-regs not specific only to the retina can offer protection, with implications for the development of T-reg-based therapies for humans, where the triggering ocular antigens are often unidentified (NEI)

■ Elucidation of the role of neuron location—in the striate or extrastriate cortex—in choice-related activity in macaques (NEI)

■ Structural analysis of DNA strand slippage that generates deleterious mutations underlying disease, supporting a decades-old but yet-unproven idea (NIEHS)

■ *TLR4* gene found to protect against tumor development in mice, suggesting that targeting the innate immune system may be useful in fighting human diseases, including cancer (NIEHS)

■ Discovery of a retinal synapse that triggers neurotransmitter release by calcium influx through glutamate receptor channels (NINDS)

■ Demonstration that Notch receptor activation promotes the survival in vitro of human embryonic neural stem cells and, in vivo, generates increased precursor cells and improved motor skills in adult rats with ischemic brain injury, with implications for the field of regenerative medicine (NINDS)

■ Global expression profiling of mouse embryonic stem cells and adult neural stem/progenitor cells revealing three distinct phases—undifferentiated ESCs, primitive ectoderm-like cells, and neural progenitor cells—defining a developmental path to neural fate and providing a scale for the degree of commitment/differentiation (NIA)

■ Elucidation of the mechanism of IL-21 regulation of CD8+ T lymphocytes, suggesting ways to exercise control over this cytokine (NHLBI)

■ Finding that children with bipolar disorder display greater limbic activation and misread neutral facial expressions as hostile when asked to rate degree of hostility than do unaffected children, implicating this face-processing deficit in the poor social skills characteristic of this disorder (NIMH)

■ Findings on MRI that children with high IQs show more rapid cortical thickening during childhood and peak later than in age peers, perhaps reflecting a longer developmental window for higher-level thinking circuitry and consistent with fMRI findings that levels of prefrontal activation

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correlate with IQ (NIMH)

■ Identification of the first novel Birt-Hogg-Dubé binding protein—folliculin interacting protein—and further elucidation of the molecular mechanisms involved in kidney cancer formation, suggesting that tumor growth may be partly controlled by molecular agents that target the mTOR pathway (NCI)

■ Demonstration in clinical studies in patients with pediatric sarcoma that interleukin-2 therapy significantly expands suppressive regulatory T cells, indicating that new T-cell growth factors that do not induce this expansion should be studied for use in cancer immunotherapy and that therapeutics that induce in vivo depletion of suppressive T cells would likely augment antitumor immunity (NCI, CC, VRC)

■ Elucidation of changes in chromatin structure and mobility in living cells at sites of DNA double-strand breaks, further elaborating the mechanism by which DNA breaks are detected and repaired and informing the design of drugs to potentiate this response (NCI)

■ Elucidation of the effect of ionizing radiation on unhit neighboring bystander cells and of differences between hit and unhit cells in the formation of DNA double-strand breaks, a better understanding of which may lead to improved cancer radiation treatment (NCI, CC)

■ Reversal of age-related defects associated with truncated lamin A protein in both normally aged cells and the cells of patients with progeria, identifying a novel molecular mechanism in human aging, establishing progeria as a useful model to study human aging, demonstrating the reversibility of the cellular aging process, and providing an experimental system to study the molecular basis for the absence of tumors in the cells of progeria patients and the link between aging and cancer at the molecular level (NCI)

■ Findings that an iron-sulfur protein regulates mitochondrial iron homeostasis and that compromised iron-sulfur cluster assembly results in mitochondrial overload as a result of abnormal mitochondrial-to-nuclear signaling, with implications for the study of Friedreich's ataxia (NICHD)

■ Crystallographic and functional analysis of glutamate receptor ligand complexes, elucidating the differences between kainite and AMPA receptors, with implications for understanding the gating mechanism of glutamate receptor ion channels and the suggestion that glutamate receptors are capable of much larger movements than previously thought (NICHD)

■ Characterization of the previously unknown ligand-binding selectivity of the

NMDA receptor NR3A subunit, expressed widely in the embryonic and early postnatal nervous system of mammals, paving the way for crystallographic analysis and better understanding of the functional role of this subunit (NICHD)

■ Elucidation of distinct mechanisms for acute and long-term synaptic modulation by neurotrophin-3, and the tracking of two parallel but distinct molecular pathways to elicit long-term changes in synaptic function and structure, with implications for understanding cell biological mechanisms underlying synapse development and plasticity (NICHD)

■ First localization of brain sites—in the ventral tegmental area and the nucleus accumbens—within which cannabinoids have rewarding actions, linking cannabis reward regions to the brain regions involved in the rewarding actions of cocaine, amphetamine, heroin, and nicotine (NIDA)

■ Demonstration for the first time that selective dopamine D₃ receptor antagonism constitutes a new and promising pharmacotherapeutic approach to the treatment of nicotine dependence (NIDA)

■ Establishment by event-related functional MRI that two largely distinct neural networks mediate stimulus-driven (bottom-up) and intentionally driven (top-down) control of visuospatial selective attention (NIDA)

■ Discovery that administration of MDMA and methamphetamine to rats increases plasma serotonin to levels high enough to stimulate mitogenic responses in pulmonary artery smooth muscle cells, suggesting that these abused stimulants may increase the risk of developing idiopathic pulmonary arterial hypertension (NIDA)

■ Design and synthesis of noncompetitive metabotropic glutamate receptor subtype 5 antagonists and their evaluation in animal models of drug abuse and anxiety (NIDA)

Development of new or improved instruments and technologies for use in research and medicine

Advances in imaging

■ Findings via fluorescence resonance energy transfer in living cells of dynamic membrane changes—conformational change in the B-cell receptor and a dynamic reorganization of the local membrane lipid environment—providing a new view of B-cell activation in live cells that may lead to novel targets for enhancing or dampening B-cell responses (NIAID)

■ Development of a powerful nuclear magnetic resonance method, based on paramagnetic relaxation enhancement, to detect and visualize transient, low-popu-

lation encounter complexes in macromolecular protein-protein and protein-nucleic acid interactions, enabling study of such dynamics as the search for specific binding sites by transcription factors diffusing along DNA (NIDDK)

■ Development of quantitative MRI techniques for in vivo pharmacokinetic analysis of drug transport in the eye, with implications for clinical applications (NEI, DBEPS, NINDS)

■ Development of fluorine-18 radiochemically labeled protein for PET imaging of HER2 receptor, with potential use in breast-cancer diagnosis (NIBIB, NCI)

■ Real-time MRI successfully guided recanalization of total arterial occlusions in animals, laying the groundwork for future studies of image-guided opening of blocked arteries as an alternative to surgery in humans (NHLBI)

■ Solid-state NMR examination of the structure of amyloid fibrils formed in vitro from purified recombinant Sup35, elucidating the [PSI(+)] prion phenomenon (NIDDK)

■ New insights into the structure of influenza virus via cryoelectron tomography suggesting the existence of an alternative pathway for the budding of nascent virions from host cells in which matrix protein is minimally involved, with possible implications for vaccine design (NIAMS)

■ PET studies in awake monkeys showing that species-specific vocalizations evoke robust activity in homologues of human perisylvian language areas, hinting at the key neural mechanisms of the last common ancestor of macaques and humans that may have been recruited during the evolution of language (NIDCD, NIMH)

■ Development of two new fluorescent protein techniques: 1) a high-resolution microscopy technique—photoactivated localization microscopy—that is capable of optical resolutions beyond the limit imposed by diffraction, and 2) fluorescence protease protection, an assay that enables determination of a protein's topology in living cells via a fluorescent read-out before and after trypsin-induced destruction of green fluorescent protein attached to a protein of interest (NICHD)

Advances in bioinformatics

■ Development of the Clinical Study Information System to support efficient management and analysis of clinical data to better inform clinical decisionmaking, currently used in the study of α -galactosidase activity in Fabry disease (CIT, NINDS)

■ Development and enhancement of tools (PubMatrix SE) for the storage, retrieval,

and mining of genetic-associations data in the biomedical literature, using natural language processing and statistical methods to assess the strength of associations among various entities (CIT, NIA)

■ Development of tools to query, process, quantify, and visualize data—including behavioral, genomic, imaging, video, dysmorphology, and clinical-trial research data—from the National Database for Autism Research, serving to expedite autism research (CIT, NIMH, NICHD, NINDS, NIEHS, NIDCD)

■ The production and public release of high-density genotype data throughout the human genome in a series of 270 individuals with Parkinson's disease and 270 neurologically normal individuals, providing access to the largest collection of publicly available genotypes in a case-control cohort and facilitating research on Parkinson's and other neurodegenerative disorders (NIA, NINDS; see <https://queue.coriell.org/Q/snp_index.asp>

■ Development of an integrative computational framework to study human macronutrient metabolism and body-composition regulation (NIDDK)

■ Creation of a model of biological charge transfer to study the electric current through a chain of single-file water molecules using sophisticated computer-simulation techniques. (CIT, NIDDK)

■ Determination of the genomic landscape of major histone modifications in human T cells, showing a correlation of modification patterns with transcriptional regulatory elements and suggesting that the combination of these patterns with comparative genomics is an efficient strategy of annotating the human genome (NHLBI)

Advances in biotechnology

■ Development of a unified theory of force-induced molecular transitions for single-molecule pulling experiments, with application to DNA unzipping (CIT, NIDDK)

Development of new or improved approaches for preventing or delaying the onset or progression of disease and disability

■ Development of a model (<<http://dceg.cancer.gov/melanomarisksite/>>) for use during a routine physical exam to estimate the five-year absolute risk of a first primary melanoma among whites between 20 and 70 years old (NCI)

■ Findings that long-term survivors of pediatric sarcoma are at increased risk of persistent psychological distress, musculoskeletal impairments, cardiovascular disease, and infertility, suggesting long-term man-

agement approaches (NCCAM, NCI, CC, NICHD, NHLBI)

■ The finding that, separate from their antioxidant effects, polyphenolic compounds from blueberries prolong the lifespan of *Caenorhabditis elegans* by 20 percent, demonstrating for the first time that these compounds have beneficial effects on whole animals as well as cells and suggesting that fruits and vegetables containing polyphenolic compounds may promote human longevity (NIA)

■ Long-term dietary energy restriction, whether by intermittent fasting or a low-calorie diet, found to produce changes in heart rate, blood pressure, and heart rate variability in rats opposite those associated with aging, suggesting the study of dietary energy restriction in humans as another means to achieve cardiovascular fitness effects typically associated with aerobic exercise (NIA)

■ First-time prevalence estimates for *BRCA1* and *BRCA2* mutations in a population-based case-control study of black and white American women ages 35 to 64, yielding also significant predictors of each mutation (NHGRI, NCI, NICHD)

■ Finding that overweight and obese men have decreased fertility, with a 20-pound increase yielding a 10 percent increase in infertility risk (NIEHS)

■ Launching of three major intramural clinical studies—the first product of a new integrated focus on autism—to define the characteristics of different subtypes of autism spectrum disorders; to examine the effectiveness of the antibiotic minocycline in treating regressive autism; and to address the widespread but unproven theory that autism may be treated successfully by chelation therapy to remove heavy metals from the blood (NIMH)

■ Demonstration that oral glucosamine does not cause or significantly worsen insulin resistance or endothelial dysfunction in either lean or obese people and that steady-state glucosamine levels do not change with oral dosing, a finding that will aid in evaluating future studies of glucosamine's efficacy (NCCAM)

■ Launching of a randomized, prospective clinical trial to compare the efficacy of tai chi chuan, a mind-body practice, with aerobic exercise in improving the cardiovascular and psychological status of adult cancer survivors (NCCAM)

■ Finding from the first cohort study addressing the 1986 Chernobyl accident that children and adolescents exposed to the radioactive iodine experienced a large increase in thyroid cancer (NCI, NIDDK)

■ Finding from a population-based study that excess risk of acute myeloid leuke-

mia following treatment for Hodgkin's lymphoma was higher among patients who received chemotherapy in addition to radiotherapy, those over 35 at the time of treatment, and those treated before 1984 (NCI)

■ TNF and IL-10 polymorphisms, separately and even more so in combination, found to confer increased risk of non-Hodgkin's lymphoma, especially diffuse large B-cell lymphoma, based on data from the International Lymphoma Epidemiology Consortium (NCI)

■ Excess body weight during midlife, including overweight as well as obesity (as defined by body-mass index) found to be associated with an increased risk of death from all causes in otherwise-healthy people who had never smoked (NCI, NIA)

■ Women with prenatal exposure to diethylstilbestrol found to have an increased risk of breast cancer after age 40, according to results of the first prospective study on the subject (NCI)

■ First report from ongoing genetic analysis of complex cardiovascular and personality traits among individuals living in the relatively isolated populations of Sardinia to identify the impact of genetic influences on risk factor variations, with the aim of identifying targets for intervention to prevent the development of cardiovascular disease (NIA)

■ Design of clinical studies to test the hypothesis that specific spectral photoprotective filters—vermilion sunglasses that reduce both rod activation in bright ambient light and the accumulation of toxic photoproducts like A2E in the retinal pigment epithelium—will lessen A2E levels and stymie progression of both early and moderate age-related macular degeneration following cataract surgery and intraocular lens implantation and in young patients with Stargardt's macular dystrophy (NICHD, NEI)

Vaccine development

■ Development and testing of the second component of a live attenuated tetravalent dengue virus vaccine, which was found to be safe and highly immunogenic in healthy adult volunteers (NIAID)

■ Development of an H5 DNA influenza vaccine, built on existing VRC DNA plasmid platform technology, now being tested in a Phase I clinical trial to evaluate safety and immunogenicity in adult volunteers (VRC)

■ Testing of a single-shot adenovirus Ebola vaccine in a Phase I vaccine trial to evaluate safety and immunogenicity in adult volunteers (VRC)

■ Testing of a second-generation West Nile

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virus DNA vaccine for humans, using an improved expression vector expressing WNV proteins, in a Phase 1 vaccine trial to evaluate safety and immunogenicity in adult volunteers (VRC)

■ Achievement of long-lasting and transmission-blocking activity of antibodies to *Plasmodium falciparum* in mice administered immunogenic protein conjugates of surface protein Pfs25, with implications for the development of a malaria vaccine (NICHD)

Development of new or improved ways to diagnose disease and disability

■ Development of a microbore static tissue-sampling needle combined with a flow immunoassay lab-on-a-chip for the assessment of in situ tissue inflammation in muscle and skin disease (DBEPS, NCI, CC, NIAMS)

Gene expression patterns

■ Development of an antibody-based microarray assay for small RNA detection that eliminates the need to manipulate RNA, thereby improving reproducibility and sensitivity of microarrays for these key regulators of gene expression (NIAID)

■ Development of a loss-of-function RNA interference screen for molecular targets in cancer, an "Achilles heel" methodology that uncovers a key signaling component in diffuse large B-cell lymphoma and can be used to classify cancers based on which regulatory proteins and pathways promote proliferation or prevent cell death (NCI, CIT)

■ Demonstration that gene expression profiling distinguishes the more aggressive Burkitt lymphoma from diffuse large B-cell lymphoma when current methods of pathological diagnosis fail to do so, leading to intensive chemotherapy regimens and superior survival for patients with this molecular diagnosis of Burkitt lymphoma (NCI, CIT)

Development of new or improved ways to treat disease and disability

■ Development of monoclonal antibodies to vaccinia virus B5 protein that neutralize vaccinia and smallpox viruses, protect mice against vaccinia virus, and may also be useful for protection against other pox viruses, such as monkeypox virus (NIAID, ORS)

■ Discovery of the mode of action of PA-824, a drug that may shorten the duration of tuberculosis treatment regimens and is now in early-stage clinical trials, with implications for improved drug design and accelerated TB drug development (NIAID)

■ Anakinra, a recombinant soluble interleukin-1 receptor antagonist, found to rapidly and dramatically reduce systemic inflammation in patients with neonatal-onset multisystem inflammatory disease, a devastating inherited autoinflammatory disorder refractory to other therapies (NIAMS, NEI, NIDCD, NINDS, CC, NCI, NIAID, NIDDK)

■ Finding that having two copies of the less-common version of a gene encoding the serotonin 2A receptor increases the odds of a favorable response to antidepressants and that this version is more than six times more prevalent in white than in black patients, helping explain racial differences in treatment outcome and supporting the importance of the serotonin receptor in the mechanism of antidepressant action (NIAAA, NIMH)

■ Symptom relief achieved in as little as two hours for patients with treatment-resistant depression following a single I.V. dose of ketamine in a preliminary randomized study, a major improvement over the typical eight weeks or more for a treatment effect from current antidepressants (NIMH)

■ Establishment of safety and suggestion of efficacy in a Phase 1 clinical trial of ciliary neurotrophic factor, delivered by encapsulated intraocular implants, in the treatment of retinal neurodegeneration, raising the possibility of also using this approach to deliver therapeutic proteins in retinal diseases not caused by genetic mutations (NEI, NIDCD)

■ New insights into the immune recovery process after allogeneic stem-cell transplantation in leukemia patients, pointing to the importance of natural killer cell recovery and strategies to boost the graft-vs.-leukemia effect in the first month post-transplant (NHLBI, CC)

■ Discovery that carrageenan, an inexpensive polysulfated carbohydrate found in many consumer products, including some over-the-counter sexual lubricants, is an extremely potent inhibitor of genital herpesvirus infection (NCI)

THE JOURNEY OF THE STEM CELLS

continued from page 1



Last Steps: (top to bottom) Hanh Khuu (right) and Sue-Ellen Frodigh, lead medical technologist, prepare the mix to dilute the cord-blood units after thaw; a few days later, Frodigh carefully thaws a cord-blood unit in a 37 ° C water bath; the graft is then diluted with the thaw mix and transferred to a larger bag for centrifugation; finally, after automated cell counting, labeling, and other clerical procedures, Khuu walks the cells to the patient-care area, where the bag will be spiked and hung for infusion

Photos by Elizabeth Read

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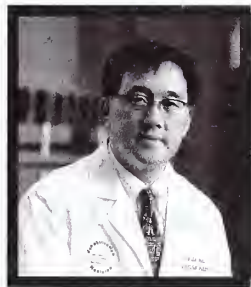
Leighton Chan received his M.D. degree from the University of California at Los Angeles in 1990. He did his residency in physical medicine and rehabilitation and was a Robert Wood Johnson Clinical Scholar at the University of Washington in Seattle, where he also received his M.P.H. He spent 10 years on the faculty of the University of Washington while also working at the Center of Medicare and Medicaid Service's Seattle regional office. In January 2007, he joined NIH as chief of the Rehabilitation Medicine Department at the Clinical Research Center (CRC).

If one were to select a single institution to monitor health care in the United States, it would likely be Medicare. Medicare is the largest purchaser of health care in this country, accounting for 20 percent of all health-care dollars spent here. This includes 20 percent of all physician bills, 10 percent of all skilled-nursing facility spending, 32 percent of all inpatient costs, and 70 percent of all inpatient rehab costs. In all, there are 44 million Medicare enrollees whose medical care costs about \$220 billion per year.

As a health-services researcher, I have focused my research efforts on using Medicare billing data to monitor secular trends, to measure geographic variation, and to support the evaluation of specific conditions, treatments, and procedures.

Much of my prior work dealt with issues around improving Medicare's payment policy. For instance, I performed a large cohort study of approximately 300,000 Medicare rehabilitation inpatients and found that certain types of hospitals were incentivized to prolong patients' hospital stays to maximize profits. This policy cost the federal government more than \$200 million over a seven-year period. These results helped galvanize changes in this payment methodology over the past few years.

I have also used Medicare billing data to examine outcomes after specific surgical procedures, most recently bariatric surgery for obesity. Using Medicare billing data, we collected the largest bariatric surgery cohort to date—more than 16,000 patients—and determined that short-term mortality rates were exceptionally high for individuals over 65 years old and for individuals whose surgery took place in hospitals that performed the procedure infrequently. These results helped lead to changes in Medicare's payment policy



Leighton Chan

for bariatric surgery.

More recently I have become interested in the concept of health-care disparities, in particular the notion that disability—whether it involves mobility or communication or is cognitively based—is a risk factor for poor health care. I have been using a large Medicare survey dataset that is designed so that one can draw conclusions from the entire Medicare population.

Our findings suggest that—after controlling for important and known demographic confounders—individuals with disabilities are indeed at risk for inadequate primary care, poor satisfaction with care, and higher health-care costs. We are in the process of confirming these results through triangulation with other datasets.

In my new position as chief of the CRC's Rehabilitation Medicine Department, I plan to expand the activities of the department's Physical Disabilities Research Branch. This branch focuses its efforts on the biomechanics of movement. I plan to continue this important work as well as add areas of focus, including health-services research and possibly cardiopulmonary rehabilitation.

Ultimately, my hope is to create models of care for individuals with disabilities to maximize their function and reduce or eliminate health-care disparities.

Patrizia Farci received her M.D. degree from the University of Cagliari Medical School, Cagliari, Italy, in 1979 and became a board-certified specialist in infectious diseases and in gastroenterology. She had her postdoctoral training at the Molinette Hospital in Torino under Giorgio Verme and Mario Rizzetto and at the Royal Free Hospital, University Medical School, London, under Sheila Sherlock. In 1989, as a visiting scientist, she joined the NIAID laboratory of Robert Purcell. She returned to Italy in 1994 and in 2000 became full professor of medicine and director of the Liver Unit and of the Laboratory of Molecular Virology, as well as director of the Post-Graduate School of Gastroenterology at the University of Cagliari. Earlier this year she moved to the Laboratory of Infectious Diseases, NIAID, where she is a senior investigator and head of the Hepatic Pathogenesis Unit in the Hepatitis Viruses Section.

Christopher Wanjek
Patrizia Farci

Most of my work has been devoted to the study of chronic viral hepatitis, especially hepatitis C. My research has been driven by my natural inclination to merge clinical medicine with basic research.

In the early 1990s, soon after the discovery of HCV, I developed one of the first PCR assays for HCV and used it to define the molecular events that occur during the natural history of HCV infection in humans and chimpanzees,

providing evidence that HCV continuously replicates for more than 20 years. I became fascinated by the extremely high propensity of HCV to induce chronic infection, and I focused my research on trying to understand the mechanisms whereby HCV escapes immune recognition.

Among the most significant findings, we showed that HCV does not confer protective immunity in either humans or chimpanzees and that it may cause multiple episodes of acute hepatitis C in the same individual. Because of the major implications of these observations for the development of an effective vaccine against HCV, we investigated why HCV does not confer protective immunity in the host.

We were able to demonstrate for the first time in vivo that HCV does elicit neutralizing antibodies, but their efficacy is isolate-restricted and ineffective against minor viral variants present in the complex quasispecies. We then identified HVRI, the most variable region of the HCV genome, as a major target of neutralizing antibodies.

Capitalizing on these observations, I started to focus my research on understanding the biological implications of HCV genetic heterogeneity (quasispecies) for viral persistence, pathogenesis, therapy, and prevention of hepatitis C. One of the most important observations was the discovery that the early evolution of the viral quasispecies during primary HCV infection predicts the outcome of acute hepatitis C (resolution vs. persistence).

Another major interest has been hepatitis D, the most severe and progressive form of chronic liver disease that leads to cirrhosis in 80 percent of the cases. We demonstrated that high doses of α -interferon are required for the treatment of this disease and that interferon significantly improves the long-term clinical outcome and survival of patients with

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chronic hepatitis D, providing the basis for current treatment guidelines.

Moreover, our 20-year long-term study convincingly showed the regression of advanced hepatic fibrosis (and probably cirrhosis) after interferon therapy, thus contributing to a paradigm shift in our understanding of chronic liver disease, challenging the dogma that cirrhosis is an irreversible process.

I am now in the process of establishing the Hepatic Pathogenesis Unit within the Hepatitis Viruses Section. I will pursue two major lines of research: the study of the molecular mechanisms underlying the pathogenesis of chronic viral hepatitis and the search for new hepatitis agents.

I will be continuing studies on the mechanisms of liver disease progression, shifting the focus to the molecular level and engaging proteomics, gene arrays, and bioinformatics analyses, powerful new tools to uncover patterns of disease in which hundreds of genes are jointly regulated.

In particular, I am very interested in the molecular mechanisms that determine the pace of progression of liver fibrosis or, conversely, the regression of liver fibrosis. A major question is to understand why the development of cirrhosis may take decades in chronic hepatitis C, but only one to two years in chronic hepatitis D. I will also investigate the relationship between inflammation, fibrosis, and hepatocellular carcinoma (HCC), cirrhosis being the highest predisposing factor for the development of HCC.

Another major area of research will aim at the identification of new etiologic agents responsible for viral hepatitis or other forms of hepatic inflammation. We will attempt transmission of putative etiologic agents to nonhuman primates, especially chimpanzees, as evidenced by perturbation of specific immunologic or metabolic pathways and then will use global discovery techniques for virus identification.

I am very grateful to my first mentor, Angelo Balestrieri, and to many collaborators, especially Robert Purcell and Harvey Alter, and I hope to continue to expand my trans-NIH collaborations, which represent for me the greatest strengths of this unique place.

Andy Golden received his Ph.D. from the State University of New York at Stony Brook in 1990. He completed a postdoctoral fellowship at the California Institute of Technology in Pasadena in the labo-

ratory of Paul Sternberg and in 1995 became a program fellow at the NCI-Frederick. In 2000, he joined the Laboratory of Biochemistry and Genetics, NIDDK, where he is now a senior investigator.

Errors in chromosome segregation during meiosis are responsible for the majority of spontaneous miscarriages in humans and also account for disorders such as Down syndrome. Understanding the regulatory mechanisms of chromosome segregation during meiosis is the primary goal of my laboratory.

We have taken a genetic approach to understanding this process. Using the free-living soil nematode *Caenorhabditis elegans*, we have isolated mutants that are defective in chromosome segregation during meiosis.

In *C. elegans*, oocytes are fertilized in prophase of meiosis I. In a screen for temperature-sensitive mutants, we isolated over 30 mutants whose embryos arrest at metaphase of meiosis I. These mutants defined five genes, all of which coded for subunits of the anaphase-promoting complex (APC). This complex is an E3 ubiquitin ligase, which ubiquitinates substrates and targets them for degradation by the 26S proteasome.

Our findings demonstrated that the APC is maternally stored in oocytes to drive the meiotic divisions upon fertilization. Oocytes defective in the APC arrested as one-cell meiotic embryos and failed to develop further.

Spermatocytes defective in the APC also failed to segregate their chromosomes during both meiotic divisions, but surprisingly, still differentiated into spermatids. These sperm were able to fertilize oocytes despite their lack of chromosomes. These embryos undergo a number of divisions before dying.

To further understand the players in meiotic chromosome segregation, we isolated 26 extragenic mutations that restored viability to these APC mutants at the nonpermissive temperature. These 26 mutants defined at least eight different genes. Four of these genes code for known regulators of the APC. One was FZY-1, an APC activator. Three others were orthologs of the spindle assembly checkpoint (SAC).

The SAC functions during mitosis to monitor the assembly of the spindle and the attachment of chromosomes to the spindle microtubules. Defects in either of these processes triggers the SAC to inhibit

the APC, thus allowing the cell more time to correct these defects before separating chromosomes at anaphase.

Our findings suggest that the SAC also functions during normal meiotic divisions (in the absence of any obvious spindle damage), perhaps to regulate the timing of the meiotic divisions after fertilization. The identification of the remaining suppressor mutants from this screen is one of our immediate goals.

We have also used a genetic approach to find suppressors of a mutant separase allele. Separase is the protease that cleaves the cohesion molecules that hold metaphase chromosomes together. This mutant has severe defects in meiotic chromosome segregation and cytokinesis.

This strategy has identified only two suppressors, one of which is a conserved, but uncharacterized, phosphatase. We are investigating the mechanism by which a mutation in this phosphatase suppresses the separase phenotypes.

In addition, we are currently working toward the molecular identification of the other suppressor.

Though our studies have focused on the maternal factors in the oocyte that drive the meiotic divisions, we are also curious as to how fertilization triggers the oocyte to resume its meiotic divisions. Sperm are likely the source of this signal, because normal meiotic divisions are not observed in the absence of sperm.

SPE-11 is a protein that is contributed by the sperm that is absolutely essential for meiotic resumption upon fertilization. Mutations in the *spe-11* gene result in embryos that fail to complete the meiotic divisions after fertilization and subsequently die during embryonic development.

To understand how paternal SPE-11 triggers meiotic resumption, we have recently begun an extragenic suppressor screen to identify mutants that permit the survival of *spe-11* mutants.

Presumably such a screen will identify components of the pathway through which SPE-11 communicates with the oocyte to initiate meiotic resumption. This screen may identify additional paternal factors involved, or at least other maternal factors that receive this sperm signal.

I enjoy the genetic approaches we have taken to understand the regulation of the meiotic divisions in *C. elegans*. These screens have allowed us to take a naïve approach without making any assump-



Christopher Wanjek

Andy Golden

tions about the types of genes for which we should be looking.

In this way, we have isolated rare gain-of-function alleles of some genes and hypomorphic alleles of essential genes. These types of alleles allow a more nuanced examination of the roles of these genes in meiosis and early development.

Ellen Leibenluft received her M.D. degree from Stanford University, Stanford, Calif., in 1978. She did her residency at Georgetown University in Washington, D.C., where she served as director of the psychiatric inpatient unit and day hospital before joining NIMH in 1989. She is currently a senior investigator and chief of the Unit on Bipolar Spectrum Disorders in the Emotion and Development Branch of the Mood and Anxiety Disorders Program, NIMH.

My research has two main goals: to elucidate the pathophysiology of pediatric bipolar disorder (BD) using the principles and techniques of cognitive neuroscience and to ascertain whether children with extremely severe irritability and symptoms of attention deficit hyperactivity disorder (ADHD) are exhibiting a phenotype of pediatric BD.

Our studies of the brain mechanisms mediating BD in youth involve administering standardized behavioral paradigms to assess emotional and cognitive information processing. On paradigms in which patients and control subjects differ behaviorally, we use rapid event-related functional MRI to study between-group differences in neural activation.

Using such techniques, we found that youth with BD have deficits in their ability to identify facial emotion. For example, compared with control subjects, youth with BD rate a neutral face as more hostile, are more afraid of the face, and have increased amygdala activation when rating the hostility on the face or their fear of it (but not when performing a non-emotional rating of a facial feature). Deficits in face labeling and/or increased amygdala activation differentiate youth with BD, not only from controls, but also from those with anxiety, depression, and ADHD.

Recently, we found that deficits in labeling face emotion are also present in unaffected youth at high risk for the disorder, that is, those who have a parent or sibling with BD. Thus, we are now studying whether face emotion-labeling deficits may be an endophenotype of BD, as

well as associations between polymorphisms and these behavioral and neuroimaging findings.

We have also found that youth with BD have deficits in their ability to adapt their behavior flexibly in response to changing emotional stimuli. This deficit may be pathophysiologically related to the fact that patients with BD have marked response inflexibility when they are manic or depressed (for example, they are unable to respond appropriately to rewarding stimuli when depressed). Response-flexibility deficits are evident on response-reversal tasks and on tasks in which subjects must inhibit a repetitive response or substitute an alternative one.

We found that patients with BD, compared with control subjects, have decreased activation in the ventrolateral prefrontal cortex and striatum when they try to inhibit a motor response but fail to.

These data indicate that patients with BD may have a deficient striatal error signal and, in concert with the data presented above, implicate amygdala-striatal-prefrontal circuitry in the patho-

physiology of BD.

Our second, and parallel, research focus is on youth with extremely severe irritability and ADHD-like symptoms, a syndrome that we have named "severe mood dysregulation" (SMD).

Although youth with SMD are frequently diagnosed with BD in clinical settings, our research indicates that they are at particularly high risk of developing major depression, rather than BD, in early adulthood, and that BD youth are more likely than SMD youth to have a parent with BD. In addition, youth with SMD have less consistent response-flexibility deficits than do those with BD.

When engaging in a frustrating attentional task, both SMD and BD children report more frustration than do control subjects, and both have attentional deficits, as measured by evoked-response potentials. However, the specific deficits differ, with those of the BD youth centering on their inability to focus their attention when frustrated and those of the SMD youth centering on their failure to attend to a stimulus throughout the task.

These data all argue against SMD be-

ing a phenotype of BD. However, it is important to note that SMD youth, like those with BD (but unlike those with depression, anxiety, or ADHD) have difficulty labeling facial emotions, indicating that there may be some shared pathophysiological dysfunction between SMD and BD.

We are currently comparing amygdala-striatal-prefrontal activation in SMD, BD, and ADHD youth, as well as in control subjects, during an emotional face-processing task, a motor-inhibition task, and a motor-flexibility task.

The question of whether SMD youth are exhibiting a phenotype of BD is important, because the treatment for BD is very different from that for ADHD or the other psychiatric illnesses for which SMD youth meet diagnostic criteria (such as anxiety disorders). Thus, this line of research should ultimately help to clarify the classification, and thus treatment, of SMD. In addition, research into the pathophysiology of both BD and SMD should provide knowledge that will be relevant to the development of novel treatments for these very impairing illnesses in youth.

Clement J. McDonald received his M.D. from the University of Illinois in 1965. After his internal medicine residency at Boston City Hospital and Cook County Hospital in Chicago and a two-year fellowship at NIH, he joined the faculty at the Indiana University Medical School and the Regenstrief Institute in Indianapolis, where he developed large-scale medical-record systems. In November 2006, he became the

director of the Lister Hill National Center for Biomedical Communications at the National Library of Medicine. He is a member of the Institute of Medicine and a founding fellow of the American Institute for Medical and Biological Engineering.

As an intern at Boston City Hospital, I spent most of my day gathering, organizing, and analyzing patient data, cross-checking new data against the

old and what was expected, and adjusting treatments and testing accordingly. The days were consumed by hordes of little data-gathering and -checking tasks—work more like that of a bank clerk summing and double-checking deposits and receipts than that of Sherlock Holmes.

However, back then bank clerks had computer help. Physicians did not and, partly as a result, would sometimes fail to review tasks and therefore overlook an abnormality or a preventive opportunity.



Ellen Leibenluft



Christopher Warjck

Clement McDonald

RECENTLY TENURED

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Physicians need a computerized medical record to organize and watch their patients' records—something like a faithful sheepdog that calls attention when it “sees” danger lurking.

When I arrived at Marion County Hospital and the Regenstrief Institute in 1972, I set out to build one such medical record system, one that could accomplish three missions:

- Eliminate the logistic problems of the paper record: lost or unavailable, disorganized, or illegible

- Provide reminders to physicians about clinical situations that need action

- Provide query access across patients for research purposes

The project started with 32 patients in a diabetes clinic and then expanded to cover all patients. Early on, we developed a reminder system that could review the patients' records according to guidelines and remind physicians when it saw that patients needed specific tests, treatments, or immunizations.

In a series of randomized trials beginning in 1973, we showed that such computer reminders increased the appropriate use of such interventions among eligible patients by 15 to 2,000 percent compared with the control state.

The largest of these studies included more than 400 care providers, 1,000 reminder rules, 12,000 patients, and 50,000 visits. In late 1980, we developed one of the first physician order-entry systems and showed in a randomized trial that it significantly reduced costs compared with paper-based ordering.

Along the way, it became obvious that standards were needed for delivering patient data from the computers that produced them (such as pharmacy and laboratory systems) to other computers that needed them (such as medical-record systems). So we developed ASTM 1238, the first standard data structure for interchanging clinical observations between computers.

That structure was adopted by Health Level Seven, an accredited standards-developing organization that focuses on clinical and administrative data. ASTM 1238 is now used worldwide. We also developed a coding system for clinical variables, such as laboratory results and survey questions, called LOINC, which is also used internationally.

The medical record system has grown over the years and has expanded to include all of the Indianapolis hospital systems. It now includes a billion discrete results from 3 million patients and 15 different hospitals, as well as the Indiana

State Medicaid and Well Point, and Rx Hub.

It digests HL7 message streams from over 200 distinct computers that carry 180 million HL7 messages per year. It serves direct patient care, public health, and research functions. It also delivers diagnostic study reports and dictations produced by the 15 hospitals to Indianapolis' physicians—all 3,800 of them. It is now the longest continuously operating electronic medical record system in the world and the best example of a Regional Health Care Network in the United States.

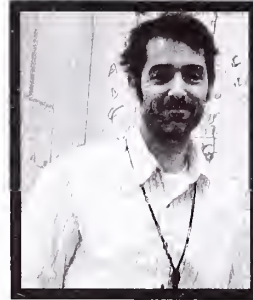
My goals at NIH are to develop similar informatics tools, systems, and processes, including data de-identification for preserving patient privacy, text understanding, statistical analysis, and linkage—tools to improve availability and research utility of the clinical data contained in electronic medical records and long-term clinical studies.

Andrew Singleton received his Ph.D. from the University of Newcastle upon Tyne, U.K., in 1998. His doctoral work focused on genetic causes and contributors to dementia, particularly Alzheimer's disease and dementia with Lewy bodies. He had postdoctoral training at the Mayo Clinic in Jacksonville, Fla., before joining NIA as an investigator within the newly created Laboratory of Neurogenetics in 2001. He is currently chief of the Molecular Genetics Unit in that lab.

My group focuses on the genetic basis of neurological diseases—particularly the role of genetic variability in Parkinson's disease, ataxia, dystonia, and stroke—in addition to working on genetic influences on phenotypes of aging.

Driving this research is the belief that this approach is the first step toward understanding the complex clinical and pathological manifestations of disease and aging and that ultimately genetic insights will highlight disease mechanisms and implicate pathways amenable to therapeutic intervention.

Undoubtedly our largest success over the past five years has been in the field of Parkinson's disease genetics. In 2003, we were the first group to identify α -synuclein locus multiplications as a cause of Parkinson's disease and Lewy body disorders; in 2004, we identified mutation of the gene *LRRK2* as a cause of Parkinson's disease; and in 2005, we showed that a particular mutation in *LRRK2*, G2019S, is the most common



Fran Pollner

Andrew Singleton

known genetic cause of this disorder, underlying Parkinson's disease in an estimated 20,000 North Americans.

Each of these findings was a paradigm shift for the Parkinson's disease field. The first highlighted the role that overexpression of normal wild-type protein can play in diseases of protein deposition.

The second finding has provided clues to the underlying biology of Parkinson's disease. The third has had an impact on the field's understanding of the clinical and pathological entity of Parkinson's disease.

My group continues to use familial forms of disease to find monogenic causes of neurological disorders, but most recently we have expanded on this family-based work in order to define the genetic basis of typical sporadic forms of neurological disease, including Parkinson's disease, amyotrophic lateral sclerosis, and stroke.

In performing this work, we have generated approximately one billion genotypes, about 400 million of which are already in the public domain. It is my belief that this work lays the foundation for future research into the genetic basis of these conditions.

Doris K. Wu received her Ph.D. from the University of California at Los Angeles in 1983. She did her postdoctoral training in the Department of Genetics at Harvard Medical School in Boston. She joined NIDCD as a staff scientist in 1993 and became a tenure-track investigator in 2000. She is currently the acting chief of the Section on Sensory Cell Regeneration and Development in the Laboratory of Molecular Biology, NIDCD.

The vertebrate inner ear is a highly intricate organ that is responsible for relaying auditory and vestibular information to the brain. Any malformations of this complex structure during development are likely to result in functional deficits. My research program focuses on:

- Identifying the molecular mechanisms underlying inner ear formation using both the mouse and chick as experimental models

- Understanding how mutations in specific genes cause human deafness

The proper formation of the inner ear depends on signals emanating from surrounding tissues. In our work to identify and characterize such signals, we demonstrated in both mouse and chicken that Sonic hedgehog (Shh), secreted from the

ventral neural tube and notochord, is required for the formation of the primary auditory apparatus, the cochlear duct.

The mammalian cochlear duct is a coiled structure that is tonotopically organized, such that the base of the cochlear duct is most sensitive to high-frequency sounds and the apical region to low-frequency sounds.

We showed that apical and basal regions of the cochlear duct depend on different levels of Shh signaling.

The apical, low-frequency region depends on high levels of Shh signaling, whereas the basal, high-frequency region requires lower levels of Shh.

We also discovered that various levels of Shh activate different amounts of Gli transcription activators and repressors that mediate Shh's functions. In addition, our results provide an explanation as to why mutations in one of the Gli transcription factors, Gli3, cause low-frequency hearing loss in Pallister-Hall syndrome patients.

Proper inner-ear morphogenesis is a dynamic process directed by cellular interactions and proper temporal activation of various molecular pathways within the developing otic epithelium, in response to extrinsic signaling factors from surrounding tissues. Two of the major molecular pathways that we have been studying involve bone morphogenetic proteins (BMP) and fibroblast growth factors (FGF).

The primary sensory cells of the auditory and vestibular systems, referred to as hair cells, are clustered within the various sensory regions of the inner ear. These sensory regions are embedded within complex, highly specialized labyrinths formed by nonsensory tissues. We provided insight into how the formations of sensory and nonsensory regions of the inner ear are coordinated during development.

We demonstrated that three vestibular sensory patches, the presumptive cristae, most likely regulate the formation of their associated nonsensory structures, the semicircular canals, through the actions of secreted molecules such as BMP4 and FGF10.

We are currently investigating whether similar molecular mechanisms are involved in the coordinated development of the sensory and nonsensory components of other auditory and vestibular sensory organs.

Keji Zhao received his Ph.D. in molecular biology from the University of Geneva in Switzerland in 1996. He did his postdoctoral training with Gerald Crabtree at Stanford University, Palo Alto, Calif., before joining NHLBI in 1999 as a tenure-track investigator. He is currently a principal investigator in the Laboratory of Molecular Immunology, NHLBI.

Eukaryotic DNA forms a complex chromatin structure by interacting with histones and nonhistone proteins in the cell. Our research has focused on understanding how the chromatin structure is regulated and how it regulates gene expression.

Chromatin structure can be modified (or remodeled) by two major mechanisms. One is the activity of ATP-utilizing

enzymes exemplified by the yeast SWI/SNF complex, which uses ATP-derived energy to alter the DNA-histone interactions and thereby allows regulatory enzymes to access their target sites in chromatin.

The other mechanism is the post-translational modification of histones—including acetylation, methylation, ubiquitination, and phosphorylation—which may affect gene expression by providing specific recognition platforms for various regulatory enzymes on the chromatin substrate.

The BAF complex is the mammalian homolog of the yeast SWI/SNF complex. The BAF complex remodels nucleosomal structure *in vitro*, but its function and mechanisms *in vivo* are not well understood. Our group was the first to identify several BAF target genes, including the cell-cycle inhibitor p21 and interferon-inducible genes, in human cells.

Mutations of the complex have been correlated with various cancers, suggesting it can act as a tumor suppressor. We demonstrated that through its regulation of p21 expression, the BAF complex regulates the activity of the tumor suppressor protein pRb. Furthermore, we found that rapid activation of cellular antiviral activities depends on BAF complex priming of the chromatin structure of interferon-inducible genes.

The nonclassical left-handed zigzag DNA structure (Z-DNA) was discovered three decades ago and, in the absence of known biological function, has been considered "junk" DNA. We recently dem-

onstrated that chromatin remodeling by the BAF complex induces Z-DNA formation at the CSF1 gene promoter.

Both the Z-DNA formation and BAF activity are required for the CSF1 gene activation, indicating that Z-DNA structure plays a role in modifying the chromatin structure.

The availability of genomic sequences of many model organisms has enabled us to monitor the chromatin modification events on a genome-wide scale.

Because the only available technique for high-throughput analysis of chromatin modifications—"ChIP (chromatin immunoprecipitation)-on-chip"—depends on the selected probes on the DNA microarrays, we developed an unbiased genome-wide mapping technique by combining ChIP and serial analysis of gene expression to cover the entire human genome.

Using this technique, we generated the first comprehensive map of major histone modifications in human T cells. Analysis of the histone-modification patterns re-

vealed 46,000 "histone acetylation islands," which represent functional regulatory elements of chromatin and transcription.

Interestingly, the methylation of H3 lysine 4 has been considered an "active" mark, while the methylation of H3 lysine 27 has been considered a "repressive" mark. Our genome-wide analysis, however, revealed that these two apparently opposite marks

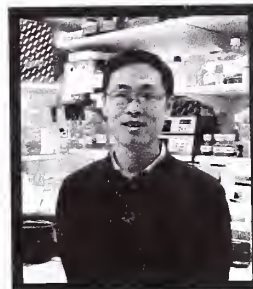
are co-localized at thousands of genomic loci, suggesting that they may together define the chromatin status.

We have also combined comparative genomics and histone acetylation data to identify functional enhancers of transcription. We found that histone acetylation patterns can predict both conserved and nonconserved enhancers, suggesting a novel method for annotating the functional regulatory elements in the human genome.

The chromatin modifications—including DNA methylation, histone modification, and ATP-dependent remodeling—may collectively define epigenomes that contain distinct epigenetic signals unique for each differentiated cell type and for maintaining the stability of cellular identity through cell divisions. Our current goal is to define the epigenomes using the genome-wide techniques and to understand how the epigenetic signals regulate genome function. ■



Doris Wu



Christopher Wanjek

Keji Zhao

CATALYTIC REACTIONS?

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

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

In Future Issues...

- Talking to the Press
- MRI Heart Imaging
- NIH Databases Used Worldwide

Kids' Catalyst: Volunteerism To Stimulate the Mind



In many of the buildings you see through the trees on the NIH Bethesda campus, experiments are taking place around the clock that aim to benefit humanity. Research protocols, found at

<http://clinicaltrials.gov>,

often need healthy volunteers for all different types of experiments. You could flex your ankle 100 times to study muscle movement, walk back and forth with sensors attached to you to study gait, or have neurotransmitters measured with an MRI.

But by far the most interesting study I've participated in was one run by Leonardo Cohen of NINDS, the National Institute of Neurological Diseases and Stroke. The aim of this study is to learn how to help stroke patients return to previous levels of functioning. Stroke victims may lose control of one side of their body, and it takes a lot of re-learning to regain this control. Imagine having to learn how to write, or type, or even wave all over again! The study seeks to make this learning process faster and better—we don't just want a motor-skills cram session that is forgotten in a week; we're looking at lifelong learning.

So for three months, a member of Cohen's team, Janine Reis, studied how I, and many others, learned.

An oversimplified version of the experiment (you can get the full protocol by going to the site mentioned above and typing NCT00314769 in the search box) is this: Stimulate the brain while performing a new a motor skill and see how quickly it is learned and how long it is remembered. What is the stimulation? It sounds like an old science fiction novel—transcranial direct current stimulation (tDCS) on a very specific part of the brain—but tDCS in the right place could do wonders.

It was like playing a video game—same motions, over and over. As with playing video games, I got better with practice. But how much better, and how quickly, and how long would I remember? Early findings suggest that those who receive stimulation learn faster, are more accurate, and keep the skill longer than those who do not. Maybe forever.

So if you decide to take the neurology path in your medical career, perhaps you'll be one of the brilliant and dedicated minds studying the mind in the Clinical Center. I'll be a happy test subject!

Or perhaps you, too, would get a kick out of being a healthy volunteer in a study like this one—just one example of the fascinating science that can be experienced firsthand at NIH, either as a volunteer or a researcher.

—Jennifer White

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

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