Fostering Communication and Collaboration

The NIH Catalyst

A Publication for NIH Intramural Scientists

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Smoke and Mirrors

Smoking and Parkinson's

By Eddy Ball, NIEHS

Smokers have very little to cheer about. Euphemistically one could say that they are spared the tyranny of growing old. Or, perhaps, they are blessed with a handy excuse to duck out of a tedious office conversation in order to puff away beside the stench of the Dumpster on the loading dock. But for every cancer, stroke, and emphysema threat you throw at them, smokers can always volley back one uncanny fact, albeit while coughing: Smoking reduces the risk of Parkinson's disease.

For the past 50 years, countless observational studies have shown that long-time smokers are only half as likely to develop Parkinson's disease (PD) as people who have never smoked. Recently, NIEHS epidemiologist Honglei Chen led a study that provided new insights into this seemingly incongruous association.

Typically, lifetime tobacco exposure is measured in pack years—a calculation of the number of cigarettes smoked per day multiplied by the number of years a person has smoked. But instead of looking at the combined measure of pack years, Chenclinis team examined the independent effects of duration and intensity (daily number of cigarettes).

Steve McCaw, NIEHS

NIEHS epidemiologist Honglei Chen, who led a study that shed new light on how long-term smokers are less likely than people who have never smoked to develop Parkinson's disease, says "nobody would advocate smoking to prevent [the] disease."

continued on page 14

Blood For Sale

In-House Blood Supply Is a Boon for NIH Researchers

By Susan Chacko, CIT

Tucked away down a long windowless corridor lies one of NIH's—if not the biomedical community's—best kept secrets: the NIH Blood Bank. As convenient as a corner store, the Blood Bank provides blood and plasma not only to Clinical Center patients but also to NIH researchers who have customized and sometimes challenging demands.

All: Michael Spencer, NIH

DTM's Cynthia Matthews is checking on Henry Anderson, Jr., who is donating white blood cells, through an apheresis machine, for NIH researchers.

The Blood Bank has an impressive track record of delivering the goods. If it hadn't been for the NIH Blood Bank, NIH researchers might not have been able to study the interaction between macrophages and lymphocytes, identify platelet-derived growth factors, or discover the first human RNA tumor virus. The Blood Bank's role? It provided the scientists with white blood cells for their pioneering work, which paved the way for other accomplishments such as the elimination of AIDS and hepatitis from the nation's blood supply.

Today, the NIH Blood Bank provides white blood cells as well as other blood components to hundreds of researchers across NIH. Some components are derived as byproducts of whole blood that is donated for transfusion into Clinical Center patients; others, including units of whole blood, come from people who donate their blood specifically for research.

Scientists have been doing research using blood for centuries. In 1670, Dutch scientist Anton van Leeuwenhoek invented the microscope and discovered blood cells as well as other microscopic structures and organisms. Blood transfusions were done

continued on page 10

CONTENTS

1 Smoking and Parkinson's
Blood for Research
2 From the DDIR
3 Primary Immune Deficiency Clinic
4 Training Page
5 Developing Brains Abbreviations
6 Scopolamine and Depression
7 Research Briefs SIG Beat
8 Recently Tenured
14 NIH History: As Told By Stetten Fellows
15 Announcements
16 Confessions

From the Deputy Director for Intramural Research

Summer Stock

MIchael Gottesman

Almost no one becomes a laboratory scientist without having had some kind of formative experience, perhaps as a student or as an intern in a laboratory.

My own first experience was after my senior year in high school. I wanted to graduate from my chemistry set and amateur rocketry projects and find out what a real lab was like. Fortunately, my high school chemistry teacher had a Ph.D. (in those days, a secure teaching position was a desirable career for a scientist) and spent his own summers working in a neurochemistry lab at the Albert Einstein College of Medicine (New York).

One summer I worked with him and did pH titrations on lipid micelles of various compositions to determine how many phosphate groups were exposed to the aqueous medium. I learned to keep a notebook, make serial dilutions, and design experiments to address specific hypotheses. By the time the summer ended, I was hooked.

Many investigators have had similar student experiences—in research laboratories or clinics—at universities, medical schools, health-care institutions, and even NIH.

Every summer, the NIH intramural program provides about 1,000 students—selected from more than 5,000 applicants—with this critical opportunity to get firsthand experience in what research is like.

Responsibility

Whether we are principal investigators, staff scientists, or postdocs, we have a responsibility to future scientists to provide them with a positive experience and to exemplify what it means to be a first-rate scientist at the federal government's premier biomedical research institution.

It's important that we serve as excellent role models for and mentors to the students who spend their time at NIH this summer. Everything that they see and hear becomes the basis for their view of science and scientists. We may say "Do as I say, not as I do," but our own behavior becomes the lesson that our students learn best.

What the students see of the generation and presentation of data and ideas should be first-rate and meet the highest standards of honesty and integrity. A student who learns that his or her credibility as a scientist is an invaluable asset is less likely to be careless in collecting and presenting data than one who observes that the volume of output trumps quality. We have a unique opportunity to make a lasting impression on our summer trainees.

Role Models

We also need to be role models when it comes to how we treat other scientists and trainees. Students must learn to listen, treat others' ideas with respect, and care about the welfare of other scientists and students and the animals in the lab.

Students also have to learn to think critically and to be skeptical about ideas that are not well supported by data. The fine line between skepticism and cynicism should remain uncrossed, however. (I don't mean to exclude humor from the laboratory, but it should not mock or belittle others.)

On a practical level, we try every summer to convince our students that their laboratory safety is of paramount concern to the NIH. We tell them to wear eye protection, lab coats, long pants, and footwear that covers their toes and feet. Most students are eager to adapt the practices and styles of their mentors and advisors and would readily follow directions that prevent injuries from caustic or other dangerous materials.

Let's be sure that what students see in the lab is what we want them to emulate.

Opportunities

NIH has tried to institutionalize some of these lessons for summer students by providing the *NIH Summer Handbook* (http://www.training.nih.gov/student/common/summer-handbook.pdf), a lecture series, coursework, and an opportunity to present work in a poster session.

Elsewhere in this issue of *The NIH Catalyst* is an article about the opportunities the Office of Intramural Training and Education makes available to our summer students (see page 4). Most NIH institutes and centers also sponsor wonderful activities that will enrich the students' time on our campuses.

I hope you will help your interns select useful seminars, workshops, and journal clubs. Please work with them to schedule their research responsibilities to allow their participation in these important training opportunities.

I'd be interested in hearing about experiences that have made a difference in your careers. And please share your thoughts on other ways that we can improve the summer experience for students who come to the NIH. You can send your comments to me at catalyst@nih.gov. ■

—Michael Gottesman, DDIR

The Taming of the Immune System: NIAID's Specialty Clinic

By Julie Wu, NIAID

An immune system gone awry can yield clues as to how a healthy immune system works. By trying to tame immunodeficiency diseases, clinicians in NIAID's Primary Immune Deficiency (PID) Clinic are helping patients and researchers alike. In fact, the clinic recently helped NIAID scientists identify a genetic mutation that may account for certain immune system disorders.

The clinic's patients have primary immune deficiency diseases (PIDDs), which are caused by inherited flaws in the immune system that increase susceptibility to infections. PIDDs can trigger recurrent and difficult-to-treat bacterial and viral infections, persistent respiratory infections, severe allergies, and sometimes cancer. Some patients require hospitalization for infections that, in people with intact immune systems, could be conquered with antibiotics and a few days of bed rest. Approximately 500,000 people in the United States have been diagnosed with one or more of the 150 known PIDDs. But many remain undiagnosed.

"Our goal is to offer a comprehensive diagnostic and therapeutic consultation service to people affected by PIDDs [and to] their physicians," said PID Clinic co-director Gulbu Uzel. The clinic is also an ideal meeting place for people with immune system disorders and researchers looking to uncover how the healthy immune system operates, noted NIAID's scientific director Kathryn Zoon and deputy scientific director Karyl Barron.

Mutation in DOCK8 Gene

In a study published last year in the *New England Journal of Medicine*, NIAID clinical investigator Helen Su, Uzel, and others identified a mutation in the *DOCK8* gene that may account for a combination of severe health problems, including acute allergies and asthma (*N Engl J Med* **361**:2046–2055, 2009).

The study involved 11 PID Clinic patients who had an undefined form of combined immunodeficiency disease and were plagued by persistent bacterial and viral skin infections, severe eczema, acute allergies and asthma, and cancer. The scientists used comparative genomic hybridization—a process by which patient DNA is analyzed on computer chips fixed with large numbers of DNA probes—to look for gene changes in tissue samples from five different groups: the 11 patients; six patients with autosomal dominant hyperimmunoglobulin E syndrome, a disorder characterized by increased levels of immunoglobulin E antibodies, bacterial and fungal infections, and eczema; 32 patients with other immunologic diseases; 15 healthy blood donors of various ethnic backgrounds; and 100 healthy white control subjects.

Patients with PIDD are more susceptible to difficult-to-treat infections. (Top) The patient has molluscum contagiosum, a viral infection of the skin. (Bottom) This patient has both the molluscum contagiosum virus and eczema (atopic dermatitis). Images by: NIH Medical Photography.

Compared with healthy individuals, the people with *DOCK8* mutations had fewer CD8-positive T cells, which are needed to fight viral infections; fewer antibody-producing B cells; and increased numbers of eosinophils, immune cells associated with allergy.

More Accurate Diagnosis

The research yielded not only a more accurate disease diagnosis for these patients and identified a new form of PIDD—DOCK8 immunodeficiency syndrome—but also provided new insights into the normal function of *DOCK8* in healthy people. *DOCK8* is essential for defense against viral infections and for preventing the development of cancer and allergies, according to Su. Further work is required, however, to determine whether *DOCK8* mutations occur in other people with similar disease symptoms.

Meanwhile, the PID Clinic, a national referral center that has treated some 140 patients since its opening in 2007, is continuing to diagnose and treat patients with known or suspected PIDDs. The clinic is run by Uzel and Sergio Rosenzweig, includes NIAID clinician-investigators Steven Holland and Harry Malech, and is staffed by fellows from the allergy and immunology training program and a dedicated nursing staff. It draws on clinical expertise from across NIH in allergy and immunology, infectious diseases, genetics, rheumatology, dermatology, gastroenterology, pulmonology, cardiology, otolaryngology, microbiology, nursing, and psychiatry.

Clinic Has Grown

"The clinic has grown from treating one or two patients per week to an average of five patients," said Rosenzweig. "Each patient arrives with hundreds of pages of medical history that needs to be carefully classified and reviewed, so we are grateful to have Ashleigh Hussey, our registered nurse [who's] responsible for having everything organized and accessible to the clinic consultants." The clinic will soon be hiring a nurse practitioner, too.

Uzel and Rosenzweig hope that as the PID Clinic becomes better known it will engage more NIH clinicians, either through consultations in the clinic or by regular reviews of difficult cases. The clinic is also working with NIH's Center for Human Immunology, Autoimmunity, and Inflammation to improve the efficiency of diagnoses that are based on the complete phenotyping of the human immune system. For more information about the clinic, visit http://www3.niaid.nih.gov/topics/immuneDeficiency/pidClinic. ■

Julie Marquardt, NIAID

The Primary Immune Deficiency Clinic's medical team treats patients with primary immune deficiency diseases. Left to right: Harry Malech, Sergio Rosenzweig (director), Gulbu Uzel (director), and Steven Holland.

The Training Page

From the Office of Training and Education: NIH Summer Intern Invasion

By Lori Conlan, OITE, and Betsey Wagener, OITE

Summers in the Metro D.C. area are synonymous with summer interns learning more about careers. NIH is a hotspot of summer intern activity, with more than 1,000 trainees—high school, college, graduate, and professional school students—joining the Intramural Research Program.

From mid-May through August, these budding scientists will be on campus, absorbing new scientific information and exploring career opportunities. This year we even have a new program for community college students. All these "recruits" share a common goal: to explore life in the lab to see whether a career in science is right for them.

NIH aims to support and nurture these trainees while they are on our campuses. Everyone contributes: from the principal investigators who agree to host students, to the postdocs and graduate students who mentor their daily activities, to the administrative staff who ensure the trainees get paid, to the Office of Research Services instructors who educate our new labmates on safety issues. Training offices at many institutes and centers also provide support for summer interns.

Our NIH Office of Intramural Training and Education (OITE) offers orientation sessions to ensure that the summer interns understand what to expect in the lab and how to get the most out of their summer. We also offer weekly workshops on how to succeed in science, including how to read journal articles, score high on the Graduate Record Exams and Medical College Admissions Tests, and explore career options in the biomedical sciences. Finally, we encourage summer interns to meet with our career counselors to gain insight into the graduate and medical school application process as well as to obtain information on scientific careers.

One of the summer's highlights is the Graduate and Professional School Fair (Thursday, July 8, 2010), at which interns can meet representatives from more than 100 graduate and professional schools. And on Thursday, August 5, 2010, be sure to stop by the Summer Poster Day at the Natcher Conference Center to see all the excellent research NIH interns have completed during the summer. And take note—you will likely see many of these faces on the NIH campus again as postbacs, graduate students, postdoctoral fellows, and clinical fellows.

If you are reading this as a summer intern, welcome from all of us at the NIH. Be sure to take advantage of all the opportunities available to you. For more information, refer to the *2010 NIH Summer Handbook* (http://www.training.nih.gov/student/common/summer-handbook.pdf). ■

For more on the summer intern program, see Michael Gottesman's column on page 2.

From the Fellows Committee: What Do You Want to Be When You Grow Up?

By Sonia Bhangoo, NIDCR

Some of you may be pondering a big question: What do I do with my Ph.D.? Whether you are choosing the traditional road to academia or considering leaving the bench, the annual Career Symposium will give you the tools and information necessary to move forward in your career.

The third annual NIH Career Symposium was held Tuesday, May 18, 2010, from 8:00 a.m. to 4:30 p.m. in the Natcher Conference Center (Building 45) on the NIH Bethesda campus.

The symposium provided NIH postdocs and other trainees with information about different career options as well as an opportunity to network with established professionals.

This year, the symposium featured keynote speaker Kathie Olsen, who was recently appointed Vice President of International Programs at the Association of Public and Land-grant Universities. She spent 24 years in the federal government and held senior leadership positions at the National Science Foundation (NSF), the National Aeronautics and Space Administration (NASA), and the Office of Science and Technology Policy in the Executive Office of the President. She is a former science advisor, deputy director, and chief operating officer at NSF and was a chief scientist at NASA.

After the keynote address, trainees had the opportunity to participate in informative panel sessions that highlighted a variety of career options in fields such as industry, academia, science policy, and government.

In addition, a series of 10-minute Skills Blitz sessions covered such topics as résumé and CV writing, interviewing and networking, and more. The sessions helped people build skills they need to achieve success in their careers.

The day culminated in a networking event, which was held at the Black Finn Restaurant at 4901 Fairmont Avenue in Bethesda. This was an excellent time to practice newly acquired networking skills as trainees interacted with each other and symposium speakers.

The symposium is not the only way for you to find career advice. You can also visit OITE's Career Services Staff and Career Library—which are located in Building 2 on the main NIH Bethesda campus—any time. If you want to be sure you can speak to someone, it's best to schedule an appointment. E-mail OITE-Careers@od.nih.gov.

If you are working at one of NIH's other campuses, OITE staff can help you, too. Career counselors regularly visit the Baltimore campus, NCI Frederick, and NIEHS in North Carolina. Telephone consultations are available to trainees at Rocky Mountain Laboratories, Phoenix, and Detroit.

The counselors can provide guidance on career directions, options, and self-evaluation, as well as assistance with interviewing, networking, and CV and résumé development. For more information, visit the OITE Web site at http://www.training.nih.gov. Hope you made it to the 2010 Career Symposium. For more details, visit http://tinyurl.com/OITE-2010-05-18. Hope you can join us next year. ■

The Brains of Young Lives

Judith Rapoport Delivers Anita Roberts Lecture

By Gail Seabold, NIDCD

The time-lapse video showed a 3-D image of a brain maturing—with gray matter thickening and thinning as neurons appeared and disappeared—over a 20-year time span. The morphing image was a composite of magnetic-resonance imaging (MRI) brain scans, taken every two years, of children aged five to 20 years old. Judith Rapoport, Chief of NIMH's Child Psychiatry Branch, and her research team have been using tools such as MRI scans to study normal and abnormal brain development in children and adolescents.

As the brain matures, the front and back develop first, the parietal lobes next, and the prefrontal cortex, which handles more advanced functions like reasoning, last. During the brain's development, neuroadaptations—such as dendritic and axonal arborization, synaptic pruning, and myelination of white matter—continue throughout childhood, Rapoport explained in a presentation entitled "Brain Development in Healthy, Hyperactive, and Psychotic Children," which she gave on March 25, 2010, as this year's annual Anita B. Roberts Lecture.

Judith Rapoport (NIMH) explained that composite MRI scans show how the brain matures throughout childhood. Irregularities in brain development are associated with neuropsychological problems such as ADHD.

Irregularities in early brain development are associated with neuropsychological problems, such as attention-deficit hyperactivity disorder (ADHD), child-onset schizophrenia (COS), and obsessive-compulsive disorder. In studies examining the relationship between brain development and intelligence, Rapoport and NIMH colleagues Philip Shaw, Nitin Gogtay, and Jay Giedd measured the volume of the cerebral cortex—or gray matter—over time. They discovered that the cortex thickens during childhood and then goes through a thinning process during adolescence. The trajectory, or growth pattern, of volume changes in the cortex correlated with standard measures of IQ. And, by studying twins, the researchers are investigating the relative roles that genetics, age, sex, and environmental factors play in brain development.

Brain imaging studies yield not only clues about the normal brain maturation process but also about pediatric mental disorders—often years before symptoms appear. In children with ADHD, the developmental trajectory of the brain is normal, but there is a three- to five-year delay in maturation of some areas of the cortex. In other neurodevelopmental disorders, however, the trajectory of brain development differs greatly from that of normal children.

Rapoport discussed COS, a rare disorder that affects one out of 40,000 children and begins before the age of 13. Ordinarily, schizophrenia starts in adolescence and is rare in younger children. COS is not associated with pre- or perinatal complications, genetics, or social-environmental factors, Rapoport explained. Imaging studies have shown that during the teenage years, patients with COS had a striking loss of brain cortical gray matter in their frontal lobes.

Rapoport extolled the advantages of being in the intramural program at the NIH, where researchers can conduct longer-term studies—such as the extensive mapping of pediatric and adolescent brain changes over long periods of time—than might be possible in a grant-supported setting. ■

The Roberts Legacy: Anita B. Roberts spent 30 years at NCI before her death from gastric cancer in May 2006. She was chief of the Laboratory of Cell Regulation and Carcinogenesis and became well known for her groundbreaking work on transforming growth factor–beta and its role in the growth of epithelial and lymphoid cells. In 2003, Thomas Scientific's Science Watch *listed her among the 50 most-cited scientists from 1982 to 2002, in a feature called "Twenty Years of Citation Superstars." The "Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH" honors the contributions Roberts and other successful female scientists have made to the NIH research community.*

NIH ABBREVIATIONS

CC: NIH Clinical Center

CIT: Center for Information Technology

FAES: Foundation for Advanced Education in the Sciences

FelCom: Fellows Committee

IRP: Intramural Research Program

HHS: U.S. Department of Health and Human Services

NCCAM: National Center for Complementary and Alternative Medicine

NCI: National Cancer Institute

NCMHD: National Center on Minority Health and Health Disparities

NEI: National Eye Institute

NHGRI: National Human Genome Research Institute

NHLBI: National Heart, Lung, and Blood Institute

NIA: National Institute on Aging

NIAAA: National Institute on Alcohol Abuse and Alcoholism

NIAID: National Institute of Allergy and Infectious Diseases

NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIBIB: National Institute of Biomedical Imaging and Bioengineering

NICHD: National Institute of Child Health and Human Development

NIDA: National Institute on Drug Abuse

NIDCD: National Institute on Deafness and Other Communication Disorders

NIDCR: National Institute of Dental and Craniofacial Research

NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases

NIEHS: National Institute of Environmental Health Sciences

NIGMS: National Institute of General Medical Sciences

NIMH: National Institute of Mental Health

NINDS: National Institute of Neurological Disorders and Stroke

NINR: National Institute of Nursing Research

NLM: National Library of Medicine

OD: Office of the Director

OITE: Office of Intramural Training and Education

OIR: Office of Intramural Research

New Future for an Old Drug

By Erika Ginsburg, NCI

The motion sickness medication scopolamine may one day be used to treat severe depression, too.

NIMH scientists Maura Furey and Wayne Drevets found that scopolamine reduced the symptoms of depression within three days. With conventional antidepressants, it can take three to four weeks for treatment to become effective. (*Biol Psychiatry* **67:**432–438, 2010)

Some 15 million adults in the United States suffer from major depressive disorders, which are the leading cause of disability for people ages 15 to 44. Treatments include psychotherapy, antidepressant medication, and a combination of the two. Newer medications like selective serotonin reuptake inhibitors (SSRIs)—which include fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro)—may take three to four weeks to become effective and don't always work in patients with severe depression.

Other drugs may be as effective but have unpleasant side effects. And although ketamine was the first FDA-approved drug found to rapidly improve mood, it's unlikely to become a conventional treatment because it's been widely abused for its hallucinogenic properties.

Promise

So now scopolamine shows promise. Like other tricyclic antidepressant medications, it temporarily blocks muscarinic cholinergic receptors (found in neurons), which are thought to be overactive in people suffering from depression and other mood disorders. Tricyclic antidepressants have been avoided because of unwanted side effects—such as constipation, sedation, and confusion and memory problems—and aren't typically prescribed unless SSRIs have been tried first and are ineffective. But SSRIs are not as effective in providing timely relief.

The NIMH scientists were surprised that scopolamine could relieve symptoms of depression and that it could do so quickly. "We were conducting a study for attention and memory, using three intravenous doses of scopolamine, while imaging the brain," Furey said. "The broad effect we first observed on depression was unexpected."

Furey and Drevets set up additional studies to explore this anecdotal effect of scopolamine. Twenty-two subjects, ranging in age from 18 to 45 years with a near-equal number of males and females, were assigned in a double-blinded trial to a placebo or scopolamine treatment group. For one month, during each of seven sessions scheduled three to five days apart, the subjects received a 15-minute intravenous dose of either saline or the drug. The antidepressant response was measured before and after treatment and was based on a rating scale assessing components such as happiness, sadness, drowsiness, irritability, alertness, anxiety, and restlessness. Even though this study's sample size was small and did not include smokers or elderly or pediatric subjects, nor did it specifically examine gender effects on scopolamine's antidepressant activity, the data were significant. The researchers think that the effects of scopolamine may have been missed in earlier studies because lower doses were used.

NIMH scientists were surprised that scopolamine could relieve symptoms of depression . . . quickly.

"The antidepressant effects lasted for several months for at least half of the participants," said Furey. For those patients with the most severe symptoms, this is good news.

So good that NIMH has filed a use-patent for this novel use of scopolamine in the treatment of depression. Drevets and Furey are identified as co-inventors on the pending patent application.

The future is bright, said Furey. As the study's results await confirmation by independent laboratories, she continues to recruit for the current clinical trial and adds, "Several pharmaceutical companies are interested in scopolamine's fast-acting remedy," especially in emergency situations.

However, a user-friendly route of administration is still out of reach. ■

Update "I Am Intramural"

The NIH campus is abuzz with the "I Am Intramural" campaign. You may have noticed the giant "I Am Intramural" banners on display throughout the campus. And you may have shared your stories about your work at one of the events celebrating NIH intramural research.

Here are a few comments taken from a recent retreat for fellows and young investigators in NCI's Center for Cancer Research:

"One can have all the things like personal, professional, and social development under one roof."

"Excellent collaboration and opportunities for career development that [are] unsurpassed elsewhere."

"As a visiting fellow, [I find] working here is a great opportunity to meet people with the same interest and to also do good science!"

See what else is being said about the Intramural Program at http://iamintramural.nih.gov/stories.html.

You may have noticed the "I Am Intramural" banners displayed on various light poles around campus. Use these banners as a reminder to visit our Web site http://iamintramural.nih.gov to share your thoughts and read what others have been saying. Let us know why you are passionate about working for the Intramural Program.

Follow us on Twitter: i_am_intramural, where you will receive daily tweets that include your co-workers' comments, information on various NIH Intramural events' and NIH press releases. Visit http://twitter.com/i_am_intramural.

—Natalie Giannosa, NCI

Natalie Giannosa, NCI

NHGRI intramural researchers showing off their "I Am Intramural" mugs. Left to right: Peggy Kwong, Richelle Legaspi, and Mal Stantripop.

Research Briefs

NCI: Health-Care Utilization Rates and Colorectal Cancer Disparities

Higher rates of colorectal cancer incidence and mortality experienced by African-Americans may be driven largely by differences in health-care utilization and less by biology, according to a new study led by NCI researchers. In more than 60,000 people screened for colorectal cancer, researchers found that blacks and whites were equally likely to need a follow-up colonoscopy after a screening sigmoidoscopy, but blacks were less likely to actually receive the follow-up. There was no statistically significant difference in the risk of colorectal cancer by race. [*J Natl Cancer Inst* **102**:538–546, 2010]

NICHD, NIDCR: Stem Cells Near Cartilage-Rich Regions in Bones

A new research finding may be the first step in using bone stem cells to repair damaged bone. NICHD and NIDCR scientists—and colleagues from elsewhere—were the first to pinpoint the location (in mice) of bone-generating stem cells, or bone stromal cells, in the spine, at the ends of shins, and in other bones. The researchers inactivated one copy each of two genes, *Prkar1a* and *prkaca*. *Prkar1a* has been implicated in a variety of rare human cancers, including cancers of the bone, nervous system, and thyroid. When the two genes are working correctly, bone cell growth proceeds normally and cancerous overgrowth is kept in check. The researchers predicted that disabling only one copy of each gene would offer protection from bone tumor growth. But they were wrong. Further studies to identify the chemical signals that trigger bone or tumor formation may lead to new techniques for regenerating damaged bone as well as preventing or treating bone tumors. [*Proc Natl Acad Sci U S A*, http://www.pnas.org/cgi/doi:10.1073/pnas.1003680107]

NIAAA: Scientists Find Genes That Influence Brain-Wave Patterns

NIAAA scientists have identified new genes and pathways that influence an individual's typical pattern of brain electrical activity, a trait that may serve as a surrogate marker for more genetically complex traits and diseases. Using genome-wide association study techniques, the researchers identified multiple genes that were associated with the amplitude of two of the four electrical frequencies that make up the wave patterns in electroencephalographic recordings. One finding was that genetic variation in one of the genes for theta-wave variability was also associated with an altered risk for alcoholism. [*Proc Natl Acad Sci U S A,* http://www.pnas.org/cgi/doi/10.1073/pnas.0908134107]

NIAMS, NCI: Key HIV Macromolecule Structure Solved

Researchers at NIAMS, NCI, and Oxford University (Oxford, England) have identified the three-dimensional structure of the protein Rev (regulator of virus), an essential regulatory macromolecule of the human immunodeficiency virus. Protein structures are usually determined by X-ray crystallography; until now, however, Rev's propensity to form irregular aggregates has prevented crystallization. The researchers generated a customized monoclonal antibody that binds to Rev to form a complex that yields well-ordered crystals. Key surfaces that have been identified may potentially be targeted in the design of antiviral inhibitors. [*Proc Natl Acad Sci U S A* **107**:5810–5814, 2010]

NIDA: Nogo Receptor–1 Regulates Formation of Lasting Memories

Formation of lasting memories is believed to rely on structural alterations at the synaptic level. NIDA scientists and collaborators in Sweden found that increased neuronal activity downregulates Nogo receptor–1 (NgR1) in brain regions linked to memory formation and storage. They showed that mice with inducible overexpression of NgR1 in forebrain neurons have severely impaired month-long memory in both passive avoidance and swim maze tests. Understanding the molecular underpinnings of synaptic rearrangements that carry lasting memories may facilitate development of treatments for memory dysfunction. [*Proc Natl Acad Sci U S A* **106:**20476–20481, 2009] ■

The SIG Beat:
News from NIH Scientific Interest Groups

New SIG: Infectious Diseases Interest Group

The Infectious Diseases Interest Group (IDIG) is fascinated by all aspects of host-pathogen interactions that occur during bacterial, parasitic, viral, or fungal infection. Major focus areas are the analysis of virulence factors and their host targets as well as the investigation of protective strategies employed by the host. The main goal of the IDIG is to facilitate interaction among NIH researchers and to foster collaborations within the NIH infectious diseases community. IDIG provides a forum for students and postdoctoral fellows to present their own work and to meet intra- and extramural scientists. Typically there will be two intramural seminar speakers in each session, preferentially postdoctoral fellows or students. Occasionally, we will have presentations from invited speakers outside the NIH or from intramural investigators. For more information or to join the IDIG email list please contact moderator Matthias Machner (machnerm@mail.nih.gov).

Biomedical Computing Interest Group Book Club

The BCIG Book Club meets on the fourth Thursday of the month, from 5:30 to 7:30 p.m., in the (old) Medical Board Room in Building 10, Room 2C116. All are welcome. For more information, visit http://www.altum.com/bcig/. The 2010 books (and when they will be discussed) are:

May 27: *Precancer: The Beginning and the End of Cancer* (by Jules Berman and Bill Moore)

September 23: *Fooled by Randomness: The Hidden Role of Chance in the Markets and in Life* (by Nassim Nicholas Taleb)

October 28: *You've Got To Be Kidding: How Jokes Can Help You Think* (by John Capps and Donald Capps)

For more information on NIH Scientific Interest Groups, visit http://www.nih.gov/sigs. To find out how to create a new SIG, contact OIR Communications Director Christopher Wanjek (wanjekc@od.nih.gov).

Colleagues

Recently Tenured

Electron Kebebew, NCI

Electron Kebebew, NCI

When an Ethiopian electrical engineer named his children Electron, Positron, Neutron, Deutron, and Proton, he had high hopes that they would pursue engineering careers, too. His youngest son, Electron Kebebew, was indeed headed down the engineering path and even earned a B.S. in chemical engineering from the University of California, Los Angeles. But he was already being pulled in a different direction—toward medicine. He enrolled in medical school at the University of California, San Francisco, earned an M.D. in 1995, stayed on to do a residency—including time as chief resident—in general surgery, and then did a surgical oncology basic-science fellowship, and, as soon as he finished his training in 2002, joined the faculty. He became a research scientist as well as an internationally recognized endocrine surgeon and performed more than a thousand operations on the thyroid, parathyroid, and adrenal glands. In 2009, he was recruited to NCI as a senior investigator to head the Endocrine Oncology Section in the Surgery Branch.

The Endocrine Oncology Section's mission is to provide outstanding clinical care for patients who have endocrine cancers and to conduct research to develop innovative ways to diagnose and treat them. Endocrine malignancies (including thyroid, adrenal, pancreas, parathyroid, and neuroendocrine cancers) are among the fastest growing cancer diagnoses in the United States, but it is difficult to distinguish benign from malignant tumors by routine clinical, laboratory, and imaging studies. So even patients who have seemingly benign endocrine tumors often choose to undergo surgery to get a definitive diagnosis in the hopes of ruling out cancer. Once endocrine cancer has metastasized, there is limited effective treatment.

In our research, we use genomic techniques to investigate endocrine cancers and translate our findings into innovative diagnostic approaches and treatment. Specifically, we use a pan-genomic (mRNA and microRNA expression and global methylation profiling) approach in human tumor tissue samples to identify candidate diagnostic markers. We then determine the accuracy and utility of these markers in clinical biopsy specimens. We also test the dysregulated genes as targets for therapy. We characterize their role in regulating tumor-cell biology by using in vitro models of 12 human endocrine cancer cell lines and mouse models. In addition, we use the pan-genomic data to determine the mechanism of gene dysregulation in endocrine cancers.

NIH investigators have made many seminal contributions to the surgical management of endocrine tumors over the past 30 years. They have described many of the clinical characteristics and susceptibility genes for familial cancer syndromes. As we accelerate the search for early cancer diagnosis, we aim to develop more effective cancer therapies, including personalized ones. ■

Paul A. Wade, NIEHS

Senior investigator Paul Wade leads the Eukaryotic Transcriptional Regulation Group in NIEHS's Laboratory of Molecular Carcinogenesis. A native of Texas City, Texas, he earned a B.S. in dentistry from Case Western Reserve University (Cleveland) and a Ph.D. in molecular biology from Indiana University (Bloomington). He did postdoctoral training at the University of Colorado Health Sciences Center (Denver) and at NICHD in the laboratory of the late Alan Wolffe. From 2000 to 2004, Wade was an assistant professor in the Department of Pathology at Emory University School of Medicine (Atlanta). And in 2004 he and his wife, a physician, moved to North Carolina. She took a training position at the University of North Carolina (Chapel Hill) and he became a tenure-track investigator at NIEHS in Research Triangle Park. He is also an adjunct associate professor in the Department of Pathology and Laboratory Medicine at the University of North Carolina. Wade has published several book chapters and more than 50 peer-reviewed articles in leading biomedical journals.

I have a long-term interest in understanding how eukaryotic cells turn genes on and off—particularly instances in which cells change the portions of their genome that are transcribed to respond to developmental, nutritional, hormonal, or pathologic signals. Since I was a postdoc at NICHD, a major component of my work has been aimed at understanding how local DNA packaging affects this process. Cells manipulate gene expression, in part, by altering the subunit composition of key enzymes that directly regulate chromosomal structure and function.

Recently, we began using the mammalian immune system as a model to understand how the modification of chromosomal proteins and chromosomal DNA play roles in the gene regulatory process. This work has been challenging and rewarding and has forced us to acquire new skills to interpret the large datasets that have been generated in our experiments. In the long term, we hope to contribute to the

Steve McCaw,NIEHS

Paul Wade, NIEHS

understanding of an important process in human health and disease—how chromosomes respond to the changing demands of development, differentiation, and activation of immune cells.

NIH offers an extraordinary environment for research. The level of resources and financial stability here permit us the luxury of doing high-risk and high-reward science. But the most special thing about the NIH is its the people. My colleagues make it fun to come to work every day. ■

Maggie Bartlett, NHGRI

Shawn Burgess, NHGRI

Shawn Burgess, NHGRI

Before coming to NHGRI in 2001, Shawn Burgess was part of a group at the Massachusetts Institute of Technology (Cambridge, Mass.) that pioneered the use of pseudotyped retroviruses for mutagenesis in zebrafish. This technology provided a major breakthrough in the ability to identify genes that are important in the early development of vertebrates. Compared with chemical mutagens, the use of retroviruses reduces the time required for gene identification from years to weeks. The ability to expose zebrafish to these retroviruses and then quickly identify relevant mutations allows geneticists to perform large-scale mutagenesis and rapid phenotypic screening in a vertebrate system. Burgess got a B.A. in Biology from Wesleyan University (Middletown, Conn.), and a Ph.D. from Johns Hopkins University School of Medicine (Baltimore). He is a senior investigator in NHGRI's Genome Technology Branch and heads the Developmental Genomics Section.

My laboratory studies developmental processes and their relationship to human genetic disease. We use modern molecular biology methods to identify and functionally characterize novel developmental genes involved in organogenesis of the ear and maintenance of stem-cell populations.

Hearing loss is one of the most common medical conditions affecting humans, particularly older adults. Twenty-eight million Americans, including one in three over the age of 60 and half over the age of 85, have some level of hearing loss. Unlike other vertebrates, mammals are unable to significantly regenerate the sensory neurons (hair cells) required for hearing and balance after losses caused by cell damage or cell death. We study hair cell regeneration in the zebrafish (*Danio rerio*), which has a remarkable capacity for regeneration. After injury, zebrafish tissues as diverse as the retina, heart, fin, spinal cord, and inner ear can recover completely. We use a combination of genetic and genomic approaches to elucidate the gene network that is activated in the zebrafish inner ear stem cell population—known as "supporting cells"—during regeneration.

Two major projects are central to this research. One involves the transcriptional profiling of the zebrafish inner ear after intense exposure to sound. Extended, high-energy sound can damage and kill the hair cells of the inner ear. In this project, zebrafish hair cells are killed by 48 hours of exposure to sound and then allowed to fully regenerate over the course of a week. We have collected tissue from zebrafish inner ears at several intervals after the exposure and then determined which genes exhibit significant increases or decreases in expression.

Several phases of the regeneration process have been identified, and more than 1,800 genes have been implicated in regeneration. With these data as a foundation, we use a combination of genetic, embryological, and computational approaches to better define the critical genes involved in the regeneration process.

A second, related project involves classical genetic screening for genes involved in ear function and hearing regeneration. For this, we use retroviruses as mutagens and high-throughput analyses to map the precise position of retroviral integrations. Akin to P-element mutations in Drosophila, this approach is creating a large zebrafish mutation pool that can be screened for phenotypes relevant to hearing function and inner ear regeneration. Once such mutations are identified, their roles in development, function, and tissue repair can be determined.

By integrating the information emerging from these different projects, we will develop a deeper understanding of the underlying network of tissue regeneration in the ear. We hope our work may one day provide the basis for developing new therapeutic approaches for human hearing loss. ■

Calling All Recently Tenured

If you are an NIH intramural scientist or clinician and have been tenured within the past year or so, we'd like to invite you to write about your work in an upcoming issue of *The NIH Catalyst*. It's a great way for the NIH community to get to know you. Look for our e-mail invitation or contact Laura Carter, managing editor of the *Catalyst,* at carterls@od.nih.gov or 301-402-1449. ■

Blood Bank

continued from page 1

as far back as the 1600s, but they weren't considered safe for humans until the early 1900s after Austrian physician Karl Landsteiner discovered blood groups and developed a system of blood typing that classified blood into A, B, AB, and O groups. Transfusing the wrong type of blood into a person can trigger an immune response that can be life-threatening. In 1930, Landsteiner won the Nobel Prize in Physiology or Medicine for his work. In 1937, physician Bernard Fantus invented the term blood bank and started the first one at Cook County Hospital in Chicago.

In the 1940s, NIH researchers were conducting studies on the sterilization of blood and preservation of red blood cells using human volunteers. The NIH Blood Bank wasn't created until the Clinical Center opened in 1953, and blood from its volunteer donors was used only to treat patients and wasn't generally available for research.

NIH scientists who needed whole blood for their work were likely to ask their colleagues to contribute a syringeful of the substance. Others went regularly to the Blood Bank to donate blood for their own work, according to Harvey Klein, chief of the Department of Transfusion Medicine (DTM). Researchers were also allowed to request certain components—such as white blood cells—that were unwanted byproducts derived from whole blood donations. Back then, however, there was no formal oversight or informed consent for blood donations used for laboratory research.

Buffy Coats

The white blood cells that were, and still are, available to researchers were contained in buffy coats. A buffy coat is the thin, pale, yellow-brown or buffy-colored layer of concentrated white blood cells that forms when a container of blood is spun in a centrifuge. The yellowish, translucent plasma rises to the top, the buffy coat forms a thin layer underneath, and the heavier red blood cells fall to the bottom. The buffy coat would otherwise be discarded because it is unsuitable for transfusion. Researchers who want them submit a written request to DTM. The DTM staff assigns codes to the products to protect the identity of the donors.

Top: Whole blood that has been collected for transfusion is spun in a centrifuge to separate the plasma, the buffy coat (containing white blood cells), and the red blood cells.

Second: Medical technologist Debrean Loy has placed the blood collection bag in a plasma extractor so she can siphon off the plasma and then the thin buffy coat.

Third: The red blood cells will be used for transfusion. An adenine saline solution will be added and any remaining white blood cells will be filtered out.

Bottom: Loy has weighed the buffy coat bag and is entering information into a computer system. Next she will notify the appropriate researcher that the order is ready for pick up.

In the 1970s, then–NIDCR investigator Joost Oppenheim used DTM buffy coats to study the interaction between macrophages and lymphocytes, two types of white blood cells. His group used whole blood samples to study the lymphocyte-activating factor, which was later found to be a precursor to the proinflammatory cytokine interleukin-1. Today, as an investigator at the National Cancer Institute–Frederick, Oppenheim continues to rely on blood components provided by DTM. DTM provides white blood cells collected through apheresis—a procedure in which the blood is passed through an apparatus that separates out the desired cells and returns the remainder to the donor—for Oppenheim's work with chemokines and alarmins, protein molecules that activate the immune system.

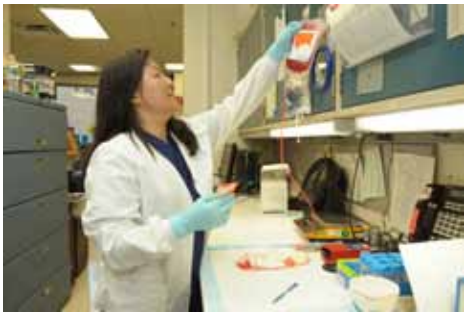
"The great advantage of using human blood for research is that the research results are completely translatable to the human condition," said Zack Howard, an investigator in Oppenheim's lab. "Observations do not have to be filtered through the 'if mouse and man are similar at this stage' process."

Research Blood Program Formalized

Without DTM's research blood donor program, the work of Oppenheim, Howard, and countless other NIH investigators who rely on human blood products for their research might not have progressed so far.

In 1976, Klein formalized the NIH research blood donation program to encourage researchers to obtain whole blood from the Blood Bank instead of from each other. People who donated blood for research were paid and required to sign a one-page consent form. The Blood Bank kept records to track and limit the amount of blood each donor gave annually and recorded the total compensation received. Researchers were not charged for the products, however.

It all starts with the donor. Research blood donor Henry Anderson, Jr., a regular at the NIH Blood Bank, is donating white blood cells through apheresis—a two- to three-hour procedure in which blood is passed through an apparatus that separates out the desired cells and returns the remainder to the donor.



DTM's Sue Williams prepares the white cells that have been collected for distribution to NIH intramural labs.

A more rigorous process was developed in the 1990s to further protect the donors. Susan Leitman, chief of DTM's Blood Services Section, wrote a protocol to build a registry of healthy volunteers whose donations would be used for intramural research. As with all protocols involving human subjects, it had to be approved by the Institutional Review Board (IRB), a part of the U.S. Department of Health and Human Services' Office for Human Research Protections, which sets policies governing research with human subjects. "The current consent [form] is now seven pages long and describes many of the potential research uses of the subject's blood, but also lets them know that genetic . . . research will not be done on their blood unless [it] is anonymized," said Leitman. "I am the custodian of their privacy and protection." Research donors can have their blood drawn every couple of weeks to every two months, depending on the product they are providing.

Today, intramural laboratories obtain their blood products from the NIH DTM, another IRB-approved collection protocol, or commercial sources. DTM's research blood is no longer free to NIH investigators, but the cost is only a tenth to half as much of what commercial companies charge. The DTM charges, instituted a few years ago, have made labs careful not to waste anything and to order only the products they need, Oppenheim pointed out.

Ordering

NIH intramural researchers can register online at the DTM Web site for the blood components they need. The Blood Bank is almost always able to fill orders even from groups that have complex requirements. In a typical request, "a researcher might say, 'I would like 100 samples over three months, derived from equal numbers of males and females, and I want half of them to be African-American,'" said Leitman, who is in charge of blood product collections for research use. The Blood Bank will then schedule the collections, process the components, anonymize the samples, and maintain the required records to ensure compliance with existing policies and that the researcher gets what he needs. Sometimes there is a waiting list, but all researchers are eventually accommodated.

The DTM keeps track of researchers' orders and collected components via a computer system. The donors remain anonymous, but limited information—such as age, sex, and race—can be provided.

The most common research donation is white blood cells collected by apheresis. Other products include plasma, platelets, and certain byproducts—like buffy coats—that are derived from whole blood donations. The cell-processing section separates the blood components and produces samples that are enriched with specific types of blood cells that are then are used both for clinical trials and bench research. DTM also collects stem cells that are used in gene therapy.

Ready for Pick Up

Once the order is ready, researchers are notified so that the carefully packaged and labeled products can be picked up.

Intramural researchers whose labs are not on the main Bethesda campus send couriers to pick up the blood. Here, courier Paul Barr puts the blood components in a cooler to transport them to the NCI-Frederick campus.

DTM provides labs with limited information about the donors—age, race, and sex. It would be difficult, time consuming, and intrusive to provide detailed medical histories, lists of all medications, and the like, Leitman explained. She recommends that researchers who need such detailed information write their own protocol and recruit their own donors. The donors would still come to DTM to have their blood drawn.

Due to DTM's limited resources, only intramural researchers can obtain these blood products. This comes as a shock

continued on page 12

Blood Bank
continued from page 11

Lead tech Cynthia Williams (left) and the Chief of the Blood Services Section, Susan Leitman (right), are preparing donated blood for pickup by researchers. In the 1990s, Leitman wrote a protocol to build a registry of healthy volunteers whose donations would be used for intramural research.

to postdocs who had grown accustomed to using DTM's products while they were at NIH but have since moved to an outside institution, said Leitman. Their local blood banks may provide only transfusion blood products, and commercial sources are quite expensive. Leitman has received e-mails from former postdocs saying, "I never realized what a wonderful resource [the DTM] is."

If Researchers Discover Something

Donors are never told if something unusual is discovered about their blood. The IRB protocol does not allow for informing donors of research results. Howard recalled that in the late 1990s, NIH geneticists found that people with the CCR5 Delta 32 genetic modification were protected against HIV infection. The results were published in a medical journal but, in accordance with the IRB protocol, the donors were never directly informed of the findings.

The Researchers

Harry Malech is one of DTM's close collaborators. For more than 20 years, his group has used the gamut of DTM products, ranging from easy-to-collect red blood cells and platelets all the way to components that were produced through a complex process. Malech's Genetic Immunotherapy Section, in the Laboratory of Host Defenses at the National Institute of Allergy and Infectious Diseases (NIAID), is developing gene therapy and stem-cell transplantation approaches to treating a variety of inherited primary immune deficiencies. One focus of the gene therapy program is X-linked chronic granulomatous disease (CGD), in which the patients' phagocytes (a type of white blood cell) are unable to kill certain pathogens, leading to chronic infections. When CGD patients get a life-threatening infection that is unresponsive to other treatments, they may need transfusions of granulocytes, another type of white blood cell.

"Dr. Leitman was the pioneer in learning how to collect granulocytes properly many years ago," said Malech. "The NIH is still one of the few places [that] can provide a really high quality product of granulocytes."

NIAID investigator Harry Malech is one of DTM's close collaborators. For more than 20 years, his group has used the gamut of DTM products, ranging from easy-to-collect red blood cells and platelets to components that were produced through a complex process.

Malech's group also runs a bone-marrow transplant program that treats patients who have primary immune deficiencies with transplants of hematopoietic stem cells, which give rise to all blood cell types. Over the years, DTM staff has collaborated with Malech to become expert in purifying these stem cells from the apheresis products collected from donors and patients. The staff grows hematopoietic stem cells that are used for gene transfer—using virus-type gene-transfer vectors to put new genes into the cells—in patients undergoing gene therapy.

"Without that specialized expertise, there would be no such protocol here at the NIH," Malech said. "The survival of many of my patients depends on the intimate and critical involvement of the Blood Bank at many different levels."

NIAID's Laboratory of Clinical Infectious Diseases uses whole blood for research on phagocyte defects and their associated infections. Here, infectious disease specialist Donald Vinh is picking up donated blood for work he's doing with lab chief Steve Holland.

NIDCR researcher Larry Wahl uses DTM's leukapheresis collections to obtain monocytes for his studies on cytokines, HIV infection and replication, and signal-transduction pathways involved in the production of enzymes called matrix metalloproteinases. It would be "highly unlikely if not impossible to obtain the number and quality of these cells from another source," Wahl said.

Transfusion Donations

Although DTM supplies blood to researchers, its main function is to provide blood for transfusion and products used to treat Clinical Center patients. The Blood Bank aims to be 100 percent self-sufficient in red blood cell, platelet, plasma, and other transfusion components, said Leitman. Indeed, the DTM is close to being self-sufficient except when there is a sudden massive need for an unusual blood type.

Blood for transfusion is collected from unpaid volunteer donors, including NIH personnel, people from the community, and patients' friends and family members. NIH staff have probably seen those familiar e-mails saying, "Acute shortage of blood—please consider donating," and may have noticed that these are most often requests for type O blood. In the last few years the Blood Bank has been chronically short of group O blood, in part due to the hematopoietic transplant programs—run by Malech, Ron Gress at NCI, and John Barrett at NHLB. In situations in

which the transplant donor and recipient do not have the same blood type, the patient is generally given group O blood immediately before and after transplant. There just aren't enough group O donations to meet that need.

There are several advantages to having an in-house program, Leitman explained. The program can be tailored to meet clinical and research needs. And DTM can conduct its own research including ongoing studies on transfusion safety. Harvey Alter's group at DTM freezes samples from donor-recipient pairs who have given consent. If a new infectious agent is discovered that might be transferred through transfusion, DTM can go back and check all the paired donor-recipient samples pre- and post-transfusion. In addition, Leitman is leading studies to manage hemochromatosis—a disorder in which too much iron accumulates in the body—by having patients donate blood to get rid of excess iron. Such blood is also safe for transfusion; about 15 percent of the red cell units transfused at the NIH come from hemochromatosis patients.

Most large medical centers have departments of transfusion medicine that provide some of the services that the NIH Blood Bank does. But "we may be one of the few institutions that can do it all," said Malech. ■

Helpful Web sites:

DTM: http://www.cc.nih.gov/dtm

DTM's Blood Products Request System (NIH only): http://www2.cc.nih.gov/bprs

Interested in donating? See http://www.cc.nih.gov/blooddonor

DTM protocol for collection and distribution of blood components from healthy donors for in vitro research use: http://clinicaltrials.gov/ct2/show/NCT00001846

HHS Office for Human Research Protections: http://www.hhs.gov/ohrp

NIH Office of Human Subjects Research: http://ohsr.od.nih.gov

NIH Blood Bank Facts and Figures

- 12,000 aliquots of research blood are distributed annually
- 7,000 units of whole blood are collected annually
- 4,600 active donors of whole blood
- 2,800 plateletpheresis procedures conducted annually, yielding 30,000 units of platelets
- 1,200 leukapheresis procedures are done annually
- 1,042 active donors of platelets
- 414 active donors of research blood

The NIH Blood Bank collects blood for research (left) as well as for transfusion into Clinical Center patients.

- 200 intramural laboratories use NIH Blood Bank products
- Donor blood group distribution:
  44% group O
  41% Group A
  11% group B
  4% group AB
- 60% of transfusions require Blood Group O
- 70% of whole blood donors are intramural NIH staff
- 70% of platelet donors are from the nearby Bethesda community
- 30% of whole blood donors are family members of patients and nearby community members
- 30% of platelet donors are patients' family members and NIH staff

Safer Transfusions

Forty years ago, close to one-third of blood transfusion recipients developed viral hepatitis, or inflammation of the liver. In 1964, NIH geneticist Baruch Blumberg and then–DTM research fellow Harvey Alter co-discovered the Australian antigen, which later proved to be the surface coating of the hepatitis B virus (HBV). In 1970, this antigen became the basis for the first donor-screening test for HBV. This assay and the adoption of an all-volunteer donor system reduced the incidence of transfusion-associated hepatitis by approximately 70 percent.

Alter undertook postgraduate training in hematology after receiving his M.D. from the University of Rochester (Rochester, N.Y.). In 1969, he became a senior investigator at the Clinical Center at NIH. He and his associates, particularly Robert Purcell in NIAID, noted that a large group of transfusion recipients developed hepatitis from blood that was unrelated to the hepatitis A and B viruses. They subsequently launched a program to identify the agent that caused what they named "non-A non-B" hepatitis (NANBH). Though that virus proved elusive, Alter's group developed surrogate markers for the agent that further reduced the incidence of hepatitis.

In the meantime, Michael Houghton, leader of a group of scientists at Chiron Corporation, pursued a search for this elusive agent using the tools of the then-emerging science of molecular biology. That five-year effort culminated in the cloning of the hepatitis C virus (HCV) and the demonstration by Alter and colleagues that HCV and the agent of NANBH were the same and responsible for 90 percent of residual transfusion-associated hepatitis.

In 2000 Alter and Houghton were jointly awarded the prestigious Lasker Award for their work on hepatitis C. ■

—Dan Lednicer, NIH Office of History

Smoking and PD

continued from page 1

The researchers—who included other scientists from NCI and NIEHS as well as from Pennsylvania State University (University Park) and Westat Inc.—reported recently in *Neurology* (*Neurology* **74**:878–884, 2010) that long-term smoking is more important than smoking intensity in the smoking–Parkinson disease relationship. "The number of cigarettes smoked per day became irrelevant once adjusted for smoking duration or years since last smoking," they observed.

The findings are based on information obtained from more than 300,000 participants in the NIH-AARP (American Association of Retired Persons) Diet and Health (DH) Study. The NIH-AARP DH cohort was assembled in 1995 and 1996 by NCI to investigate the roles of diet and lifestyle in cancer etiology and was composed of 556,402 AARP members (ages 50 to 71) who had completed a comprehensive survey on diet and lifestyle. From 2004 to 2006, more than 300,000 participants responded to a follow-up survey—to update lifestyle exposure and occurrence of major chronic disease including PD—and were eligible for Chen's study.

Compared with the reference group of never-smokers in the cohort, past smokers who had smoked for 40 years or longer had a 46 percent reduction in risk for PD. Past smokers who reported smoking for fewer than 10 years showed an eight percent reduction in risk.

So what now? Light up and keep at it? "Nobody would advocate smoking to prevent Parkinson's disease," Chen said.

Rather, this pure epidemiological study has broad clinical and laboratory implications. For example, nicotine is routinely investigated as a neuroprotectant. The high-dose, acute administration of tobacco chemicals in laboratory studies might need to be substituted with experiments based on low-dose and long-term administration, Chen and his colleagues wrote.

The goal, as more researchers become convinced that cigarettes have some protective effect against Parkinson's disease, is to reveal the underlying mechanisms and develop a drug—ideally one that will prevent PD without rotting out your lungs and arteries and turning your fingers yellow. ■

NIH History: Stetten Symposium

NIH History on Display
Second Annual Stetten Symposium
Tuesday, June 15, 8:30 a.m.–5:30 p.m.
(come at 8:00 a.m. for coffee)
Natcher Building (Building 45)
Conference Room D
Light refreshments will be provided

The DeWitt Stetten Fellows in the NIH Office of History will regale you with tales of how NIH has been helping to shape biomedical sciences in the 20th century. Each fellow will give a 30-minute presentation followed by a 15-minute commentary by an expert in the field and a 15-minute open discussion. All are welcome.

Stetten Fellow: Chin Jou
"Hope and Caution: Media Coverage of the Leptin Discovery, 1994–2010"
Commentator: Van S. Hubbard, Rear Admiral, U.S. Public Health Service; Assistant Surgeon General; Director, Division of Nutrition Research Coordination, NIH

Chin Jou's work focuses on contemporary obesity research and on the consequences of the discovery of leptin, a hormone responsible for regulating appetite.

Stetten Fellow: Todd Olszewski
"Bridging Evidence and Practice: The Office of Medical Applications of Research and the Consensus Development Program at the NIH, 1977–2010"
Commentator: John H. Ferguson, Medical Consultant, Office of Rare Diseases Research, NIH

In preparing a history of the Office of Medical Applications of Research, Todd Olzsewski explores risk in the context of translational research efforts at NIH.

Stetten Fellow: Doogab Yi
"'A Medical Vietnam?' Reappraising Institutional and Scientific Legacies of the Special Virus Cancer Program, 1968–1980"
Commentator: Daniel S. Greenberg, freelance Washington journalist and novelist

Through examining the tumor virology program of the 1970s War on Cancer, Doogab Yi documents key legal and policy issues that have influenced the emergence of big-scale, target-oriented biomedical research.

Stetten Fellow: Sharon Ku
"Who is the Nanobio Scientist? A Social History of the Nanotechnology Characterization Laboratory"
Commentator: Anil K. Patri, Deputy Director, Nanotechnology Characterization Laboratory, NCI-Frederick

Sharon Ku traces the social history of the Nanotechnology Characterization Laboratory—the first government-owned entity in charge of translational cancer research—to understand the entanglement of academia, government, and industry.

Stetten Fellow: Brian Casey
"'Murder of the Mind?' The Furor Over Psychosurgery and the Mission of the National Institute of Mental Health"
Commentator: Judith Rapoport, Chief,

Child Psychiatry Branch, NIMH

Brian Casey explores the role the NIMH played during the public debate on the science, ethics, and uses of the re-emergent lobotomy.

Stetten Fellow: Eric Boyle
"Complementary and Alternative Medicine at the NIH: From the Study of Unconventional Medical Practices to Integrative Care"
Commentator: Jack Killen, Deputy Director, NCCAM

Eric Boyle investigates the history of NCCAM and how NIH reconciles medical knowledge about complementary and alternative healing practices with its vigorous commitment to rigorous scientific investigation.

Stetten Fellow: Laura Stark
"The 'Healthy Patient' Paradox: The Legacy of NIH Normal Control Subjects in American Ethics"
Commentator: Christine Grady, Acting Chief, Department of Bioethics; Head, Section on Human Subjects Research, Clinical Center, NIH.

Laura Stark explores the workaday life of scientists, lawyers, administrators, and research subjects inside the gates of NIH, where the rules for the treatment of human subjects were first prepared to open the revolutionary NIH Clinical Center.

—Sejal Patel, Office of NIH History

The NIH Office of History exists to advance historical understanding of biomedical research within the NIH and the world. For more informtaion, visit http://history.nih.gov.

ANNOUNCEMENTS

Embase Training Seminar:
Search Beyond PubMed
Thursday, May 27; 1:00–2:30 p.m.
Lipsett Amphitheater (Building 10)

Don't miss finding relevant research information. Learn to use Embase (Excerpta Medica database), one of the world's largest biomedical and pharmacological databases, with more than 20 million indexed records from more than 7,000 active, peer-reviewed journals. Embase has international content and provides comprehensive coverage of drug-related information, pharmacology, pharmaceutics, human medicine (clinical and experimental), basic biological research, health policy and management, substance dependence and abuse, psychiatry, veterinary science, and biomedical engineering and instrumentation. Become familiar with the updated features of this valuable resource, which is available to all NIHers.

NIH Google Search Appliances—Functions, Features, and Reports
Wed., June 16, 2010; 1:00–3:00 p.m.
Natcher Conference Center (Bldg. 45)
Balcony A

Many NIH ICs use Google Search Appliances (GSA) to provide "internal" or site search services. The appliances have many features and reporting capabilities that can help communications and web teams understand what visitors are searching for on their Web sites. Sung Nguyen, Google Software Systems Engineer, will explain how the Google Search Appliance works —in plain, nontechnical language. He will also talk about the GSA's features that can improve visitors' experiences with searching NIH sites, describe standard and advanced reports available, and answer questions. No RSVPs required. Contact Ann Poritzky (301 496 0959; poritzkya@mail.nih.gov) for more information.

TGF-beta Superfamily SIG Symposium
Thursday, July 1; 9:00 a.m.–4:30 p.m.
Natcher Conference Center (Bldg. 45)

Learn about TGF-beta–related research being conducted on the NIH campus. Morning sessions will feature short talks by principal investigators who will highlight recent developments. There will be a two-hour poster session in the afternoon. To register, send your name and e-mail address to Joe Sousa (sousaj@niddk.nih.gov).

Graduate and Professional School Fair
Thursday, July 8; 8:00 a.m.–3:30 p.m.
Natcher Conference Center (Bldg. 45)

NIH summer interns and postbacs, and college and university students from the Washington, D.C., area are invited to explore graduate and professional education programs in biomedical and health-related fields and learn how to create education plans and prepare for interviews. More than 100 outstanding colleges and universities will be represented. Medical Scientist Training Program directors will discuss M.D.-Ph.D. programs. Exhibits will be open from 9:30 a.m. to 12:00 noon and from 1:00 p.m. to 3:30 p.m. For more information and to register, go to http://www.training.nih.gov.

Director's Seminar Series
Friday June 18, 12:00–1:00 p.m.
Wilson Hall (Building 1)
Yasmine Belkaid (NIAID), "Control of Treg Induction and Function by Microbes."

Wednesday Afternoon Lectures
Wednesdays, 3:00–4:00 p.m.
Masur Auditorium (Building 10)

June 2: Bruce Spiegelman (Dana-Farber Cancer Institute/Harvard Medical School), "Transcriptional Control of Adipogenesis and Systemic Energy Homeostasis"

June 9: Yuan Chang (University of Pittsburgh), "A New Virus as a Culprit in Human Cancer"

June 16: Rafi Ahmed (Emory University, Atlanta), "Memory CD8 T-Cell Differentiation"

June 23: Karen Duff (Columbia University Medical Center, New York), "It Takes Tau to Tangle: Plaques, Tangles and Neurodegenerative Disease"

June 30: Joan Steitz (Yale University, New Haven, Conn.), "Regulating the Activity of MicroRNAs in Vertebrate Cells"

For more information, go to: http://wals.od.nih.gov/2009-2010/home.html.

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Catalytic Reactions?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life), a quotation or confession that scientists might appreciate and 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: 301-402-4303; or mail: *The NIH Catalyst*, Building 1, Room 333.

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

In Future Issues...

- Undiagnosed Diseases
- Global Health
- Pain Research

Laboratory Confessions:

The Building 10 Runaround

By Name Withheld

I confess I wasn't as nice as I could have been to someone in Building 10 seeking directions. This obvious outsider from Building 37 was looking for the NMR Center conference room. The room number, scrawled hurriedly on a tiny piece of scrap paper, provided little insight: 10/B1D104. This would be useful if, say, you were standing in 10/B1D103, although given the maze that is Building 10, this is debatable.

But we weren't even close. Someone, somewhere, told this poor soul that B1D104 was in the northeast wing of the CRC, the "new" part of Building 10. Maybe it was the random arrangement of letters and numbers that pointed him in this direction. There's no B1 over here, mind you. We skip that for some reason and go straight for B2. But there is an E in some addresses, which one might think is close to D.

Anyway, he wound up near the Nutrition office in B2-2426, where workers rarely see the light of day and where the hallways hum with the heigh-ho, heigh-ho singing of tiny, white-bearded miners. His desire to go to the NMR Center clear across Building 10 was akin to asking me directions from Harvard Square to Devil's Tower (Wyo.).

How would I even start to explain? Do I bother to note that the 3000 corridor has no logical relationship to the 2000 and 4000 corridors? Do I direct him to the shortcut down the corridor of a thousand unpleasant sounds? Do I painstakingly describe the location of the magical elevator known only by insiders that, if taken, would transform this otherwise 20-minute voyage into a 1-minute saunter?

I had prepared an answer. "Take the south elevator in the east wing up one floor from B2 to 1, turn down a long corridor, get out to the main section, turn left, then right, then left, then... then..." Then I abandoned the idea. I told this guy I had no idea where the NMR Center was. And I wished him good luck. Now I'm racked with guilt knowing I willfully denied help to a colleague.

Editor's note: NIH Security reports that this person seeking directions was found two days later in the C wing slightly disoriented and thirsty but otherwise in good health. If you have a laboratory confession you'd like to share, please contact us (see "Catalytic Reactions?" at left to find out how).

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