THE NIH CATALYST

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Germ-Free Mice

New Facility for Microbe Study

BY JULIE WU, NIAID

Some 100 trillion beneficial microorganisms—bacteria, fungi, and viruses—populate your body inside and out. Many species keep us healthy by helping with digestion, producing nutrients, and strengthening the immune system. But what would happen if we didn't have this assortment of beneficial, or commensal, microbiota living within us? To find out, NIH scientists are studying germ-free mice that have not been naturally colonized by microorganisms.

NIAID is home to one of the few facilities in the United States that houses so-called gnotobiotic mice. These mice are born in germ-free conditions, and investigators control the microbiota by inoculating the animals with specific microorganisms. The word "gnotobiotic" comes from the Greek words *gnostos*, for known, and *bios*, for life.

When the field of commensal research exploded in the mid-2000s, many NIH investigators already were conducting research on microbiota. "But there were very few intramural resources available for studying commensals [at NIH]," said NIAID senior investigator Yasmine Belkaid. "It became obvious we needed a germ-free animal facility to support investigations on campus."

Belkaid got her wish soon enough. In July 2008, investigators and staff in NIAID'S Comparative Medicine Branch (CMB), directed by veterinarian Randy

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Robotic Arms

Physical Therapists of the Future?

BY SARAH HERRMANN

In a small room tucked away on the first floor of the Clinical Center (CC), NIH scientists are building robots. But don't expect to see armies of cyborg clinicians marching through the hallways any time soon. These robots are mechanical devices that provide physical therapy assessment and training to patients whose muscles have been weakened by cerebral palsy, traumatic brain injury (TBI), or other neurological disorders. The machines can even be operated remotely. For example, a clinician in an office could control a robot that is providing therapy to a patient at home.

HYUNG PARK AND JONGHYUN KIM, CC

NIH researchers have developed tele-rehabilitation robots that can treat weakened elbow joints. The clinician manipulates the haptic mannequin device (top), which sends signals from a computer via the Internet to remotely maneuver the wearable stretching device (bottom) worn by the patient. The patient device sends signals that make the mannequin arm move and feel just like the patient's.

"We are coming to a Renaissance in robotics," said Leighton Chan, chief of the CC's Rehabilitation Medicine Department. They "can play a huge role" in physical therapy.

Guided by computers, these first-of-their-kind rehabilitation robots can help patients by assessing muscle-related tasks or training weakened muscles to regain their strength. Hyung-Soon Park, a staff scientist in the CC's Functional and Applied Biomechanics Section (FABS), leads the design and development of the robots. FABS chief Diane Damiano works with patients and develops clinical questions that robotics technology can address.

Usually a patient who needs physical therapy must come to a clinical facility. But Park is developing a tele-rehabilitation system that can remotely assess a patient's

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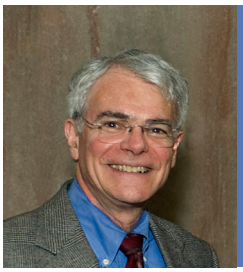

Giving Credit Where Credit Is Due

BY MICHAEL GOTTESMAN, DDIR

In June, the NIH Animal Care and Use Program was evaluated by a team of 12 outside experts as part of our triennial Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) site visit. This review, like other rigorous reviews—such as the upcoming Association for the Accreditation of Human Research Protection Programs' (AAHRPP) evaluation of our human subjects research program; the Joint Commission's evaluation of the Clinical Center's patient-care services; and the Accreditation Council for Graduate Medical Education's (ACGME) review of the Clinical Center's medical residency programs—is an important component of the oversight that ensures the high quality of our programs. Three points are worth making:

1. The NIH Intramural Program is a federated structure of multiple institutes and centers that are responsible for their own research activities. But in the cases of animal care and use, human-subjects research, patient care, and medical residencies, we have strong programs with centralized management and oversight to ensure consistency. Each program involves standard operating procedures that are endorsed and implemented by our institutes and centers. For AAALAC, the review process reflects more than 25 years of effort. For AAHRPP, we are in the middle of standardizing our procedures so that when we are first site-visited early next year we can make a convincing case for uniformity in a single human-subjects-protection program. For the Joint Commission, the Clinical Center provides important oversight and acts as the glue that keeps our clinical programs together and ensures high-quality patient care. And the ACGME assesses and helps to advance the quality of the Clinical Center's resident physicians' education.

2. For these evaluations to result in accreditation, it is critical that everyone responsible for various aspects of the programs be fully educated about the rules and demonstrate unequivocally that they put these rules into practice on a daily basis. The site visitors spend most of their time observing facilities and interviewing the people who are responsible for maintaining the high quality of our programs and, in the case of the ACGME, reviewing documentation indicative of compliance with training requirements. If even one individual is unable to describe and explain appropriate procedures, operational policies, or training requirements, this is duly noted and contributes to possible loss of accreditation.

3. The success of our accreditation programs depends on a lot of hard work by an incredible number of people. There are months of preparation so that we can put our best foot forward. We should all be grateful to the staff members who give these accreditation processes their highest attention. For AAALAC, we have just completed most of the site-visit process. The Joint Commission review was completed last year, but commission inspectors may return at any moment to confirm the continuing high quality of our patient-care services. (At our last visit, the Clinical Center received one of the highest scores possible for the quality of our facilities and clinical care). The most recent institutional ACGME review, which was completed in April 2008, confirmed that both the Clinical Center, as a sponsor for graduate medical education, and our residency programs continue to meet high standards. For AAHRPP, the work is just getting under way. We hope that everyone will put the same kind of energy into that process as we do for our regular Joint Commission, ACGME, and AAALAC accreditations.

The AAALAC site visitors were impressed by the overall quality of our program and by the dedication of the individuals who run it and participated in the interviews. There are always some things that we can improve, and these were transmitted to us in some detail. We need to determine whether any changes are needed to respond to the few concerns that were raised. In the meantime we will provide responses to the AAALAC council before they take a final vote on continuing accreditation for the NIH.

I am extremely grateful to all who work so hard to make our animal-care and -use program one of the best in the country. This achievement is particularly impressive given the complexity of our program. And this column is also an opportunity to thank those who participate in the Joint Commission and ACGME accreditation processes as well as those who will be working hard on the AAHRPP accreditation in the coming year. ●

Traffic Web Site

BY BRAD MOSS, OD

As part of the Defense Base Realignment and Closure (BRAC) process, the National Naval Medical Center will become Walter Reed National Military Medical Center on September 15, 2011. The new Center is expected to add approximately 4,300 daily commuters and will double the number of patient visits to nearly one million annually.

The Office of Research Services and the Office of Research Facilities have developed a Web site (http://traffic.nih.gov) to inform you of various construction projects and to offer tools and resources to help you with your commuting choices. The site includes timelines on construction projects, more about BRAC, and handy widgets to map the best commuter routes, complete with live traffic cameras across the entire region.

Although the increase in the number of commuters seems daunting, when viewed against the current 77,000 daily commuters in this area, it amounts to a manageable six percent increase. If NIH and others do their part to reduce traffic congestion, everyone benefits and we avoid gridlock. As employees, please consider teleworking, flexible work schedules, off-peak commuting, Transhare, and alternative commuting options such as vanpooling, carpooling, Metrorail, and NIH shuttle and public buses. Every option gets one more car off the road during peak periods. Using one or more of these strategies can make the roads accessible, reduces greenhouse gas emissions, and minimizes fuel costs.

The NIH meets regularly with state, local, and federal officials to discuss broad and specific measures to alleviate overall congestion in the area. A number of roadway improvement projects have been initiated, but these projects will create their own temporary disruptions. Even after completion, the traffic will still exceed capacity. Ultimately, it will be up to each employee to determine which mitigation strategy works best in his or her own situation. (Note: Some of these options, such as telework and alternative work schedules, require supervisor approval.) ●

GPU Pilot May Help Solve Computational Problems

BY ANDY BAXEVANIS, NHGRI AND OIR

CIT has added a pilot set of 16 graphics processing units (GPU) nodes to the NIH Biowulf cluster to investigate new ways of solving computational problems.

GPUs are specialized microprocessors originally designed for video and rendering. More recently, computation-intensive programs in the life sciences have been ported to GPUs to explore potential performance benefits of their massive computing power.

Biowulf was designed and built at NIH and is one of the largest general-purpose biomedical computing clusters in the world. The system is designed for large numbers of simultaneous jobs that are common in bioinformatics as well as large-scale distributed memory tasks such as molecular dynamics.

During the pilot, CIT and NIH researchers will:

- Identify applications available for use with GPUs and evaluate and integrate them into the Biowulf production environment.
- Identify user simulations that will most benefit from running on GPU systems.
- Develop or port new applications to run on GPUs.
- Determine the cost and energy effectiveness of using GPU technology.

Experience shows that running any application on GPU nodes does not guarantee improved performance. It is vital that users benchmark their application to determine the effectiveness of using the GPUs. CIT staff benchmarked several biomedical applications on the GPU nodes, including NAMD, AMBER, GROMACS, MATLAB, and several bioinformatics programs.

For information on how to submit jobs to GPU nodes and to run existing GPU applications, and to see results from the application benchmarks, visit: http://biowulf.nih.gov/gpu.html. The Biowulf staff encourages users to share their GPU benchmarks by sending them to staff@biowulf.nih.gov.

One application domain found to benefit from computing with GPUs is the program NAMD for molecular dynamics simulations of large molecules (about one million atoms). With a large simulation such as STMV (satellite tobacco mosaic virus), systems with a 2:1 ratio of CPUs to GPUs give an increase in performance over that of CPU-only systems. ●

FROM THE FELLOWS COMMITTEE

Volunteering at the Children's Inn

BY CAROLYN GRAYBEAL, NIAAA

Imagine having to teach a science class to a group of children—between the ages of five and 18—with no idea how many you will be speaking to, what their background is, or whether they even speak English. Recently, two NINDS fellows did just that and discovered the experience to be rewarding and even fun.

Katherine Bricceno and **Kelly Shaffer** volunteered for Explore-Inn to teach science at NIH's Children's Inn, a family-centered residence for pediatric outpatients on the Bethesda campus. Coming up with a project was the first hurdle.

"I wanted to find something visual and active," explained Bricceno, a graduate student working on a Ph.D. in biochemistry and molecular genetics. She stumbled upon an activity using red cabbage juice as an acid-base indicator. When mixed with an acidic solution such as vinegar, the juice turns reddish; when mixed with basic solutions such as ammonia it turns blue-green. Over the winter holidays, she tested the experiment at home and won over her mother, who was worried about the unavoidable mess. "I figured if I could get my family excited, this would work for kids too," said Bricceno.

The classes are optional, so teachers don't know in advance who will be attending. The one thing they could count on was a mess, however. "We thought we were going to be working with lots of little children," said Bricceno. "There was going to be liquid everywhere."

Turnout was small so Bricceno and Shaffer had plenty of one-on-one time with the children. Teachers and students had a blast. "By the end of the hour, one boy was just mixing liquids together to see the colors," said Shaffer, a medical school graduate who is working on a Ph.D. in neuroscience. "If he had been left alone he would have created a volcano."

The experience caused Shaffer to reflect on how her best teachers tailored their approaches to the abilities of students. "I need to explain things on the other person's level and then be able to bring them to my level," she said.

Bricceno agreed. "My own work is so detailed and specific. How can I make it interesting for someone else?" she said. "I think it is about making the science accessible [and] engaging so it is interesting."

And for the children? "They don't have to think about [being] sick," said Shaffer. "They are just normal kids, doing normal things." ●

FROM THE OFFICE OF INTRAMURAL TRAINING AND EDUCATION

Postbac Posters Wow the Crowds

BY SHARON MILGRAM, OITE

More than 300 postbaccalaureate students showed off their research posters in May. Here's a sampling:

NCI postbac **Dena Tran** established the importance of mTOR (mammalian target of rapamycin) in waging a healthy immune response and uncovered the mechanism of action of the immunosuppressant drug rapamycin. Genetically engineered mice that expressed only half of the normal level of mTOR had small spleens, fewer B cells, and decreased antibody production.

Hannah Bergman's project merged her interests in psychology and the military. She worked with researchers in NCI's Cancer Control and Population Sciences Division to investigate smokeless tobacco use in the military and demonstrated the need for more studies to identify risk factors. She co-authored a paper that was submitted to the *Journal of Tobacco and Nicotine Research*.

Peter O'Halloran, in NICHD, hopes to find drugs that will combat the neurological symptoms of a cholesterol-synthesis disease called Smith-Lemli-Opitz syndrome (SLOS). He will help test FDA-approved drugs to see whether they can restore cholesterol synthesis in affected neurons. He is thrilled to have helped create SLOS neurons—from patient skin biopsies—that will be useful for drug screening.

Inspired by the 2010 NCI Symposium on Chromosome Biology, NCI postbac **Nikosi Adejola** studied chromosome territory organization in mouse tissue. By collaborating with researchers in his and another lab, he learned how to perform fluorescent in situ hybridization on mouse mesenteric tissue. Preliminary data suggest that specific mouse chromosomes cluster in close proximity to each other.

Camille Kemble, a first-year postbac working in NHLBI, relied on her electrical engineering background to improve X-ray imaging so it can be used on soft tissue as well as bones. She is the first author on a paper that appeared in *Optics Express* and hopes to publish a second paper soon. ●

A list of selected posters can be found on the OITE Web site: https://www.training.nih.gov.

LIPS Service: New Assay Method May Revolutionize Antibody Testing

BY CHRISTOPHER WANJEK

When Peter Burbelo contemplated a more efficient way to perform antibody assays, a light bulb lit up over his head—or perhaps it was luciferase, the enzyme behind the bioluminescence of fireflies.

Burbelo, the staff scientist for NIDCR's Neurobiology and Pain Therapeutics section, came to the NIH from Georgetown University (Washington, D.C.) in late 2006 with a working model of his assay technique, called luciferase immunoprecipitation systems, or LIPS. His section chief, Michael Iadarola, hoped to use the technology for humoral (antibody-mediated) immune reactions.

Researchers can learn to profile antibodies using the LIPS technique by watching a video at http://www.jove.com/details.php?id=1549.

A few tweaks and some 40 peer-reviewed journal articles later, Burbelo and Iadarola have crafted what may become the assay of choice for detecting antibodies implicated in dozens of disorders as diverse as type 1 diabetes, Sjögren syndrome, and infectious diseases, for which detection sensitivity is crucial but has been lacking. Many of these studies are being conducted in collaboration with other NIH scientists.

Burbelo describes LIPS as a traditional bait-and-bind diagnostic assay, in which the bait—an antigen, or protein snippet known to elicit an antibody response—is fused to a luciferase enzyme. This bait then binds to the target antibody in serum or other bodily fluids and glows; the brighter the glow, the greater the amount of antibody caught.

The sensitivity of the LIPS technique is three or more orders of magnitude greater than the traditional technique, enzyme-linked immunosorbent assay (ELISA). One reason is that, with LIPS, antigens maintain more of their three-dimensional shape as they interact with antibodies because the assay is performed in solution rather than in formats in which the protein is adsorbed onto a two-dimensional surface or a membrane.

And with its relatively low cost and ease of use, LIPS is poised to become a universal format for the detection of antibody responses to almost any protein antigen.

Among Burbelo's early successes was detecting antibodies in previously diagnosed patients with Sjögren syndrome, a chronic autoimmune disorder affecting the lacrimal and salivary glands. He found that nearly three-quarters of the patients had antibodies not detected by ELISA. Digging deeper, his NIDCR-based team found that 14 percent of the subjects with Sjögren syndrome had antibodies against a thyroid antigen, 16 percent had antibodies against an antigen associated with autoimmune gastritis, and 12 percent had antibodies to aquaporin-4. All the subjects who had anti-aquaporin-4 autoantibodies showed neurological symptoms including peripheral neuropathy.

This "suggested that autoantibodies against glial cell components might be biomarkers or play a role in peripheral neuropathy," said Iadarola.

Burbelo has also worked on Lyme disease, river blindness, Kaposi sarcoma-associated virus, tuberculosis, and upward of 25 additional pathogens. In some cases, LIPS can be used to distinguish different conditions caused by a single infectious agent. LIPS can also be used to simultaneously detect antibodies against partial and whole proteomes, such as those from the human immunodeficiency virus and hepatitis C.

Burbelo and Iadarola recently finished a project with NIAID's Steven Holland on people with thymic malignancies. They found that anti-cytokine autoantibodies may promote opportunistic infections.

Iadarola sees the LIPS assay as part of a comprehensive disease surveillance technology. He believes LIPS could be used in routine medical assessments throughout a patient's lifetime as a means of obtaining highly informative and potentially predictive information on a wide spectrum of diseases, including cancer and neurological and degenerative diseases.

LIPS is now semiautomated with a 96-well format, enabling the Iadarola lab to run upward of a thousand samples in one day. The technique is depicted in a video titled "Antibody Profiling by Luciferase Immunoprecipitation Systems (LIPS)" at http://www.jove.com/details.php?id=1549. The video features Kathryn Ching, also a scientist in Iadarola's lab and co-author on many papers.

The video describes everything you need to perform the LIPS assay in your lab, said an, uh, inundated Burbelo. ●

An Exit Interview with NIH Library Director Suzanne Grefsheim

BY CHRISTOPHER WANJEK

MICHAEL SPENCER

The NIH Library has undergone a transformation over the past 20 years in both its spirit and its physical appearance. Gone are most of the stacks, not to mention the dark rugs. Brilliant light now fills its first floor, which is best described as an information commons where users can relax and even, dare we say, eat and talk.

Suzanne Grefsheim, who came to direct the library in 1992 from a similar position at the University of Michigan in Ann Arbor, nurtured this transformation. As she prepared to retire on May 31 to turn her attention to her gardening hobby, Suzanne spoke to *The NIH Catalyst* about what she helped plant and grow at the NIH. The following is an edited transcript of that interview.

You oversaw some rather dramatic changes in library services in the 1990s. Perhaps this wasn't entirely different from one of your favorite hobbies, gardening.

Yes. When we were trying to create the learning organization in the late '90s, the staff would ask, "Why do we need to change so much?" And I said, "Well, it's like a garden. You see ways that it could be so much better. So you pull it up and reconfigure it." We did that with the library physical space as well as with its mental space—compartments that library staff put themselves into.

Was this place a weedy mess in 1992?

Not really. Just different. When I came to NIH, the library was committed to service in an exemplary way, but it was not looking at how things were changing. The staff felt that its role was to do the work. My vision was to create a self-sufficient user population. There was a bit of resistance among the librarians to taking on a teaching role at first. There was resistance among the users, too, because they were so used to having someone do things—like searching—for them. But that resistance was quickly overcome.

How easy was this in 1992? Did the state of technology even allow this?

We were the first at NIH to offer the Internet. We were the first to provide unlimited access to Medline (now PubMed) to NIH, too. When I was at the University of Michigan health sciences library, we were the first to negotiate an agreement with a Medline provider so we could have unlimited access to Medline for a flat rate. For the NIH Library, I made a similar deal with the National Library of Medicine. I knew from experience that once Medline was freely accessible, users would love it.

How long did it take for things to change?

I spent the first five years changing the mindset about the kinds of services we could provide. The next five years we tried to change the way the staff itself worked. We had to be more nimble, willing to take on new responsibilities and roles, and not be stuck in the traditional "wait till people come to you" mindset. If we were pushing out all our resources to users' desktops, we had to figure out a way to reach them. This whole period of learning and growing and staff development led to and culminated in the informationist program, which is now blossoming.

NIH LIBRARY

The NIH Library's reading room before Suzanne Grefsheim arrived in 1992 (above), was not as inviting and sun-filled as it is today (below).

NIH LIBRARY

Ah, another garden reference. Informationists are embedded librarians who house themselves physically among the research team they serve. Is this concept growing elsewhere, too?

Not in the same way we are doing it. There was a recent article in the *Journal of the American Medical Association* describing the informationist program. We're mentioned as one of three model programs. Ours is more clinical- and basic-research-oriented because of the nature of this institution. (*JAMA* **305**:1906–1907, 2011)

Some people never step inside the NIH Library. Does that bother you?

No! Actually, that was the goal—that they wouldn't have to come here. The purpose of the library isn't to be a physical place. The library is the suite of services and resources that we make available, in whatever format, in whatever location they're needed. Librarians are what make that happen. But there is a role for a physical facility, and we have spent the last five or six years trying to repurpose ours into what the new library can be. It's now sort of an intellectual meeting place. It also provides space that's needed for fellows who don't have offices.

What was it like when you came?

It was brown, very brown.

Like some gardens?

Well, not a particularly nice garden. The carpeting was brown—with high shelves all over blocking out sunlight. Very book oriented, very journal oriented. And wood, the same color as the carpet. Everything was brown. It really was an uninviting place. The most heavily used part of it was the photocopy center—long, long lines of people waiting for the nine photocopiers that we had and being told they could only stay at the photocopier for five minutes. The library was originally designed, in a way, to limit access. But we wanted to break down the barriers and let people get as much as they wanted whenever they wanted it with no limits. The electronic resources allowed us to do that.

What services are you particularly proud of?

We were the first on campus to offer the Internet in the early '90s. We were the first to have wireless access. We were the first to do many things that brought the NIH into the information age. Outside of NIH the informationist program is viewed as a groundbreaking area. The bioinformatics program has been hugely successful and will likely grow. We've conducted research studies to identify emerging needs and what the scientists wanted from us. That's what led to the formation of our writing center. Our services have always exemplified what the library is. It's the content, not the container.

Peering into the future, what dangers do research libraries face?

You have to be thinking 10 years ahead. A lot of libraries aren't. If they think that the library is the books and the journals and the place, and that people will come to them, they aren't going to survive. Libraries that are built as showcases tend to be underutilized. They become too invested in doing the same things in a new space instead of doing new things in a minimum space. I was once asked whether I wanted a new building. I said "Absolutely not." We are right where we need to be, among the people who use us the most.

NIH LIBRARY

Many of the library's training programs are held in attractive glassed-in rooms like this one (above). Outside, library patrons can read, relax, and even compute on the terrace (below).

BRADLEY OTTERSNON

How about advice for the next NIH Library director?

You have to understand the community you are serving, know its culture, and understand how researchers think and approach information. You cannot assume that you have the answers. ●

Research Briefs

FIC: MEXICAN FLU PANDEMIC STUDY SUPPORTS SOCIAL DISTANCING

Would closing schools, movie theaters, and restaurants help improve health? Yes, at least in terms of mitigating unusual infectious disease outbreaks. According to NIH researchers, these social distancing interventions proved effective during the 2009 influenza pandemic in Mexico. Mexican health authorities implemented a nationwide mandatory school closure policy, effectively reducing disease transmission by more than one-third. The research team provided the first comprehensive epidemiological description of the age, geographical, and severity patterns of the 2009 pandemic in Mexico. Eighteen-day periods of mandatory school closures and other social distancing measures were associated with a 29 to 37 percent reduction in influenza transmission rates in Mexico during the 2009 pandemic. The authors applied mathematical modeling to influenza surveillance data compiled by a large private health system, the Mexican Institute for Social Security, which covers 40 percent of the population. (NIH authors: G. Chowell, C. Viboud, L. Simonsen, J. Tamerius, M.A. Miller; *PLoS Med* **8**:e1000436, 2011)

NCI: STUDY RULES OUT XMRV AS CAUSE FOR HUMAN DISEASE

The road to finding the cause for disease is sometimes paved with disappointment. Retrovirologists were excited to explore the role of a retrovirus known as xenotropic murine leukemia virus-related virus (XMRV), which was thought to contribute to prostate cancer and chronic fatigue syndrome (CFS). However, recent studies have shown a lack of association between the XMRV and human disease. NCI researchers, in collaboration with others, have provided an understanding of when and how XMRV arose and explained the original, incorrect assumption. They examined human prostate cancer cells, which contained XMRV, as well as the tumors from which these prostate cell specimens arose after they were grafted into mice. Based on this genetic analysis, the scientists concluded that XMRV was not present in the original prostate tumor samples but arose only after they had been put into mice. Another study in the same issue of the journal found a lack of association between XMRV and CFS. (NIH authors: T. Paprotka, K.A. Delviks-Frankenberry, W. Hu, M.J. Fivash Jr., V.K. Pathak; *Science* DOI: 10.1126/1205292)

NINDS, NCI: PROBING THE ACTIVITY OF A NEW MULTIPLE SCLEROSIS DRUG

Daclizumab is one of the newest therapies for treating multiple sclerosis (MS), a chronic disease marked by inflammation in the central nervous system and development of lesions in the brain. Scientists knew that the therapy works by targeting a single molecule on immune cells, but they didn't understand how. Now NIH investigators have gained insights into the drug's effects and the basic biology of the immune system. Their data reveal a previously unknown mechanism and suggest that the expression of cytokine signaling chains on various cells of the immune system can regulate T cell functions through a single cytokine. This information may provide a basis for the development of more effective therapies. (NIH authors: S. Wuest, J. Edwan, J. Martin, S. Han, J. Perry, C. Cartagena, E. Matsuura, D. Maric, T. Waldmann, B. Bielekova; *Nat Med*: **17**:604–610, 2011)

NCCAM, NLM, NIAID: ACUPUNCTURE FOR PATIENTS WITH JOB'S SYNDROME

Hyper-immunoglobulin E (IgE) syndrome (HIES)—a rare immunological disorder—received its more common name, Job's syndrome, from a biblical passage in which Job was smote "with sore boils from the sole of his foot unto his crown." Job's syndrome patients suffer from a variety of symptoms, which often include abscesses similar to boils. NIH conducted a retrospective case series and demonstrated that acupuncture is a clinically useful and safe therapy for symptom management in patients with HIES. Acupuncture treatments were given to eight adult patients with HIES, ages 23–56, who had varying symptoms. Treatment efficacy was measured and evaluated using a 0–10 assessment instrument pre- and post-treatment. Acupuncture treatments uniformly decreased the self-reported severity of symptoms. (NIH authors: A. Ge, M. Ryan, S. Holland, A. Freeman, V. Anderson, J. Fleshman; *J Altern Complent Med* **17**:71–76, 2011)

NICHD: KEY STEP IDENTIFIED IN LEGIONNAIRES' DISEASE

NIH researchers have uncovered a key step in the biochemical sequence the bacterium that causes Legionnaires' disease uses to reproduce inside cells. The disease, a form of pneumonia, is named after its discovery in people attending an American Legion convention in 1976. The bacterium activates a cell protein to help it hide from the cell's defenses while it reproduces. The researchers discovered how the bacterium switches off the protein so that its offspring can leave the cell and begin the infection process anew. The finding may one day lead to new ways to treat Legionnaires' disease and diseases caused by related bacteria. Previous studies conducted by the NIH researchers have shown that the Legionella bacteria hide out inside the phagosomes, subverting the cell's defense machinery for its own purposes. The bacterium forces the cell to camouflage the phagosome. The bacterium does this by hijacking Rab1, a protein that the cell makes. In the current study, the researchers searched the bacterium's genes and found the information needed to produce a protein called SidD. They found that the SidD protein sliced the AMP molecule from Rab1, which stopped summoning vesicles to the surface of the phagosome. (NIH authors: M. Machner, M. Neunuebel, Y. Chen, A. Gaspar, P. Backlund Jr., and A. Yergey; *Science Express* DOI: 10.1126/science.1207193) ●

COMPILED BY STEPHANIE BONHOMME, NIH MANAGEMENT INTERN ON ROTATION WITH OIR

Dogs Are Shedding . . . Light on Human Health

BY SARAH RHODES

Domestic dogs (*Canis familiaris*), which diverged from the gray wolf (*Canis lupus*) more than 15,000 years ago, have become a scientist's best friend thanks to the work of NHGRI senior investigator Elaine Ostrander and her colleagues.

At the April 29 Anita Roberts lecture, Ostrander described her work studying genes that control the morphology of some of the approximately 400 dog breeds in the world. Dogs are useful for genetic studies because selective mating has generated a diverse range of breeds that are defined by specific morphological characteristics. Scientists are able to identify genes responsible for various traits—body size, fur, leg length, skull shape, leg width, back arch, tail curl, and ear position—as well as resistance or susceptibility to cancer and other diseases.

"Each breed represents a genetically isolated population, much like the Icelandic families in human genetics," explained Ostrander, chief of NHGRI's Cancer Genetics Branch. "We can take advantage of breed structure in order to amplify the underlying genetics for some of the traits that we are really interested in for both human and dog health and biology."

Ostrander's lab conducts genome-wide association studies (GWAS) to examine the DNA of hundreds of dogs of various breeds, maps genes, and looks for correlations between gene markers and traits. A common ancestral mutation may be responsible for the same traits in different breeds.

MAGGIE BARTLETT, NHGRI

At the recent Anita Roberts Lecture, Elaine Ostrander described how her research on dog genetics is shedding light on canine as well as human development.

As a postdoc in Ostrander's lab, Nate Sutter studied the genetics of the Portuguese Water Dog. He identified a region on chromosome 15 that correlated with body size and determined that a single allele of the gene *IGF-1* is found in all small breeds. This gene is nearly absent from giant breeds. *IGF-1* is also known to influence body size in mice and humans. (Sutter is now an assistant professor at Cornell's College of Veterinary Medicine in Ithaca, N.Y.)

Graduate student Edouard Cadieu, who is back at the University of Rennes in France, showed that variants of three genes account for almost all of the coat phenotypes of different dog breeds: *KRT71* is responsible for the curliness of a coat, *FGF5* for its length, and *RSPO2* for the furnishings (moustache and eyebrows). In addition, staff scientist Heidi Parker determined that the insertion of the *FGF4* retrogene is responsible for chondrodysplasia (asymmetric dwarfism), the short-legged phenotype seen in breeds such as the Basset Hound.

Recently, Ostrander and postdoc Jeff Schoenebeck began tackling the genetics of canine skull shape. Ostrander expects to find that multiple genes are involved. So far, one of the *BMP* genes has been identified as a major player in snout development; mutations in the gene are associated with brachycephaly (shortened snout). In humans, mutations of the same gene result in syndromes with similar disruptions in facial development.

Understanding canine genetics provides a good model for understanding human development. Ostrander is certainly leading the pack in this endeavor. ●

The cover of the April 7, 2007, edition of *Science* featured a Chihuahua and a Great Dane to highlight Ostrander's and Sutter's work on the genetic determinants of size diversity in dogs.

Anita B. Roberts, who spent 30 years at NCI before her death in 2006, was known for her groundbreaking work on transforming growth factor–beta. The "Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH" honors the research contributions she and other female scientists have made. To see a videocast of Ostrander's talk or other-Roberts lectures, go to http://videocast.nih.gov/PastEvents.asp?c=151.

Major Shared and Multi-Institute Research Resources

The NIH Intramural Research Program has a long history of interactions and shared resources among its investigators. These include core facilities that support crucial research activities, such as a sequencing center, a magnetic resonance imaging facility, a mass spectroscopy service, and a protein expression service. The most prominent example is the NIH Clinical Center, the nation's largest hospital devoted entirely to clinical research, providing comprehensive services and facilities in support of clinical research sponsored by the institutes and centers. In addition, the NIH Office of Intramural Training and Education organizes and sponsors a variety of training and career-development activities for the entire intramural community. Various mechanisms are used to support these resources, including contributions from participating NIH institutes and centers such as the management funds, user fees, and program support from the Office of Intramural Research.

RESOURCES AVAILABLE TO ALL INSTITUTES AND CENTERS

Research Resource	Location	Participants	Governance	Contact	Research Services	Review
Bioengineering (Lab of Bioengineering and Physical Sciences)	Building 13	Lead IC: NIBIB	NIBIB	Richard Leapman, scientific director	Drug delivery, molecular interactions, image analysis, instrumentation development, supramolecular structure, nanoscale immunodiagnostics; http://www.nibib.nih.gov/Research/intramural/LBPS	Shared Resources Subcommittee, ICs, Coordination Committee
Center for Information Technology (CIT)	Building 12 complex	All ICs	CIT	Benes Trus, acting scientific director	Image processing, bioinformatics, computational methods and algorithms, computer engineering, bioscience, molecular modeling, mathematical and statistical computing, supercomputing, software development; http://www.cit.nih.gov/science.html	Shared Resources Subcommittee, ICs
Division of Medical Arts	Building 10, B2 level	All ICs	Office of Research Services	Lem Canady, chief	Medical illustration, photomicroscopy, photomacroscopy, scientific posters; http://medarts.nih.gov	
Division of Library Services	Building 10	All ICs	Office of Research Services	Terrie Wheeler, acting director	Full-service library, including electronic journals, electronic document desktop delivery and translations; http://nihlibrary.nih.gov	Users Committee, ICs
Division of Scientific Equipment and Instrumentation Services	Building 13	All ICs	Office of Research Services	Johnny Robbins, chief	Maintain scientific equipment and computers; design and fabricate custom instruments; lease and sell scientific and medical equipment; http://dseis.od.nih.gov (NIH Intranet only)	Shared Resources Subcommittee, ICs
Division of Veterinary Resources	Building 14–28 complex; Bethesda; Poolesville	All ICs	Office of Research Services	Charmaine Foltz, director	Veterinary services (surgery, radiology, pharmacy, nutrition, animal behavior and enrichment); animal husbandry, procurement, quarantine, and health surveillance; diagnostics (pathology, bacteriology, parasitology, serology, mouse phenotyping)	Shared Resources Subcommittee, ICs

MULTI-INSTITUTE SHARED SERVICES

Research Resource	Location	Participants	Governance	Contact	Research Services	Review
Biotechnology Core Laboratory	Building 6, Room B1–33	Lead IC: NIDDK; major client: NICHD		Joseph Shiloach, director	Production and purification of biological material, especially scale-up protein production and purification; http://www2.niddk.nih.gov/NIDDKLabs/AllLabs/CoreFacilities/BiotechnologyCoreLaboratory.htm	Board of Scientific Counselors, ICs
Bone Marrow Stromal Cell Transplantation Center	Building 10	Steering Committee: CC, NIDCR, NIAID, NIAMS, NIBIB, NCI, NINDS	Oversight Committee: NINDS, NIAID, NCI, NIDCR	Harvey Klein (CC), Pamela Robey (NIDCR)	Production facility for bone marrow stromal (mesenchymal) stem cells for clinical research	
Center for Human Immunology (CHI)	CC	Available to all ICs	Steering Commitee	Neal Young, director	Translational research in immunology, autoimmunity, and inflammation; http://www1.od.nih.gov/oir/sourcebook/ir-communictns/chi.htm	IC Director Steering Committee
Center for Inherited Disease Research	Bayview Research Campus, Baltimore	Lead contracting IC: NHGR; all ICs may participate	Review: CIDR Board of Governors	David Valle, Johns Hopkins University	Genotyping, DNA banking, statistical genetics consultation, mouse genotyping; http://www.cidr.jhmi.edu	CIDR Access Committee (Camilia Day, NHGRI)
NIH Clinical Center	Building 10 complex	Available to all ICs	Clinical Center Governing Board	John Gallin, director	Research hospital that accommodates 234 inpatients, 80 day-hospital stations, and outpatients and provides comprehensive services and facilities in support of clinical research sponsored by the ICs; http://www.cc.nih.gov	Joint Comm.; Board of Scientific Counselors; NIH Advisory Board for Clinical Research

MULTI-INSTITUTE SHARED SERVICES (continued)

Research Resource	Location	Participants	Governance	Contact	Research Services	Review
Imaging Probe Development Center (IPDC)	9800 Medical Center Dr., Building B, Room 3042, Rockville, Md.	Lead IC: NHLBI	Roadmap Initiative	Gary Griffiths, director	Production of new imaging probes for the intramural NIH research community; http://nihroadmap.nih.gov/molecularlibraries/ipdc/contact.asp	
Mouse Imaging Facility	Building 10, In Vivo NMR Center	Lead ICs: NINDS, NHLBI; Participants, all ICs but NIEHS are paid charter members	Steering Committee	Alan Koretsky, director	Mouse radiologic imaging; 7T rodent MRI, microCT, high-frequency ultrasound, laser Doppler; http://intranet.nmrf.nih.gov/ (NIH Intranet only)	Shared Resources Subcommittee, ICs, Steering Committee
NIH Chemical Genomics Center (NCGC)	9500 Medical Center Drive, Rockville, Md.	Lead IC: NHGRI		Chris Austin, director	Ultrahigh-throughput screening center of the Molecular Libraries Screening Center Network that generates chemical probes for understanding molecular and cellular functions and serve as starting points for drug development, particularly for rare and orphan diseases; http://www.ncgc.nih.gov/	
NIH Intramural Sequencing Center (NISC)	5625 Fishers Lane, 5th Floor, Rockville, Md.	Participants: NHGRI, NCBI, NIDCD, NIAAA, NIDA, NHLBI, NIDDK, NICHD, NEI, NIAMS, NINDS, NIDCR, NIEHS, NIMH	Users Committee	Eric Green, director	Production-scale DNA sequencing, assimilation and analysis of sequence data, instrumentation, sequence analysis software; http://www.nisc.nih.gov	
NIH Magnetic Resonance Imaging Facility	Building 10, In Vivo NMR Center	Lead IC: NINDS; all ICs except NIEHS	Steering Committee	Alan Koretsky, director	Human and animal MRI; other IC MRI instruments available; http://intranet.nmrf.nih.gov/ (NIH Intranet only)	Shared Resources Subcommittee, ICs, Steering Committee
PET Imaging	Building 10, Room 1C401	Lead IC: CC	Steering Committee	Peter Herscovitch, director	State-of-the-art facility with three medical cyclotrons and ten hot cells to produce positron-labeled radiopharmaceuticals, as well as four PET scanners; Good Manufacturing Practice facility with additional hot cells under construction; http://www.cc.nih.gov/pet/index.html	
Protein Expression Lab	Building 6B, Room 1B130	Lead IC: NIAMS; Participants: NHGRI, NCBI, NIDCD, NIAAA, NIDA, NHLBI, NIDDK, NICHD, NEI, NIAMS, NINDS, NIDCR, NIEHS, NIMH; any IC may request service		Paul Wingfield, chief	Expression, purification, and structural characterization of HIV and HIV-related proteins via a variety of techniques; protein EXE software; supply HIV-1 protease; http://www.niams.nih.gov/Research/Ongoing_Research/Branch_Lab/Protein_Expression/default.asp	Intramural AIDS Targeted Antiviral Program, ICs
Stem Cell Unit	Building 35, Room 3A201	Lead IC: NINDS	Steering Committee	Pam Robey, acting director	Facility uses a standardized paradigm to conduct side-by-side comparisons of the available cell lines on the NIH Human Embryonic Stem Cell Registry and shares the results with the scientific community; http://stemcells.nih.gov/research/nihresearch/scunit	
Synchrotrons:						
1. Advanced photon source	Argonne National Lab	DOE		http://www.aps.anl.gov	High-brilliance X-ray beams	

CORE FACILITIES ON A SPACE-AVAILABLE BASIS

Research Resource	Location	Participants	Governance	Contact	Research Services	Review
Facility for Biotechnology Resources (FBR): CBER Biotechnology Core Facility	Building 29, Rooms 200-208	Participants: NHGRI, NIDCD, NHLBI, NIDDK, NICHD, NEI, NIAMS, NIDCR, CC, NCI - fee-for-service	FDA's Center for Biologics Evaluation and Research (CBER)	Nga Y. Nguyen, CBER FDA	Services include: amino acid sequence analysis; DNA sequencing; oligonucleotide synthesis; peptide synthesis; mass spectrometry services; analytical and preparative HPLC services; capillary electrophoresis; http://128.231.52.66/default.htm (NIH Intranet only)	CBER
Mass Spectroscopy	Building 8A, Room B2A19–21; Building 10	Lead ICs: NIDDK, NHLBI, NIMH, NIAID, NINDS	Advisory Group		QTOF–LCMS; high-resolution magnetic sector; MALDI, LC-ion trap	Board of Scientific Counselors, ICs
Structural Biology NMR	Buildings 5, 6A, and 50	All ICs	Steering Committee	Lead ICs: Ad Bax (NIDDK), Nico Tjandra (NHLBI)	Study of macromolecular structure and interaction; 500-, 600- and 800-MHz cryoprobe NMR spectrometers; 900-MHz spectrometer	ICs

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Elkins, identified facilities in which to house germ-free mice. They then purchased 12 isolators that contain five cages each; each of the 60 cages is capable of housing five mice. The National Gnotobiotic Rodent Resource Center at the University of North Carolina-Chapel Hill provided training in how to care for, maintain, and conduct research with these germ-free mice.

Research has since spread faster than germs across the NIH through collaborations with NIAID researchers. For example, Belkaid's group is working on projects with senior investigators Julie Segre at NHGRI and Giorgio Trinchieri at NCI.

Segre, who leads the NIH Human Microbiome Project, studies the role of the skin as a barrier between the body and the environment. Her project with Belkaid involves exploring the relationship between the immune cells and bacteria at the skin barrier.

Trinchieri's lab aims to understand how gut flora affect the pathogenesis of inflammation and immune colitis (inflammation of the colon or large intestine) and, in mouse models, of colitis-associated cancer. By studying germ-free mice that are deficient in immune- or inflammation-related genes and inoculating them with defined flora, his lab can distinguish between the effects of genes and the role of commensals.

The research is not without its challenges. Gnotobiotic mice are born and raised in sterile conditions. At birth, they are removed from the mother by Caesarean section and live in the isolators with germ-free foster mothers. Investigators must perform all experiments using gloves attached to the isolators so that the animals never come into accidental contact with germs other than those that are deliberately introduced.

The NIAID Gnotobiotic User Committee—made up of veterinarians, investigators, and CMB staff—establishes requirements for working in the facility, maintaining the isolators, and monitoring the status of germ-free and other animals that must be maintained in isolators. The committee also developed a procedure for submitting proposals to use the gnotobiotic mice.

NIAID

In NIAID's gnotobiotic mice facility, technicians handle the germ-free animals with gloves attached to isolators.

NIAID's gnotobiotic facility is home to three strains of mice, and more are being generated. Fifteen projects conducted by five NIAID labs have relied on these germ-free mice. Belkaid and Elkins hope to expand the gnotobiotic facility and begin an in-house breeding program. There also are plans to establish a consortium of germ-free mice facilities across the United States, which will enable NIH to share strains and breeding pairs with others. ●

For more information:

NIH Human Microbiome Project:
http://nihroadmap.nih.gov/hmp

Belkaid's research:
http://www.niaid.nih.gov/labsandresources/labs/aboutlabs/lpd/mucosalimmunology/Pages/belkaid.aspx

Segre's research:
http://www.genome.gov/10000354

Trinchieri's research:
http://ccr.cancer.gov/staff/staff.asp?profileid=11574

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DOE: Department of Energy
FAES: Foundation for Advanced Education in the Sciences
FelCom: Fellows Committee
FDA: Food and Drug Administration
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCCAM: National Center for Complementary and Alternative Medicine
NCBI: National Center for Biotechnology Information
NCI: National Cancer Institute
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: Eunice Kennedy Shriver 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
NIMHD: National Institute on Minority Health and Health Disparities
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
ORS: Office of Research Services

Robot Arm

CONTINUED FROM PAGE 1

condition and provide treatment. Patients could be helped without ever having to leave home.

Park's lab developed two robotic mechanisms that work together to rehabilitate the elbow joint. The first, which resembles a human arm, is a haptic mannequin device (HMD) that relies on the sense of touch. It is attached to a computer in the clinician's office. The second is a mechanical arm brace, called a wearable stretching device (WSD). The patient wears the WSD and can be at home or in some other location but must be near a computer that is connected to the Internet.

Patients who suffer from involuntary muscle spasms caused by neurological impairments are one group that could benefit from this robotic tele-rehabilitation system. Normally a clinician has to have physical contact with a patient to feel the muscles, diagnose problems, and provide physical therapy. But with the HMD-WSD setup, the clinician moves the HMD mechanical arm; a signal travels via the Internet to the patient; the WSD arm brace that the patient is wearing mimics the movement and stretches the muscles. The WSD records muscle resistance and relays the information back to the HMD so it moves and feels just like the patient's arm. The two devices talk to each other, sharing information instantaneously as if the patient and the clinician are sitting in the same room.

Clinical trials with the HMD-WSD system are expected to begin in the near future. After the system has been perfected, Park hopes to develop devices that focus on the knee, ankle, wrist, and shoulder.

Whether patients are being clinically managed or participating in clinical trials, "you could test people remotely all over the country and monitor them at home," said Damiano.

The robotic arm can also be used as a tool to standardize medical assessments and to train clinicians who want to improve their physical therapy skills. It is programmed using patient data and can provide realistic, consistent movements, including imitating spasticity (muscle stiffness) and contracture (a permanent shortening of the muscle).

Park and Damiano are also developing other robotic devices. Their robotic leg may help to eliminate crouch gait in children with cerebral palsy. Crouch gait causes a child's knees to flex and turn inward, makes walking difficult and exhausting, and often leads to the permanent use of a walking aid. The robotic device could improve leg strength and help children with cerebral palsy to stand more upright.

The researchers have also developed a self-paced treadmill that is helping patients who have suffered a TBI relearn how to walk. The machine allows patients to choose their speed via sensors that are attached to the body and linked to a computer program developed by FABS. The treadmill faces a large screen onto which a virtual world is projected. Patients walk through the mock terrain, turn corners, and even navigate crowded hallways, actions that can be difficult for someone who has suffered a TBI.

"If your brain is engaged, the response to training [is] greater," said Damiano. The system also "gives you practice in a more real-world setting."

Who knows what the NIH rehab robotics team will come up with next?

To learn more about FABS, visit http://clinicalcenter.nih.gov/rmd/fab. ●

We are always looking for interesting research stories for the Catalyst. If you have an idea, contact the managing editor, Laura S. Carter, at carterls@od.nih.gov.

THE SIG BEAT

NEWS FROM AND ABOUT THE NIH SCIENTIFIC INTEREST GROUPS

Nes SIG: Trans-NIH Health Disparities Research

The National Institute on Minority Health and Health Disparities has established this interest group to focus on health disparities research that uses biomedical, behavioral, and social sciences approaches to advance the knowledge base and the translation of research to improve health. Co-chairs are William Coleman and Francisco Sy. A series of seminars will take place on the last Thursday of each month, 2:30–4:00 p.m. To join the Listserve, visit healthdisparities@list.nih.gov.

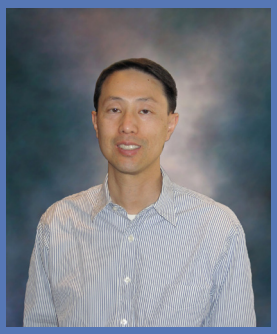
New SIG: Neuromuscular Diseases

This SIG provides a forum for networking and collaborative discussions among the research and clinical communities interested in neuromuscular diseases. Organized by a trans-NIH steering committee from NIA, NIAMS, NIEHS, NINDS, and the CC, this SIG will meet on the second Wednesday of every month from 3:30 p.m. to 5:00 p.m. Lectures and discussions will reflect emerging scientific and clinical issues including challenging research methodologies, new technologies, interventions, treatments, and training. For more information, contact Bryan Traynor (traynorb@mail.nih.gov) or Mary Kay Floeter (floeterm@ninds.nih.gov).

Rekindled and Retooled SIG: Nanotechnology

This SIG is reforming with a new moderator, Robert Blumenthal of the CCR Nanobiology Program at NCI-Frederick (blumenthalr@mail.nih.gov). Join the new Listserv by clicking on https://list.nih.gov/cgi-bin/wa.exe?SUBED1=nanosig-l&A=1.

Recently Tenured



CARSON CHOW, NIDDK

SERENA M. DUDEK, NIEHS

PATRICK E. DUFFY, NIAID

DANIEL FOWLER, NCI-CCR

KEVIN D. HALL, NIDDK

CARSON CHOW, PH.D., NIDDK

Senior Investigator, Laboratory of Biological Modeling

Education: University of Toronto, Toronto (B.A.S. in engineering science); Massachusetts Institute of Technology, Cambridge, Mass. (Ph.D. in physics)

Training: Department of Astrophysical, Planetary and Atmospheric Sciences at the University of Colorado, Boulder; Neuromuscular Research Center and the Department of Mathematics at Boston University

Before coming to NIH: Associate professor of mathematics and of neurobiology at the University of Pittsburgh

Came to NIH: In 2004

Selected professional activities: Action editor for *Journal of Computational Neuroscience*; associate editor for *Journal of Applied Mathematics*

Outside interests: Skiing, cycling, playing golf and tennis; spending time with daughter; blogging at http://sciencehouse.wordpress.com

Research interests: I am interested in mathematical and computational biology as applied to neuroscience, metabolism, obesity, gene regulation, and population genetics. I construct reduced models of complex systems that can be analyzed mathematically to answer specific questions. The interdisciplinary nature of my research involves collaborations with other labs at NIH. For example, with Kevin Hall (NIDDK), I used a simple model of human body weight change to show that the increase in the U.S. food supply over the past 30 years explains the obesity epidemic. With Stoney Simons (NIDDK), I used simple concepts from the mathematical theory of groups to make testable predictions for molecular mechanisms involved in steroid-mediated gene induction. In complex neural disorders such as autism, it is difficult to understand the connection between genotype and phenotype because genes act at the molecular level while disorders are manifested at the behavioral level. I will use computational models to analyze how molecular perturbations affect the operation of neural circuits, associate their behavior with symptoms, and collaborate with NIMH labs to obtain imaging data.

SERENA M. DUDEK, PH.D., NIEHS

Senior Investigator, Synaptic and Developmental Plasticity Group, Laboratory of Neurobiology

Education: University of California at Irvine (B.S. in biology); Brown University, Providence, R.I. (Ph.D. in neuroscience)

Training: Postdoctoral training in the Department of Neurobiology at the University of Alabama at Birmingham; Laboratory of Cellular and Synaptic Neurophysiology, NICHD

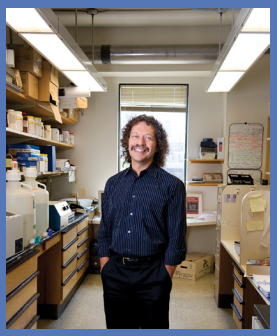
Came to NIH: In 1996 for training; appointed tenure-track investigator in 2001

Other professional activities: Edited book titled *Transcriptional Regulation by Neuronal Activity*; member of The Society for Neuroscience Program Committee

Outside interests: Volunteering as a paramedic; observing the neural development of her two-year-old daughter

Research interests: Our group studies the regulation of synaptic effectiveness and how synaptic changes early in development are consolidated to last a lifetime. During postnatal development, mammals, including humans, acquire vast amounts of information by interacting with their environments. In contrast to creatures with nervous systems that are fully prewired at birth, mammals benefit from an enormous flexibility in behavior because of the driving force of experience on their brain development. This flexibility comes at a potential cost, however, because interactions with noxious or abnormal environments can cause lasting and often deleterious changes in brain circuitry.

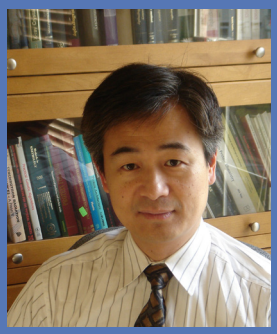
Using patch clamp and extracellular recordings in brain slices, confocal



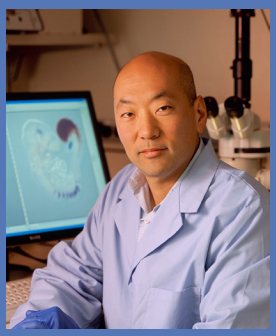
DAVID B. SACKS, CC

MARK STOPFER, NICHD

TERRY A. VAN DYKE, NCI-CCR



DI XIA, NCI-CCR



TERRY P. YAMAGUCHI, NCI-CCR

microscopic imaging, and molecular and cellular techniques, our group determines how the connections (synapses) in the brain change or are pruned in response to neuronal activity. Such pruning regulates the critical periods of postnatal development when plasticity (the ability of the brain to reorganize itself in response to the environment, experiences, and outside influences) is most robust, and our research gives clues as to why some brain regions are more plastic than others. Recently, our exploration of plasticity modulators has led us to some interesting discoveries in a previously unappreciated region of the brain, hippocampal area CA2, which we speculate could be important in several psychiatric disorders. By having a better understanding of how environmental factors play a role in forming the circuitry of the brain, we hope to address the associated problems of brain disease caused by toxicant exposure.

PATRICK E. DUFFY, M.D., NIAID

Senior Investigator; Chief, Laboratory of Malaria Immunology and Vaccinology

Education: United States Military Academy, West Point, N.Y. (B.S. in civil engineering with concentrations in English literature and basic sciences); Duke University School of Medicine, Durham, N.C. (M.D.)

Training: Residency in internal medicine at Walter Reed Army Medical Center (Washington, D.C.); medical research fellowship at Walter Reed Army Institute of Research; postdoctoral training in molecular parasitology malaria research at NIAID's Laboratory of Malaria Research

Before coming to NIH: Director of the malaria program at the Seattle Biomedical Research Institute and affiliate professor of global health at the University of Washington (Seattle); director of preclinical vaccine development for the malaria program at the Walter Reed Army Institute of Research

Came to NIH: In 1991 for training; in November 2009 returned as chief of the Laboratory of Malaria Immunology and Vaccinology

Selected professional activities: Long-standing organizer of the East African Regional Training Workshop series for young scientists working on protozoan pathogens; senior investigator for large longitudinal cohort studies in Tanzania and Mali

Outside interests: Jogging; traveling

Research interests: We conduct basic, translational, and clinical research to develop malaria vaccines. Malaria is caused by a parasite that is transmitted by mosquitoes to humans. We study malaria pathogenesis and immunity with a focus on pregnant women and infants. We performed

VICTOR ZHURKIN, NCI-CCR

seminal studies in Kenya that identified a distinct parasite phenotype that causes malaria in pregnant women. We are also investigating the pathogenesis of severe malaria in children.

Our central product development unit, which operates more like a small biotech firm than a typical research laboratory, makes prototype malaria vaccines. We also formulate antigens; develop assays and animal trials that define the potential for protection; and establish clinical trials to test vaccines in the United States and in the developing world.

We are developing two kinds of malaria vaccines: a pregnancy malaria vaccine (PMV) and a vaccine that interrupts malaria transmission (VIMT). The PMV blocks the surface proteins on infected red cells that the parasite uses to bind inside the placenta. The VIMT elicits immune responses

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Recently Tenured

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that destroy malaria parasites as they enter either the mosquito or the human host. Our lab's overarching goal is to protect children and pregnant women from malaria and to eliminate the disease from low-transmission areas of the world.

DANIEL FOWLER, M.D., NCI-CCR

Senior Investigator; Head, Cytokine Biology Section, Experimental Transplantation and Immunology Branch

Education: Kalamazoo College, Kalamazoo, Mich. (B.A. in health sciences); Wayne State University School of Medicine, Detroit (M.D.)

Training: Residency in internal medicine and pediatrics at Detroit Medical Center (Detroit); training in medical oncology at NCI

Came to NIH: In 1990 for training; became investigator in 1994; appointed tenure-track investigator in 1999

Selected professional activities: Member of the American Society of Blood and Marrow Transplantation and the American Society of Clinical Investigation

Outside interests: Parenting; playing sports; landscaping

Research interests: My research focuses on T-cell and T helper (Th) cell regulation after allogeneic (from different but matched donors) transplantation of stem cells. In animal models, we found that donor Th1 cells mediated graft-versus-host disease (GVHD), the main transplant complication, whereas Th2 cells inhibited GVHD. In 1999, in collaboration with the Department of Transfusion Medicine, I developed a method to produce human Th2 cells, filed an Investigational New Drug application with the FDA, and implemented a trial of Th2 cell therapy at the Clinical Center in NCI's Experimental Transplantation and Immunology Branch.

Recently, a student gave me a coffee mug depicting the mTOR (mammalian target of rapamycin) signaling pathway to symbolize my fixation on the immune suppression drug rapamycin. We found that Th2 cells develop resistance to rapamycin. In animal models, rapamycin-resistant Th2 cells prevented GVHD and graft rejection more effectively than did control Th2 cells.

In 2004, I initiated a second-generation clinical trial using rapamycin-resistant Th2 cells. Ongoing results indicate that such T-rapa cells safely prevent graft rejection in the "mini-transplant" setting (using low-intensity, outpatient-dose chemotherapy) and mediate graft-versus-tumor effects with reduced GVHD. In our current research, we seek to further define the role of Th1 and Th2 cell manipulation in transplantation therapy for cancer.

KEVIN D. HALL, PH.D., NIDDK

Senior Investigator, Laboratory of Biological Modeling

Education: McMaster University, Hamilton, Ont. (B.S. in physics); McGill University, Montreal (Ph.D. in physics)

Before coming to NIH: Scientist at Entelos Inc. (Menlo Park, Calif.)

Came to NIH: In 2003

Outside interests: Cycling; hiking; scuba diving; motorcycling; playing guitar

Research interests: My laboratory studies mammalian metabolism, body-weight regulation, and the physiological dysregulation that occurs in obesity, diabetes, anorexia, and cachexia (physical wasting and malnutrition associated with chronic disease). We study humans and rodents to better understand the complex mechanisms regulating macronutrient metabolism, body composition, and energy expenditure. We use mathematical models to quantitatively describe, explain, integrate, and predict our experimental results. We have created several models ranging from a single equation that describes the proportion of weight changes attributable to body fat to computational models representing the dynamics of whole body metabolism, including body composition change and metabolic fluxes. We are also developing new methods for measuring food-intake behavior over extended time periods as well as practical tools to help predict weight changes resulting from obesity interventions at the individual and population levels.

DAVID B. SACKS, M.B.CH.B., F.R.C.PATH., CC

Senior Investigator; Chief, Clinical Chemistry

Education: University of Cape Town, Cape Town, South Africa (M.B., Ch.B.)

Training: Residency in internal medicine at Georgetown University–affiliated hospitals (Washington, D.C.); residency in clinical pathology and fellowship training in clinical pathology and clinical chemistry at Washington University School of Medicine (St. Louis)

Before coming to NIH: Associate professor of pathology at Harvard Medical School (Boston); Medical Director of Clinical Chemistry and Director of the Clinical Pathology Training Program at Harvard's Brigham and Women's Hospital (Boston)

Came to NIH: In January 2011 as Chief of Clinical Chemistry

Outside interests: Listening to music; jogging; watching rugby

Research interests: We are investigating the derangements of calcium and calmodulin signaling in disease. Calmodulin is a ubiquitous, highly conserved protein that plays a critical role in many essential cellular functions. A considerable body of evidence implicates calcium and calmodulin in tumorigenesis. Several calmodulin targets, such as the estrogen

receptor (ER) and IQGAP1, contribute to tumorigenesis. We have shown that calmodulin binds to ER. This interaction both enhances the stability of ER and is required for ER-mediated transcriptional activity in the nucleus.

Calmodulin also regulates IQGAP1 function. IQGAP1 is a scaffolding protein that assembles multiprotein complexes and integrates signaling cascades. We showed that IQGAP1 binds the human epidermal growth factor receptor (HER2) and several components of the mitogen-activated protein kinase pathway. We identified several important functions of IQGAP1: It promotes cell motility, neurite outgrowth, and cell adhesion, and it participates in microbial pathogenesis. We documented that IQGAP1 enhances breast tumorigenesis. Overexpression of IQGAP1 is observed in several tumors; both calmodulin and IQGAP1 concentrations are increased in highly metastatic cells. We are elucidating the molecular mechanisms by which IQGAP1 integrates signaling pathways and promotes malignant transformation.

MARK STOPFER, PH.D., NICHD

Senior Investigator and Head, Unit on Sensory Coding and Neural Ensembles

Education: Yale University, New Haven, Conn. (B.S. in biology; M.S., M.Phil., and Ph.D. in psychology)

Training: California Institute of Technology (Pasadena, Calif.)

Before coming to NIH: Postdoctoral training at the California Institute of Technology

Came to NIH: In 2002

Outside interests: Playing guitar; feeding birds

Research interests: I'm interested in the brain mechanisms that gather and organize sensory information to build transient and sometimes enduring internal representations of the environment. Information does not flow passively from the outer environment through neural circuits, coming to rest as memories or actions. Rather, neural circuits process and dramatically transform information in myriad ways, providing multiple advantages to the animal. Using relatively simple animals, including Drosophila, our lab combines electrophysiological, anatomical, genetic, behavioral, computational, and other techniques to examine the ways that sensory stimuli drive neural circuits to process information. Recently, we've investigated several related questions: What mechanisms, including the transient oscillatory synchronization and slow temporal firing patterns of ensembles of neurons, underlie information coding and decoding? How are natural features of sensory stimuli extracted? How do sensory systems develop, how are innate sensory preferences determined, and how does innate information within the nervous system differ from learned information?

TERRY A. VAN DYKE, PH.D., NCI-CCR

Senior Investigator; Head, Cancer Pathways and Mechanisms; Director, Mouse Cancer Genetics Program; Director, Center for Advanced Preclinical Research

Education: University of Florida, Gainesville, Fla. (B.S. in interdisciplinary studies; Ph.D. in medical sciences)

Training: Postdoctoral training at the University of Florida, Stony Brook University (Stony Brook, N.Y.), and Princeton University (Princeton, N.J.)

Before coming to NIH: Professor, Department of Genetics and Biochemistry and Biophysics, University of North Carolina at Chapel Hill (Chapel Hill, N.C.)

Came to NIH: In September 2007

Outside interests: Walking in the woods and other natural areas; playing the clarinet; listening to music

Research interests: Our lab studies the mechanisms and pathways to cancer development at the genetic, molecular, cellular, and organ levels. Because cancer can develop in more than 100 mammalian cell types, and does so amidst complex cell-cell and cell-environment interactions, we have used genetically engineered mice (GEM) as the foundation for our analyses. We have established several preclinical cancer models that have facilitated analyses of the tumor suppressors p53, pRb, and PTEN, among others. Using GEM, we can do studies that are not possible in humans such as a detailed examination of the molecular and cellular events in developing tumors. We couple in vivo approaches with in vitro primary cell culture approaches to refine our discoveries.

Our projects have clarified aspects of cancer cell proliferation, apoptosis, and invasion. Studies are under way to define the chromosomal and gene-expression aberrations that characterize these events. We are also exploring the mechanisms of angiogenesis and invasiveness. We have developed preclinical models for cancers of the breast, prostate, ovary, and brain. These models are also being used to develop live-animal-imaging methodologies to characterize the disease process and monitor preclinical therapeutic testing. Thus, our lab uses a toolbox of modern technologies to approach the complexities of this aggressive and devastating disease.

DI XIA, PH.D., NCI-CCR

Senior Investigator; Head, Crystallography Section, Laboratory of Cell Biology

Education: Zhejiang University, Hangzhou, China (B.S. in chemistry); Purdue University, West Lafayette, Ind. (Ph.D. in structural biology)

CONTINUED ON PAGE 18

Recently Tenured

CONTINUED FROM PAGE 17

Training: Postdoctoral training in membrane protein structural biology at the University of Texas, Southwestern Medical Center at Dallas (Dallas)
Before coming to NIH: Assistant lecturer, Department of Biochemistry, University of Texas, Southwestern Medical Center at Dallas
Came to NIH: In 1998
Outside interests: Spending time with wife and son; reading

Research interests: Our lab studies membrane proteins, their atomic structure, and their role in multidrug resistance. Membrane proteins are important for cell-cell communication, recognition, adhesion, and membrane fusion; material exchange, transportation, and detoxification; and cellular energy conservation.

In this era of structural genomics, we have determined the three-dimensional structure of many proteins. But in spite of intense efforts, scientists have so far been able to decipher the structure of only a few membrane proteins. We use molecular, biological, and crystallographic methods to obtain atomic resolution structures of a few selected families of membrane proteins in order to understand how they function. But it's often difficult to purify large enough quantities of these proteins to yield an adequate number of crystals for analysis.

We are particularly interested in various membrane transporters that play important roles in drug resistance and in pumping protons. We are studying membrane transport proteins called ABC transporters (for ATP-binding cassette transporters). Our studies have helped to elucidate mechanisms of functions at near-atomic resolution of these membrane transporters and provided structural information essential for understanding the interactions of these proteins with various drugs.

TERRY P. YAMAGUCHI, PH.D., NCI-CCR

Senior Investigator; Head, Cell Signaling and Vertebrate Development Section

Education: University of Toronto, Toronto (B.Sc. in pharmacology and physiology; M.Sc. in anatomy and cell biology; Ph.D. in molecular and medical genetics)
Training: Postdoctoral fellow at Harvard University (Cambridge, Mass.)
Came to NIH: In 2000
Outside interests: Organizing, playing, and coaching ice hockey; playing volleyball; running; playing keyboards and guitar; entertaining son and daughter

Research interests: Our lab studies Wnt proteins, which are powerful signaling molecules that control the growth, differentiation, and movement of embryonic and adult stem cells. Genetic mutations in Wnt signaling pathways can lead to unrestrained signaling and cancer. We are particularly interested in the molecular mechanisms of Wnt signaling during development and its implications for diseases such as cancer. We have uncovered the genetic regulatory networks that control the formation of multipotent mesoderm progenitors during gastrulation, an early phase in embryonic development. The mesoderm—the middle layer of an embryo's three germ layers that form during gastrulation—undergoes an epithelial-to-mesenchymal transition (EMT) as it differentiates into connective tissue, bone and cartilage, muscle, blood and blood vessels, and other organs. We have identified Wnt-dependent transcription factors that control EMT as well as the specification and maturation of mesodermal progenitors. Because Wnt signals and EMT play critical roles in tumorigenesis and metastasis, future studies will address the role that embryonic Wnt target genes play in adult tumors caused by disregulated Wnt signaling.

VICTOR ZHURKIN, PH.D., NCI-CCR

Senior Investigator; Head, DNA and Nucleoproteins Section, Laboratory of Cell Biology

Education: Lomonosov Moscow State University, Moscow (M.S. in applied mathematics); Moscow Physical-Technical Institute, Moscow (Ph.D. in molecular biophysics); Lomonosov Moscow State University (D.Sc., in molecular biophysics)
Training: Postdoctoral training at Engelhardt Institute of Molecular Biology (Moscow)
Came to NIH: In 1989

Research Interests: We are interested in the structural aspects of protein-DNA interactions in chromatin, where DNA is accessible to the transcription factors. One such factor is the p53 protein, which mediates the transcription of hundreds of human genes and plays an important role as a tumor suppressor in human cancers.

We found that p53 can bind to its response element when it is properly exposed in the nucleosome (DNA sequence wrapped around a core of proteins called histones). The physiological importance of this result is best illustrated by comparing p53's high affinity to the response elements associated with cell-cycle arrest (CCA sites) with its low affinity to the sites associated with apoptosis (Apo sites). We predicted and found that the CCA sites are likely to be exposed on the nucleosome surface. In contrast, the Apo sites are often hidden inside. The difference may be key to p53-DNA binding and the kinetics of transactivation of the corresponding genes.

In the near future, we will consider other genes that are characterized by various kinetics of p53-induced activation. The results of bioinformatic analysis should give us a better understanding of the relationships between the mechanisms of gene regulation and the genomic environment of the p53 sites.

VILCEK FOUNDATION PRIZE FOR CREATIVE PROMISE IN BIOMEDICAL SCIENCE

Application deadline: August 14, 2011

The Vilcek Foundation will award a prize of $25,000 to a young, foreign-born scientist who demonstrates outstanding early achievement in the field of biomedical research. Graduate students and postdoctoral fellows working under the supervision of a mentor are not eligible. For more information and an online application visit http://www.vilcek.org/prizes/creative-promise/biomedical-science/index.html.

NIH GRADUATE AND PROFESSIONAL SCHOOL FAIR

Friday, July 22, 2011

9:00 a.m.–3:30 p.m.

Natcher Conference Center (Building 45)

Lister Hill Auditorium (Building 38A)

NIH summer interns, NIH postbacs, and college and university students from the Washington, D.C., area can explore programs leading to graduate and professional degrees. More than 100 colleges and universities will be represented. The fair includes workshops on making successful transitions and interviewing; and panels on getting to graduate and professional school, and careers in public health, pharmacy, and psychology. For a list of participating institutions and to register visit https://www.training.nih.gov/gp_fair.

THE SCIENCE OF COMPASSION: FUTURE DIRECTIONS IN END-OF-LIFE AND PALLIATIVE CARE

August 10–12, 2011

Hyatt Regency, Bethesda, Md.

This summit will bring together scientists, researchers, health professionals, educators, policy makers, members of professional organizations, and individuals with life-limiting illnesses as well as their caregivers. The event begins Wednesday evening, August 10 (7:00–9:00 p.m.), with "The Ethics of Science at the End-of-Life: A Town Hall Discussion," moderated by Susan Dentzer, editor-in-chief of *Health Affairs*. Leading experts in science, medicine, and bioethics will converse with the public on bioethical issues faced in both end-of-life research and in practice. The summit will continue on August 11–12, with a keynote presentation by Ira Byock (long-time palliative care physician and advocate for improved end-of-life care), three plenary discussions, and breakout sessions. To register and for more information, visit: http://www.ninr.nih.gov/ResearchAndFunding/scienceofcompassion.html.

GENOMICS: GENE DISCOVERY AND CLINICAL APPLICATIONS FOR CARDIOVASCULAR, LUNG, AND BLOOD DISEASES

September 12–13, 2011

Natcher Conference Center (Building 45)

Deadline for abstracts: August 1

Online registration closes on September 1

This NHLBI symposium will highlight research and recent discoveries including results from large-scale collaborative studies, analysis techniques, directions in functional genomics, and translational research. Researchers in molecular biology and molecular genomics, bioinformatics, and genetic epidemiology, as well as physicians specializing in heart, lung, and blood diseases, will discuss emerging science and translation to the clinic. For more information, visit http://www.nhlbi.nih.gov/meetings/Genomics/index.htm.

TOXICOGENOMICS INTEGRATED WITH ENVIRONMENTAL SCIENCES CONFERENCE

September 15–16, 2011

University of North Carolina, Chapel Hill, N.C.

William and Ida Friday Center

Free for NIH staff

Early (discount) registration ends July 31

NIEHS, FDA, and other organizations are sponsoring an international meeting that will focus on how bioinformatics and emerging technologies help researchers better understand the environmental influences behind the development and progression of human disease. To register and for more information, visit http://eseconf.sph.unc.edu/TIES2011.

PIONEER AWARD SYMPOSIUM

September 20–21, 2011

Doubletree Bethesda Hotel

8120 Wisconsin Avenue, Bethesda

Free and open to all; no registration required

The symposium will feature presentations by the 2006 "graduating class" of Pioneer Award recipients; talks by selected recipients of the NIH Director's New Innovator Award; and poster sessions by Pioneer and New Innovator awardees. For an agenda and more information, visit http://commonfund.nih.gov/pioneer/Symposium2011; send questions to pioneer@nih.gov.

CANCER IMMUNOLOGY AND IMMUNOTHERAPY: BUILDING ON SUCCESS

September 22–23, 2011

Masur and Lipsett auditoriums (Building 10)

Deadline for Abstracts: August 1

Registration: Free; limited so register early

This NCI-sponsored conference will host leaders in cancer immunology and immunotherapy. Learn about the latest findings in T-cell transfer immunotherapy, immunotherapy based on genetic engineering of lymphocytes, vaccine-based therapies, transplantation-based therapies, and immune-modulatory approaches. For more information and to register, visit http://web.ncifcrf.gov/events/Immunotherapy2011.

NCI'S NEURO-ONCOLOGY BRANCH CELEBRATES 10-YEAR ANNIVERSARY

The Neuro-Oncology Branch's Brain Tumor Clinic brings advances in science and clinical medicine together. Bioinformaticians, statisticians, molecular biologists, oncologists, radiologists, and nurses work together to better understand and treat brain tumors. Patients receive access to new therapies and procedures that are often unavailable elsewhere. To learn more, visit http://home.ccr.cancer.gov/nob.

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Building 1, Room 333
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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) or 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 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:

- OBESITY RESEARCH
- CONFESSIONS
- NIH IN HISTORY

LABORATORY CONFESSIONS

(Was) The Sign of the Times?

BY NAME WITHHELD

I am a vigilante sign remover. I have just come back from removing "Wet Paint" signs that were in the hallway for a week. Does paint really take a week to dry?

I am not anti-sign. Proper signage can protect you from exposure to biohazards and radiation and from getting paint on your new shirt. I am against people who never take down their outdated signs.

As a result of this tardiness, we become desensitized to signs and assume many no longer apply. Like the signs listing a phone number to call for service—with just seven digits? Yeah, I'm sure that number works; just show me to the rotary phone. Tell me, if a busy postdoc walks right by the big red sign that reads "Warning: Alpha-male mice competing for supremacy!" and is suddenly beset by furious, squealing rodents hurling themselves through the air, who really is to blame? I'll tell you who: It's the idiot who never removes those "kittens for sale" sign despite the fact that the cats are now fully grown.

If I can't verify that a sign no longer applies, I leave it up. But I will confess that I took a leap of faith with one sign on a glass door that read, "Warning Emergency Exit Only Alarm Will Sound." Come on, I said to myself. There's a path beaten through the grass on the other side. Clearly this is a major shortcut for people.

I indeed verified that no alarm sounded when I opened the door. But I can't bring myself to scrape the sign off the glass. I should call the proper authorities, however tempted I am to just paint over it with a new sign about kittens and see whether anyone notices.

EDITOR'S NOTE: HAVE A LATE-NIGHT LABORATORY CONFESSION? WE MIGHT PRINT IT IF IT IS INDECENT ENOUGH.

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH.

Address correspondence to:
Building 1, Room 333, NIH
Bethesda, MD 20892
Ph: 301-402-1449
Fax: 301-402-4303
e-mail: catalyst@nih.gov

Catalyst online:
http://www.nih.gov/catalyst

PUBLISHER
MICHAEL GOTTESMAN
Deputy Director for Intramural Research, OD

EDITORS
JOHN I. GALLIN
Director, NIH Clinical Center
HENRY METZGER
Scientist Emeritus

MANAGING EDITOR
LAURA STEPHENSON CARTER

WRITER-EDITOR
CHRISTOPHER WANJEK
Director of Communications, OIR

COPY EDITOR
SHAUNA ROBERTS

CONTRIBUTING WRITERS
ANDY BAXEVANIS
STEPHANIE BONHOMME
CAROLYN GRAYBEAL
SARAH HERRMANN
SHARON MILGRAM
BRAD MOSS
SARAH RHODES
CHRISTOPHER WANJEK
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