Fostering Communication and Collaboration

The NIH Catalyst

A Publication for NIH Intramural Scientists

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Obesity: Inside and Out

MRI probes uncharted territory for the obesity-disease connection

By Christopher Wanjek

Obesity has its obvious manifestations; it's a disease that is difficult to conceal. Yet less obvious is precisely how obesity can lead to other more debilitating and potentially deadly diseases, such as diabetes, cardiovascular disease, and cancer.

The answer, if only one could probe thoroughly and noninvasively, lies far below the surface in the amount, location, and type of fat.

Now, NIH researchers are pooling their expertise in metabolism, endocrinology, medical imaging, and physics for a series of clinical protocols to more fully understand the phenotypes of obese and overweight adults and their connection to disease. The protocols include an innovative imaging component that uses a new 3-tesla (3T) magnetic resonance imaging (MRI) machine—one of only a few in use in the world—in the NIH Clinical Center (CC)

(Left to right) Ronald Ouwerkerk, Ahmed Gharib, and Khaled Z. Abd-Elmoniem tweak the controls of the new Siemens MAGNETOM Verio 3T MRI to capture images of an obese patient's liver.

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Of Biobanks and Biospecimens

By Eric Schaffer

After more than a century of dedicated biomedical research, the National Institutes of Health is starting to make real strides in understanding and preventing an issue that affects all parts of the health sciences: freezer burn. Not to say that the peas in your Frigidaire are still going to be good in 10 years, but there's hope that the tissue samples we're freezing today will be contributing to research for years to come.

Understanding the impact of freezer burn on a biospecimen is a tiny but necessary step toward the establishment of a national biobank, a project that could put high-quality, well-characterized, standardized human cancer biospecimens within easy reach of researchers all over the country and all over campus. The project is headed by the National Cancer Institute (NCI) Office of Biorepositories and Biospecimens Research (OBBR), which plans to take the first steps toward collecting specimens for the Cancer Human Biobank (caHUB) in the beginning of 2010.

Some biospecimens are transported and stored in glass tubes.

"The biospecimen is the fuel for translational research that is taking us towards a new era of molecular medicine," said OBBR Director Carolyn Compton. Compton's efforts have not only shaped the national biobank project, but have also helped spark the biospecimens fever that's sweeping the campus.

Yaffa Rubenstein, program director at the Office of Rare Diseases Research (ORDR), was quick to point out that it's not just cancer biospecimens that are being pooled and cataloged. The ORDR is developing resources that will provide access to information about biospecimens representing diseases all across the board.

And repositories all over campus, from those in individual labs to institute-level biobanks are beginning to reorganize and prune their collections, with the hope of creating wide networks of biospecimens resources.

The caHUB traces its roots to a 2002 conference sponsored by the National Dialogue on Cancer (now known as C-Change), at which experts from all aspects of the fight against cancer identified their number one obstacle: the lack of appropriately collected and annotated human tissue for translational research.

The problem these experts saw wasn't a scarcity of tissue—institutions all over the country have decades-old repositories with hundreds of millions of specimens available. The problem was, and still is, that these repositories contain tissues that have been

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From the Deputy Director for Intramural Research

New NIH Scientific Resources

Michael Gottesman

Christopher Austin

Gary Griffiths

Most NIH intramural scientists know where to go if they have an idea for a new clinical protocol, need DNA sequenced, or want to find an article in an obscure journal. But what do you do if you have to synthesize a novel radioactive molecular-imaging probe or its precursor, need a fluorescent ligand for imaging a specific cell type in an animal or human subject, want to screen for new chemical compounds that interact with a cellular target you have identified, or need to identify potential cellular targets using a genome-wide RNAi library? There are new technologies that can accelerate scientific discovery, and they are now available to all intramural scientists.

For the past five years, the trans-NIH Roadmap for Medical Research initiative (http://nihroadmap.nih.gov) has supported the establishment of two centers: an NIH Chemical Genomics Center (NCGC) in the National Human Genome Research Institute (NHGRI) and an Imaging Probe Development Center (IPDC) in the National Heart, Lung, and Blood Institute (NHLBI). These programs provide outstanding, state-of-the-art facilities and are already producing publishable results.

Both centers are highly subscribed and have scientific review committees that consider proposals from all intramural scientists. We'd like to share with you some highlights and recent developments.

NIH Chemical Genomics Center

The NCGC is an ultrahigh-throughput screening and chemistry center that develops chemical probes for use in the study of protein and cell functions or of biological processes relevant to physiology and disease or as starting points for creating new therapeutics for rare and neglected diseases. The NCGC collaborates with more than 100 investigators from academic, foundation, and biopharmaceutical laboratories throughout the world, and it uses its quantitative high-throughput screening paradigm and cheminformatics and medicinal chemistry platforms to produce new insights into chemical biology and general principles of chemical interactions with living systems.

Recent successes have included identification of new compounds for the treatment of the parasitic disease schistosomiasis, in collaboration with David Williams at Illinois State University in Normal, Ill. (*Nat Med* **14**:407–412, 2008); identification of the first thyroid-stimulating hormone receptor (TSHR) agonists for potential use in thyroid cancer, in collaboration with Marvin Gershengorn at the National Institute of Diabetes and Digestive and Kidney Diseases (*PNAS* **106:**12471–12476, 2009); and genetic mapping of targets mediating differential chemical phenotypes of malaria, in collaboration with Xin-zhuan Su at the National Institute of Allergy and Infectious Diseases (*Nat Chem Biol* **5:**765–771, 2009).

More recently, the NCGC, with the support of several scientific directors, has initiated a high-throughput RNAi facility that will be available to all NIH intramural scientists. The facility's primary sponsor is the National Cancer Institute, which has a substantial need for genome-wide RNAi screens to identify new targets for cancer therapy. Other sponsors are the Office of Intramural Research and several other institutes.

Resources will be available to intramural scientists on a competitive basis. Proposals will be reviewed by a committee of intramural scientists and NIH leadership. While the RNAi genome-wide screening capacity will not be fully operational for another 6 to 12 months, smaller pilot projects can be considered. The RNAi team is also glad to advise intramural researchers on developing assays that would be amenable to large-scale RNAi screening. Interested researchers should contact Scott Martin at the NCGC (martinsc@mail.nih.gov).

Investigators who are interested in working with other NCGC resources should contact Christopher Austin (austinc@mail.nih.gov) or Jim Inglese (jinglese@mail.nih.gov). For more information on the NCGC, visit http://www.ncgc.nih.gov.

Imaging Probe Development Center

The IPDC's goal is to synthesize novel compounds—and ones already reported in the literature—that would otherwise not be available to intramural scientists for use in molecular-imaging research. The IPDC complements the work of the NCGC as well as diverse NIH programs in imaging, nanotechnology, and basic and translational research and encompasses a receptor modeling–biophysical chemistry resource and an organic synthesis facility. More than 80 NIH scientists have spoken to the IPDC about the availability or production of molecular-imaging probes or their synthetic precursors, and 49 projects have been approved by the IPDC steering committee. So far, approximately 100 probe compositions of widely different types and complexity have been prepared and distributed.

Formal or informal inquiries for the preparation of new probes are welcomed. For more information, contact Gary Griffiths (griffithsgl@nhlbi.nih.gov) or go to the IPDC website (http://www.ipdc.nih.gov), which lists projects already undertaken, details of several dozen completed syntheses, and a description of IPDC activities and capabilities. ■

—Michael Gottesman, DDIR
—Christopher Austin, Director, NCGC, NHGRI
—Gary Griffiths, Director, IPDC, NHLBI

NIH-Wide PI Recruitment

The NIH Intramural Research Program has launched a first-of-its-kind NIH-wide recruitment for principal investigators (PIs). This new recruitment method offers job seekers the chance to give us their best shot, rather than tailor their research proposals to match an ad. We are seeking the best laboratory-, clinic-, or population-based researchers.

Selectees for these PI positions will be designated "Earl Stadtman Investigators." Stadtman, one of the great biochemists of the 20th century, joined NIH in 1950 in what was then called the National Heart Institute and, for the next 50 years, conducted groundbreaking research in fields as diverse as free-radical oxidation and metabolism of fatty acids and amino acids.

This recruitment effort represents unprecedented cooperation among NIH institutes and centers. Applications will be distributed to committees of NIH experts in various research areas. The top applications will be forwarded to the intramural scientific directors and chairs of standing search committees, culminating in a seminar series early next year featuring the finalists. We expect to hire about 10 PIs, most of whom will be tenure-track investigators.

Courtesy: Office of History, NIH

Earl Stadtman (1952)

Formal advertisement began in September with a closing date in November. Stadtman was a mentor to multiple Nobel Laureates and members of the National Academy of Sciences. We hope that the Stadtman Investigators will carry on his fine tradition.

For more information on this and other NIH intramural research positions, see the NIH Science Jobs link at http://www.training.nih.gov. For information on Earl Stadtman, visit the online exhibit on him and his wife, Thressa Stadtman, an accomplished NIH biochemist, at http://history.nih.gov/exhibits/stadtman. ■

—Roland Owens,
Office of Intramural Research

Catalytic Research:

Research Briefs

CC, NCI, and NHGRI: Microbiome

Using modern DNA sequencing technology and computational analysis, NIH researchers uncovered a more diverse collection of microbes on human skin than had been detected by traditional methods of growing microbial samples in the laboratory. The research, which lays a foundation for treating and preventing skin disease, also generated information that may prove useful in efforts to combat the growing problem of methicillin-resistant *Staphylococcus aureus* (MRSA), a bacterium that can cause serious, even life-threatening, infections. NIH recently launched the Human Microbiome Project, a part of the NIH Roadmap for Medical Research, to discover what microbial communities exist in different parts of the human body and to explore how these communities change with disease. [*Science* **29:**1190–1192 , 2009]

NEI, NICHD, NIAAA: Macular Degeneration

As is well known, a diet high in omega-3 fatty acids can protect against diseases such as atherosclerosis and Alzheimer's disease. Now, according to a study conducted by NIH scientists, such a diet may also help prevent age-related macular degeneration (AMD), one of the leading causes of blindness among the elderly. The researchers found that a diet enriched in omega-3 fatty acids can ameliorate the progression of retinal lesions in a mouse model that develops AMD-like retinal lesions. In further studies, the investigators plan to evaluate other therapies and will be testing pharmacochaperones and antioxidative molecules, as well as intraocularly delivered gene therapies. [*Am J Pathol* **175:**799–807, 2009]

NIAAA: Chronic Stress

Decision-making strategies can either be goal-directed—making decisions deliberately based on their consequences—or habitual. Chronic stress can affect decision-making and, through the release of corticosteroids, may even alter brain neural circuits. But it's not known whether chronic stress influences the selection of decision-making strategies. NIH scientists found that rats exposed to chronic unpredictable stress quickly went from making goal-oriented decisions to using habitual strategies when performing lever-pressing exercises. The shift in behavior corresponded to a rewiring of the associative and sensorimotor corticostriatal circuits in the brain. "This insensitivity did not arise from an inability of the stressed animals to learn the relation between the action and the outcome or from changes in motivation, food valuation, or hedonics, but rather because stressed animals rapidly shift to a habitual strategy as training progresses," the researchers reported. [*Science* **325:**621–625, 2009]

NINR: Inflammatory Pain

Tissue injury initiates a cascade of inflammatory mediators and hyperalgesic substances including prostaglandins, cytokines, and chemokines. NINR investigators used microarray and gene-expression analyses to evaluate changes in gene expression of several cytokines following acute inflammation after oral surgery. They also assessed the correlation between the changes in the gene expression level and pain intensity. The study demonstrated that the upregulation of expression of the genes for interleukin-6, interleukin-8, and chemokine ligand–2 contributes to the development of acute inflammation and inflammatory pain. [*Pain* **142:**275–283, 2009]

NIDA: Nicotine Dependence

Changes in single units of DNA, called single-nucleotide polymorphisms (SNPs), may be associated with vulnerability to nicotine dependence. NIDA researchers performed genome-wide association studies—rapidly scanning markers across complete sets of DNA of many people to find genetic variations associated with a particular disease or condition—to look for SNPs from 480 people who had never smoked, had smoked for a long time, or had quit. Of 289 genes with SNPs that varied significantly between current smokers and people who had never been dependent on nicotine, 30 overlapped with those identified in earlier smoking cessation clinical trials; of 67 genes with SNPs that varied significantly between current smokers and people who had quit, five overlapped with those identified in the earlier trials. Many of the overlapping genes help determine plasticity of neuronal connections. Some may contribute to the role memory plays in addiction and may be potential targets for the development of new antismoking drugs. [*Mol Med* **15**:21–27, 2009]

KEY

CC:	Clinical Center
NCI:	National Cancer Institute
NEI:	National Eye Institute
NHGRI:	National Human Genome Research Institute
NIAAA:	National Inst. on Alcohol Abuse and Alcoholism
NICHD:	Nat. Inst. of Child Health and Human Development
NIDA:	National Institute on Drug Abuse
NINR:	National Institute of Nursing Research

The Training Page

From the Office of Intramural Training and Education: OITE Services for Fellows

By Sharon Milgram, Director of OITE, and Lori Conlan, Director of Postdoctoral Services

The Office of Intramural Training and Education (OITE) sponsors many career-development programs to support trainees during their stay at NIH. We offer writing courses, job-search workshops, resources for international fellows to develop English language skills, a series on the graduate and professional school application process for postbacs, and more.

Our first objective is to help trainees acclimate quickly to NIH. We publish an online moving guide and encourage everyone to direct new fellows to this valuable resource. We produce trainee handbooks—specific ones for summer interns, postbacs, graduate students, and postdoctoral fellows—that can also be found online. We hold orientations at which we highlight the research enterprise at NIH, institute and trans-NIH resources, and OITE workshops and career-development activities. Orientations are held the first Tuesday of every month for graduate students and postdoctoral fellows, every other month for postbacs, and in June and July for summer interns.

Career Counseling: OITE Career Services Center counselors and a premedical/pregraduate advisor can help trainees expand their networks, provide mock interviews, and review CVs, resumes, and cover letters. Fellows may also take free online career and work-style assessments and work with counselors to develop interpersonal and leadership skills. We encourage fellows to work with their supervisors, too, to develop plans for career success.

Communications Resources: The ability to communicate effectively, both orally and in writing, is essential. We have expanded our writing program to include four-week courses in "Basic Science Writing" and "Writing and Publishing a Scientific Paper." "Basic Science Writing"—designed for postbacs, graduate students, and postdoctoral fellows—focuses on grammar, sentence structure, punctuation, organization of ideas, and coherent writing. The "Writing and Publishing a Scientific Paper" course—for postdocs and graduate students who have sufficient data to write a rough draft of a manuscript—teaches trainees how to write abstracts and other manuscript sections, construct figures and tables, and understand the publication process.

Visiting Fellows: The "Improving Spoken English" workshop covers scientific vocabulary, diction, voice production, tempo, and general guidelines for speaking to native English speakers. For more practice, participants may register for small-group sessions, take part in brown-bag lunches for informal discussions, or sign up for language tutoring.

These opportunities are just a sampling of our services. Some programs are videocast. We can also visit satellite campuses as well as lead workshops in specific institutes, branches, or labs. For more information, visit http://www.training.nih.gov. ■

From the Fellows Committee: NIH Celebrates First Annual Postdoc Appreciation Day

By Dean Frohlich, National Center for Complementary and Alternative Medicine

Postdoctoral and clinical fellows at NIH and across the United States celebrated the first annual National Postdoc Appreciation Day on Thursday, September 24, 2009. The day, spearheaded by the National Postdoctoral Association, recognized fellows all over the country for their contributions to the U.S. scientific research enterprise.

Festivities at the NIH main campus took place on the lawn in front of the James Shannon Building (Building 1). Institute training directors handed out free ice pops; the Jazz Genome Project played live music; and some 300 fellows chatted with each other and with NIH Director Francis Collins and Deputy Director Raynard Kington. Collins and Kington even joined in for the group photo that was taken on the steps of Building 1.

Fellows also cast ballots for a favorite charity—their choices were National Postdoc Association, NIH Children's Inn, and the "I Have a Dream" Foundation—to determine which would be awarded a $500 donation by the Office of Intramural Training and Education (OITE). The "I Have a Dream Foundation" got the most votes, but the NIH Children's Inn was a winner, too. They were awarded the excess ice pops.

In addition, the "I Am Intramural" campaign representatives encouraged fellows to write—on Post-It notes that were then taped to a poster—their thoughts on why being a part of the intramural program is important to them. And the National Postdoctoral Association, the NIH Fellows Committee (FelCom), and OITE had booths that distributed information about their activities and services for fellows.

Bethesda wasn't the only NIH campus where fellows celebrated. Festivities were also held at the Twinbrook and Frederick campuses in Maryland, the National Institute of Environmental Health Sciences in North Carolina, and the Rocky Mountain Laboratories in Montana. All the group photos will be made into a collage and presented to Collins as a gift from the fellows.

For more information about FelCom, visit http://felcom.od.nih.gov. ■

Lab Offenses Call for Food

By Howard A. Young, National Cancer Institute

Maintaining positive interactions among personnel is crucial to managing a laboratory. As laboratories become more crowded, personality conflicts inevitably arise, and when they do, the entire staff may suffer from increased stress and tension. Here, I report on a unique method—the Food Offense—for reducing stress. My laboratory has used this method for many years to successfully defuse stressful situations.

A Food Offense occurs when the actions of one laboratory member disrupt the work of other members. Although there may be lively debate, a majority vote in the lab is sufficient to declare a Food Offense. The offender is given two options:

1. Start looking for another job.
2. Bring in food for the lab. (Homemade food, preferably containing chocolate, is desirable but not absolutely required; healthy foods may qualify but only if they taste like something fattening.)

Offenders typically choose Option #2.

Examples of Food Offenses are:

1. Leaving so much data on a computer associated with core equipment that others can't save or retrieve their data

2. Putting zebrafish in the wrong fish tank and not telling anybody

3. Borrowing an antibody from a neighboring lab and forgetting to return or replace it

4. Telling someone an antibody is labeled with one kind of fluorochrome when it is actually labeled with another

5. Giving someone a cell line that you know is contaminated with Mycoplasma and not telling them

6. Agreeing to review a paper and then forgetting to do it unless reminded four times

7. Hogging the only lab Matlab license so no one else can use it

8. Booking an instrument and then not using it, or using it at a different time

9. Leaving microscopes and fluorescent laser bulbs on overnight so they burn out and no one else can use the equipment

10. Turning off the gel electrophoresis power to remove your gel, then not turning the power back on so your lab mates' gels don't complete their process

11. Using gels that someone else made up (specifically for their rushed experiment) because you are too busy to make your own

12. Not training new staff in equipment usage (such as not warning folks that the ultraviolet rays from the X-ray and photography equipment can cause second-degree burns!)

13. Not properly sealing lids to reagents (so powders and liquids go flying if someone else knocks over the container)

14. Using up the last of the Taq DNA polymerase so that the next person realizes it only after they have already added everything else to their reaction

15. Leaving just a little reagent, not enough for anyone else to use, but just enough to be able to say, "There was some left in the bottle"

16. Not properly rinsing your dirty beakers and instead tossing them into the wash basin for the next person to clean

17. Forgetting to empty the autoclave once the old bacterial cultures have been sterilized

18. Not logging out after using a shared computer

19. Leaving your timer beeping for 10 minutes, annoying the entire lab

20. Borrowing all the shared Sharpies and pens and forgetting to return them

22. Not reporting (or repairing) malfunctioning or broken equipment

23. Mislabeling common reagents

24. Not refilling pipettes, culture flasks, or other items in a core area when you use the last item, especially on Friday afternoon

25. Leaving an overstuffed waste container for the next person to empty, especially on Friday afternoon

The *NIH Catalyst* invites readers to send in other examples of Food Offenses (see back page for contact details). We will publish them in a future issue. ■

The above is an update of Howard Young's article published in the September-October 2004 issue of The NIH Catalyst. *Other contributors: Vania Cao, Susan Chacko, Stephanie Cooperstein, Angel Davey, Erika Ginsburg, Natalie Goldberger, Marsha Lucas, Erin Luetkemeier, Vanessa McMains, and Jody White.*

The Offering . . .

- Homemade food, preferably containing chocolate, is desirable but not absolutely required.
- Certain foods, such as Vegemite from Australia or gefilte fish, do not satisfy a food offense.
- Healthy foods may qualify but only if they taste like something fattening.
- Trying a recipe for the first time should generally be avoided unless you are absolutely sure it is wonderful.

And Furthermore . . .

- New students are exempt for the first two weeks in the lab because they are generally expected to mess something up.
- Food offenses apply only to incidents in which other lab members are affected. If you use up the isotope, but no one else in the lab uses it, that is not a food offense.
- No one is exempt from food offenses, including the head of the lab.
- Poverty cannot be claimed as a reason to avoid providing food; a dozen doughnuts will not break anyone.
- The person who commits the food offense is allowed to partake in the eating; in fact, one might well be wary of food that is avoided by the individual who provided it.
- One cannot prepay food offenses; however any food brought for the lab is always welcome.
- If the food offense payment is really bad, the individual committing the food offense should be required to try again.

I wish to acknowledge all the past and present members of my laboratory who have cooperated fully with me in reducing stress and tension in the lab. However, I cannot imagine I could ever have committed any of the food offenses with which I have been charged.

—*HY*

NIH Scientists Conquer New Genetic Immune Disorder in Children

By Erin Luetkemeier, National Human Genome Research Institute

NIH researchers have discovered—and conquered—a rare autoinflammatory syndrome that often claims the lives of children who are stricken with this devastating genetic disorder.

The previously unrecognized syndrome, which the scientists named DIRA (deficiency of the interleukin-1 receptor antagonist), is characterized by inflammatory lesions of the skin, bones, and sometimes lungs and blood vessels. Bone tissues swell. Bones become deformed and painful. And a blistery rash spreads across the child's body. Symptoms typically begin within two weeks after birth.

But thanks to a multi-institute and international team led by Raphaela Goldbach-Mansky at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the underlying genetic mutation has been identified, and so has a successful treatment. The findings were published in the *New England Journal of Medicine* (*NEJM* **360:**2426–2437, 2009).

The nine children in the study—from Newfoundland, the Netherlands, Lebanon, and northwestern Puerto Rico—had inherited mutations in IL1RN, a gene that encodes for the protein interleukin-1 receptor antagonist (IL-1Ra), which inhibits the inflammatory protein interleukin-1 (IL-1).

Michael Spencer

Raphaela Goldbach-Mansky (right) and her team at NIAMS have recently identified a new autoinflammatory disease known as DIRA (deficiency of the interleukin-1 receptor antagonist), for which this little boy has been undergoing treatment in a research protocol at NIH's Clinical Center.

Generally these mutations are rare and appear in very low frequencies in the average population. But in northwest Puerto Rico about 2.5 percent of the population are carriers, and the mutation may be present in about 1 in 6,300 births. DIRA is recessively inherited, which means that a child must have two copies of the defective gene in order for DIRA to appear.

Treatment: The six patients who were alive at the time of diagnoses were started on daily injections of anakinra, a drug that is a synthetic form of human IL-1Ra and approved for the treatment of rheumatoid arthritis. Steroidal and other treatments had failed to help the patients, but anakinra successfully relieved symptoms in all cases.

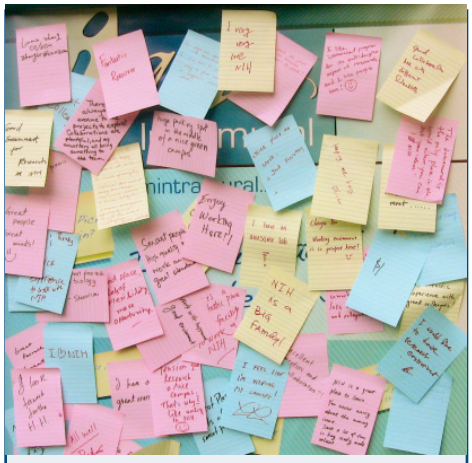
The patients have remained on anakinra treatment, with some having received treatment for more than 4.5 years; the drug has been well tolerated. The anakinra treatment appears to be most effective when it is started early in life.

Goldbach-Mansky recalls one patient who didn't respond to steroidal treatments and had been in the intensive care unit (ICU) for nine months. Within two weeks of starting anakinra treatments, "he was out of the ICU," she said. "It was a true miracle to all of those who were involved."

Next steps: Neonatal inflammatory diseases are poorly understood, but the findings from the DIRA study will help scientists understand the underlying pathogenesis in many of these syndromes. The use of anakinra may go beyond DIRA treatment and could be used for other IL-1 diseases—such as gout and type 2 diabetes—or diseases such as Behcet's syndrome that also involve inflammation of the blood vessels.

Goldbach-Mansky and her team hope to expand their study and treat DIRA patients with a longer-acting IL-1 inhibitor.

"The Clinical Center has been an incredible resource helping us to do imaging and to understand the pathogenesis of the disease," she said. "Such projects would be very difficult to do in other places." ■



Update "I Am Intramural"

The "I Am Intramural" campaign is creating a buzz on NIH's campus. Volunteers staffing the "I Am Intramural" posters are armed with pens and sticky notes for people to jot down what they like about their jobs. And the "I Am Intramural" website accepts postings anytime.

Here's a sampling of reasons why people like what they do in the NIH intramural program.

- "NIH affords me the unique opportunity to pursue bold questions."
- "You just have to think and you can do it here!"
- "Love the science, the resources and the intellectual environment."
- "Best place to do research. Chance in getting many contacts, helps in achieving long-term career objectives."
- "Twenty years and counting. . . . It only takes a minute to catch the research bug. It takes good research, outcomes and more ideas to sustain the bug!"
- "It's about the patient."
- "I am inspired by the continuing drive towards independence, the freedom to make mistakes and be guided at the same time. The availability of opportunity."
- "I am motivated by the collaborative teamwork that provides excellent research and patient care with the goal of serving the public."
- "Working here is a fabulous opportunity to make a difference by being part of a team trying to better mankind. What's not to love?"
- "Not many get such an opportunity of skilled people and abundant resources."

Tell us why the Intramural Program is a special place to work, why you do it, and what motivates you to make a difference! Please share your comments at: http://iamintramural.nih.gov. ■

—Natalie Giannosa, National Cancer Institute

NIH HISTORY

The Ames Assay: Of Salmonella, Rodents, and Humans

By Dan Lednicer, Office of NIH History and Museum

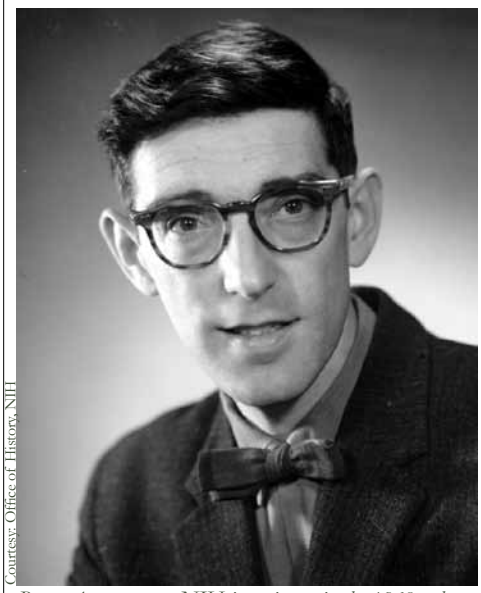
The idea that chemicals can cause cancer dates back to 1775 when the London physician Percival Pott noted a high incidence of scrotal cancer among chimney sweeps. But it would be more than 100 years before analytical organic chemistry was developed to enable scientists to identify the causal agents—polycyclic aromatic hydrocarbons (PAH), which are found in soot. More evidence for chemically induced cancers came in the 1930s when scientists found that workers exposed to aromatic amines, used in the dye manufacturing industry, developed bladder cancer.

Epidemiologic surveys and animal tests were developed to assess the carcinogenic potential of substances, but they were time-consuming, laborious, and expensive. Then in the 1960s, NIH biochemist and geneticist Bruce Ames invented a simple, rapid, and inexpensive bacterial assay to assess the mutagenicity of chemical compounds.

Ames came to NIH in 1953 as a post-doctoral fellow and worked in Bernard Horecker's lab in the National Institute of Arthritis and Metabolic Diseases. (In 1986, it split into the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.) Gaining permanent status as an independent researcher in 1954, Ames began investigating gene regulation in histidine metabolism in Salmonella. In 1962 he was made the section head of the newly created Laboratory of Molecular Biology. And, in 1964 he started work on the mutagenesis assay that would soon bear his name.

"Sometime in 1964, I read the list of ingredients on a box of potato chips and began to wonder whether preservatives and other chemicals could cause genetic damage to humans," Ames wrote in an article that appeared in the *Journal of Biological Chemistry* in 2003. "I thought it would be useful to have a test for chemical mutagens and so I decided to develop one." (*J Biol Chem* 278:4369-4380,2003).

An early version of the Ames test involved using a mutated strain of *Salmonella typhimurium* that could not make the amino acid histidine. When the histidine-deficient Salmonella bacteria were placed in media with very low levels of histidine, colonies grew until the histidine was depleted. Then only those bacteria that had spontaneously mutated back to the wild-type form continued to grow. The spontaneous mutation rate is constant for each strain. "However, when a mutagen is added to the assay mixture, there is an increase in the number of histidine-independent colonies and a dose-response curve can be obtained," Ames wrote. "During the next few years I developed a set of the most sensitive tester strains using all of the known mutagens I could get my hands on; I further improved the sensitivity of the test by eliminating some DNA repair systems in the strains."



Courtesy: Office of History, NIH

Bruce Ames was an NIH investigator in the 1960s when he began developing what was to become the Ames assay.

Ames continued fine-tuning the test through the 1970s, after he moved to the University of California, Berkeley, in 1967 as a professor of biochemistry.

"Some chemicals are not mutagens themselves but become mutagens in the presence of the liver homogenate, which can metabolize the chemicals to an active form, which then mutates the bacteria," Ames wrote. Ames found that if he added liver extracts that contained metabolic enzymes to the test medium, the compounds showed the expected mutagenic activity. For example, some potent PAH carcinogens did not show up as mutagens in the orginal assay but were active in the presence of liver extracts. As an aside, investigations at NIH by Donald Jerina (in the National Institute of Diabetes and Digestive and Kidney Diseases) uncovered the detailed pathway by which PAHs were converted to proximate mutagenic arene diols.

Of chemicals mutagenic in the Ames test and tested in animal cancer tests, 75 percent (294-393) are carcinogenic. Ames and others have pointed out that many carcinogens are not mutagens and that cell division is an important factor in carcinogenesis. Thus hormones are risk factors for cancer, and high doses of chemicals can kill cells and cause cell division and cancer.

Cancer occupied center stage among health issues in the early 1970s. President Richard Nixon launched the "War on Cancer" with his 1971 State of the Union address and the resulting legislation significantly increased the National Cancer Institute's (NCI) budget and gave NCI semi-autonomous status within NIH. At about the same time, the Ames assay went into a high-throughput mode at both Berkeley and other laboratories. Soon the test was being used by thousands of laboratories worldwide, including most drug and chemical companies.

Ames and colleagues pointed to the presence of mutagenic synthetic chemicals in some commercial products, e.g. the flame retardants in children's pajamas tris-(2, 3 dibromopropyl phosphate) and some permanent hair dyes. His and other labs also showed that a variety of naturally-occurring chemicals in our diet are mutagenic, e.g. products of cooking and natural pesticides that plants make to kill predators.

Ames and colleagues later showed that in high-dose animal cancer tests, natural chemicals are positive as often as synthetic chemicals, and that more than 99 percent of the human intake of chemicals is from naturally-occurring chemicals.

In 2002 the Ames group concluded that "[n]either epidemiology nor toxicology supports the idea that exposures to synthetic industrial chemicals at the levels at which they are generally found in the environment are important as a cause of human cancer."

The Ames assay continues to be widely used today as part of a standard battery of genetic toxicology tests that detect whether compounds, including potential drug candidates, cause DNA damage. ■

Editor's Note: This article was revised by Bruce Ames to more accurately reflect his work, and was posted online on February 3, 2010.

Can't We All Just Get Along? The Keys to Successful Collaborations

By Christopher Wanjek

There's not a researcher who hasn't been burned. Maybe it was in graduate school, when an advisor failed to list you as a co-author on a journal article despite the months of grunt work you performed to support the research. Or maybe it was more recent, perhaps here at the hallowed grounds of the National Institutes of Health, where a colleague considered your input more as a paid service than as an intellectual contribution.

More than just bruising egos, unresolved conflicts in team science—such as disagreements and differing expectations over authorship, the direction of a research project, or access to data and resources—can derail years of work.

And yet scientists do need to get along. The new research paradigm may very well be "partner or perish." With the specialization and sophistication needed for modern research methods, no lab is an island. Collaboration is now an indispensable research tool, and exploiting this tool can help take research to the next level.

So, in the same way investigators wouldn't run a $500,000 machine without reading the manual, they shouldn't enter into collaborations blindly based solely on their respect for other team members, according to NIH Ombudsman Howard Gadlin, who has seen his share of dysfunctional labs and teams at NIH. Researchers could be setting themselves up for heartbreak by not having an explicit collaboration agreement up front.

"The only people more romantic than people falling in love are people beginning collaborations," said Gadlin. "As soon as you talk about bringing together people of different specializations . . . you create an increased need for complex and sophisticated communication techniques."

Rather than continuing to run "an emergency room for failed scientific research projects," Gadlin wants to help NIH researchers enter into collaborations with the skills that will allow them to be successful.

Gadlin presented this evolving concept at the Clinical Center Grand Rounds on August 19, 2009, with Michelle Bennett, deputy director for the National Cancer Institute's Center for Cancer Research, who shares this goal. Samantha Levine-Finley in the Office of the Ombudsman has assisted Gadlin and Bennett in developing this project.

Partner or Perish

"There's a common conception that groups do not make good decisions," Gadlin said. "A lot of people are wary of participating in collaborative work because of that conception."

Yet as *New Yorker* columnist James Surowiecki details in his book The *Wisdom of Crowds* and as Gadlin and Bennett relayed, collaborations can take a team to new heights provided there is a diversity of opinions coupled with the independence to disagree and, perhaps paradoxically, to resist consensus.

More than just bruising egos, unresolved conflicts in team science . . . can derail years of work.

The challenge, however, is that many scientists find it difficult to disagree in non-hostile ways or to give or accept positive feedback. Researchers tend to be highly competitive yet conflict-adverse, Gadlin said, adding that this is a "toxic combination" because it leads to indirect or poor communication over crucial areas in which constructive disagreement would be beneficial.

Takes Two to Team

In their talk, "The Challenges of Collaboration and Team Science: Everything You Didn't Learn in Kindergarten," Bennett and Gadlin provided numerous examples of successful and unsuccessful approaches to team building. Highlights of this lecture follow.

Bennett, in her role as facilitating team science at the NCI Center for Cancer Research, has found that success in science can mirror success in business. Referring to *The Five Dysfunctions of a Team: A Leadership Fable* by business consultant Patrick Lencioni, Bennett said that successful science teams have a foundation of trust, which leads to non-hostile and nondestructive debate and underpins commitment, accountability, and results.

This framework can apply across what Bennett describes as the scientific research team continuum: from a few researchers in a small lab who engage in a low level of interaction; to a research collaboration among a few labs that each work independently on a piece of the puzzle; to an integrative research team made up of multiple labs and institutes encompassing broad expertise, with all the players meeting regularly.

Regardless of a team's size, a key to establishing the foundation of trust and maintaining a healthy, functional team is the presence of decisive leaders who can articulate their vision to the team and motivate each individual to feel a sense of commitment to that vision, Bennett said.

While these components of a successful team may sound obvious—strong leadership and clear, open communication—arriving here is not necessarily easy, Gadlin said. Scientists' tendency to shy away from conflict may combine with otherwise positive aspects such as a shared vision or respect and can lead to false or unspoken assumptions about authorship and other critical project details.

The time to talk about difficult issues such as sharing credit is at the beginning of a collaboration when all the team members are still getting along, Gadlin said.

His office, the Office of the Ombudsman in the Center for Cooperative Resolution, offers "prenuptials" for scientists. These collaborative research agreements specify who will do what, how the project will transition, and how conflicts will be addressed. In addition, they may cover other topics that can topple a research project.

Ultimately, Bennett said, the goal is to fulfill the NIH mission by training our scientists at all levels to be not only independent, but also collaborative.

For more information, contact the NIH Office of the Ombudsman, Center for Cooperative Resolution, at 301-594-7231 or visit http://ombudsman.nih.gov. ■

A video of the lecture "The Challenges of Collaboration and Team Science: Everything You Didn't Learn in Kindergarten," from which this screen shot of presenters Howard Gadlin and Michelle Bennett was taken, can be viewed at http://videocast.nih.gov/ram/ccgr081909.ram.

ANNOUNCEMENTS

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International Workshop on "The Biology, Prevention, & Treatment of Relapse After Allogeneic Hematopoietic Stem Cell Transplantation"
November 2–3
Natcher Auditorium (Building 45)

The primary aim of this meeting is to guide the National Cancer Institute in the development of an RFA (Request for Applications) addressing the problem of relapse after allogeneic hematopoietic stem-cell transplantation. For details and to register, visit http://web.ncifcrf.gov/events/relapse/default.asp.

Norman P. Salzman Symposium in Virology
"Viruses: Scourges of the Host, Surveyors of the Cell"
Friday, Nov. 6, 8:30 a.m. to 5:00 p.m.
Natcher Conference Center (Bldg 45)

The 11th Annual Norman P. Salzman Symposium in Virology and Award Program will feature presentations by several scientists including a keynote address by Herbert W. Virgin of the Washington University School of Medicine in St. Louis. To register, go to http://www.fnih.org/ and click on the icon for the Salzman Lecture.

Chen Lecture
"Viral Hepatitis and the NIH"
Friday, November 13, 10:00 a.m.
Masur Auditorium (Building 10)

The NIH Office of the Director invites you to the fourth Philip S. Chen, Jr., Ph.D., Distinguished Lecture on Innovation and Technology Transfer. Harvey Alter and Robert Purcell will present "Viral Hepatitis and the NIH: A Jaundiced View of History." Alter, the chief of the Infectious Disease section in the Department of Transfusion Medicine in the Clinical Research Center, won the 2000 Albert Lasker Award for Clinical Medical Research for his work leading to the discovery of the virus that causes hepatitis C. Purcell, the co-chief of the NIAID Laboratory of Infectious Diseases, focuses on the hepatitis viruses, with special emphasis on their molecular biology, epidemiology, and control. He is the author or co-author of more than 600 publications and a member of the National Academy of Sciences.

2009 National Graduate Student Research Festival
November 12 and 13
Bethesda Campus

This year's festival will introduce 200 advanced graduate students in the sciences to the NIH Intramural Research Program with the aim of recruiting them to do postdoctoral training at the NIH. The students have received or will receive their doctoral degrees between June 2009 and October 2010. For more information, visit http://www.training.nih.gov.

"Exploring the Science of Complementary and Alternative Medicine"
Tuesday, Dec. 8, 9:00 a.m. to 4:15 p.m.
Masur Auditorium (Building 10)

Don't miss the National Center for Complementary and Alternative Medicine's 10th Anniversary Research Symposium, which will feature presentations on natural products, mind-body medicine, and the intersection of behavioral science and integrative medicine. Keynote speaker Susan Folkman (University of California, San Francisco) will present "Stress, Coping, and Well-Being: Behavioral Science Meets Integrative Medicine." The event is open to everyone and no registration is required. This event will be videocast at http://videocast.nih.gov. For more information, visit http://nccam.nih.gov.

Postdoc Retreat: Chromosome Biology
Tues., Dec. 15, 8:30 a.m. to 5:00 p.m.
Natcher Conference Center (Bldg 45)
Abstracts Deadline: November 13
Registration Deadline: December 1

The Center of Excellence in Chromosome Biology and the Center for Cancer Research, NCI, will sponsor its fourth postdoctoral fellows retreat. The keynote speaker, Job Dekker from the University of Massachusetts (Worcester), is a leader in the field of spatial organization of genomes. Eight oral presentations will be selected from submitted abstracts. The retreat is open to all NIH principal investigators, postdoctoral fellows, staff scientists, and staff clinicians. This promises to be an interesting day discussing chromatin and chromosome biology. More information is at the meeting website, http://web.ncifcrf.gov/events/cecb.

Colleagues

Recently Tenured

Francoise Meylan

Richard Siegel, NIAMS

Richard Siegel's *interest in immunology, autoimmunity, and apoptosis began when he was an M.D.-Ph.D. student at the University of Pennsylvania School of Medicine (Philadelphia). After graduating in 1993, he trained in internal medicine and rheumatology at the Hospital of the University of Pennsylvania. In 1996, he came to NIH as a postdoctoral fellow in Michael Lenardo's laboratory, in the National Institute of Allergy and Infectious Diseases (NIAID), and studied the molecular basis of autoimmunity in the autoimmune lymphoproliferative syndrome (ALPS). In 2001, Siegel became an investigator in the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS). He is currently a senior investigator and acting chief of the Autoimmunity Branch in NIAMS and directs the Immunoregulation Section. He is also an attending physician on the rheumatology service at the NIH Clinical Center.*

My lab is working to understand how alterations in regulatory signaling pathways in immune cells may lead to abnormal immune responses, chronic inflammation, and autoimmune diseases. We have focused principally on the biology of the tumor necrosis factor (TNF) family of cytokines in normal and pathological immune responses. By investigating signal transduction and the in vivo functions of selected TNF family ligands and receptors, we have gained insights from rare diseases in which these or related molecules are mutated and cause autoimmune and autoinflammatory conditions.

We are also investigating the regulation of apoptosis signaling by Fas, a receptor that can directly induce programmed cell death and is mutated in ALPS, an inherited disorder of the immune system in which unusually high numbers of white blood cells accumulate in the lymph nodes, liver, and spleen. We are investigating the regulation of Fas and FasL cellular trafficking and the regulation of Fas function in functional and phenotypic subsets of primary T cells.

With Daniel Kastner's group in NIAMS, we are collaborating to elucidate the pathogenesis of the TNF-receptor–associated periodic fever syndrome (TRAPS), which is associated with mutations in the pro-inflammatory TNF receptor TNFR1. We have shown that TNFR1 molecules harboring TRAPS-associated mutations fail to bind to TNF but instead are misfolded and retained in the endoplasmic reticulum. We are investigating how these mutant TNFR1 molecules cause inflammation.

We have also been interested in the function of the poorly understood TNF receptor family member DR3, the expression of which is mainly restricted to T cells. Our lab has determined that this TNF family receptor plays a unique role in the pathophysiology of a wide spectrum of autoimmune and inflammatory disease models.

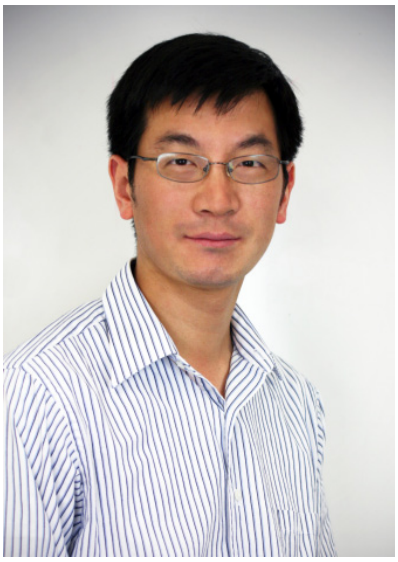
In studies of gene-targeted mice lacking DR3, we found that this receptor is essential for local T-cell expansion and tissue pathology in disease models, yet is dispensable for systemic immune responses against model antigens and several pathogens. Our lab has generated transgenic mice that express the DR3 ligand TL1A. These mice spontaneously develop intestinal inflammation similar to human inflammatory bowel disease. DR3 has thus been identified as a therapeutic target for T-cell-mediated autoimmune diseases. We are studying the underlying mechanisms and developing reagents that block TL1A-DR3 interactions to test their potential for treating mouse models of autoimmunity and ultimately human autoimmune disease.

I enjoy collaborating with my fantastic colleagues at NIH and working with students and postdocs in the lab. I have been particularly interested in enhancing the training of M.D.-Ph.D. students and allowing them to work in NIH labs. The NIH M.D.-Ph.D. partnership-training program, which I direct, was established in 2006 and now oversees the training of more than 50 combined-degree students doing the research phase of their M.D.-Ph.D. training in the NIH intramural research program. ■

Xiaoyuan (Shawn) Chen *is a senior investigator and chief of the Laboratory of Molecular Imaging and Nanomedicine (LOMIN) in the National Institute of Biomedical Imaging and Bioengineering (NIBIB). He also has an appointment at the NIH Clinical Center. He received a Ph.D. in chemistry from the University of Idaho (Moscow) in 1999. After two quick postdoctoral positions at Syracuse University (Syracuse, N.Y.) and Washington University in St. Louis, he joined the University of Southern California (Los Angeles) as an assistant professor of radiology. He then moved to Stanford University (Palo Alto, Calif.) in 2004 to help build its molecular-imaging program and was promoted to associate professor in 2008. In the summer of 2009, he came to NIBIB and oversaw the expansion of the Positron Emission Tomography Radiochemistry Group into the LOMIN.*

We are exploring the power of molecular imaging and nanotechnology in biology and medicine. We are also synthesizing molecular-imaging probes that can detect diseases early and monitor responses to therapy.

Our lab is divided into four sections: Positron Emission Tomography (PET) Radiochemistry, Biological Molecular



Jude Gustafson

Xiaoyuan (Shawn) Chen, NIBIB

Imaging, Molecular Imaging Probe Toolbox, and Theranostic Nanomedicine.

Molecular imaging is an emerging multidisciplinary field that visualizes and characterizes biological processes at the cellular and molecular levels in living subjects. It forms a bridge between the bench and the bedside and allows fresh biological findings to be translated to the clinic.

PET plays a central role in molecular imaging. We are interested in developing novel methods for incorporating radionuclides into tracers for the study of biologically important processes. Our research efforts are driven by the desire to translate our work into relevant applications for human diseases. We would like to collaborate with clinicians who share our goal of providing new imaging tools to help patients.

We also hope to identify disease-specific biomarkers and develop a molecular-imaging probe toolbox to systematically explore all processes in a biological system. We have developed probes to look at metabolism, proliferation, angiogenesis, metastasis, lymphogenesis, hypoxia, and apoptosis.

Nanomedicine, the highly specific medical intervention at the nanoscale for diagnosing, curing, or preventing diseases, involves the creation and application of nanobiomaterials and nanodevices. All-in-one sophisticated multifunctional theranostic agents will carry and deliver gene therapeutics and chemotherapeutics while simultaneously providing real-time, in vivo imaging that shows responses to those therapeutics.

I look forward to this challenge of providing these tools to the NIH community. ■

Raffit Hassan *is a medical oncologist at the National Cancer Institute (NCI). He is a senior investigator and chief of the Solid Tumor Immunotherapy Section in the Laboratory of Molecular Biology (LMB) at NCI's Center for Cancer Research. After receiving his medical degree from the University of Kashmir in Srinagar, India, in 1988, he completed an internal medicine residency at Sisters Hospital, State University of New York at Buffalo, in 1994, and a medical oncology fellowship at NCI in 1997. He subsequently joined the faculty at the University of Oklahoma Health Sciences Center (Oklahoma City) and returned to NCI as an investigator in 2002.*

I am conducting translational research on developing novel treatments for malignant mesothelioma, an aggressive cancer associated with exposure to asbestos fibers. In this disease, malignant tumors arise from the mesothelial cells lining the chest (pleural mesothelioma) and abdominal (peritoneal mesothelioma) cavities.

My work involves the use of monoclonal antibodies to target mesothelin, a cell-surface protein that is present on normal mesothelial cells and overexpressed in malignant mesotheliomas.

Steve Neal

Raffit Hassan, NCI

Although the biologic function of mesothelin is not clear, recent studies show that it binds to the mucin 16 (MUC 16) protein, which is also known as cancer antigen 125 (CA-125), a biomarker for ovarian and other types of cancer. This interaction of mesothelin and MUC 16 may result in tumor metastasis.

We are using two different molecules, SS1P and MORAb-009, to target mesothelin. SS1P is a recombinant anti-mesothelin immunotoxin developed by my collaborator Ira Pastan in NCI's Laboratory of Molecular Biology.

We showed that tumor cells obtained from patients express mesothelin and are very sensitive to SS1P. Based on these findings we did a Phase I clinical trial of SS1P and established its safety, pharmacokinetics, and the maximum tolerated dose; we have now initiated a clinical trial to evaluate its efficacy in mesothelioma.

Our strategy is to combine SS1P with standard chemotherapy. In laboratory studies, we showed marked synergy between SS1P and several chemotherapeutic agents in tumor xenograft models.

We are actively recruiting patients for the clinical trial of SS1P in combination with pemetrexed and cisplatin for frontline therapy of mesothelioma.

The second mesothelin-targeted agent we are evaluating for mesothelioma therapy is MORAb-009, a chimeric anti-mesothelin monoclonal antibody that was developed as a collaboration between NIH's Laboratory of Molecular Biology and Morphotek, Inc. We recently completed a Phase I clinical trial of MORAb-009 in patients who had mesothelin-expressing cancers.

An intriguing finding from this Phase I study was the marked increase in serum CA-125 after treatment that was most likely due to MORAb-009 interfering with CA-125 binding to mesothelin.

My laboratory is currently conducting studies to see whether MORAb-009 can inhibit tumor metastasis in animal models. Because our preclinical studies show that the anti-tumor efficacy of MORAb-009 is markedly increased in combination with chemotherapy, we are now doing a Phase II clinical trial of MORAb-009 in combination with the chemotherapy drugs pemetrexed and cisplatin for the treatment of pleural mesothelioma.

We believe that our studies on combining mesothelin-targeted immunotherapy with chemotherapy will lead to improvements in the treatment of patients with mesothelioma.

In addition, our research could have implications for the treatment of common cancers such as ovarian, pancreatic, and lung adenocarcinomas that overexpress mesothelin.

We are starting a clinical trial of SS1P in combination with bevacizumab (a drug that inhibits the formation of blood vessels to tumors) and chemotherapy for patients with lung cancer. ■

The SIG Beat:

News from and about the NIH Scientific Interest Groups

Glycosciences Community

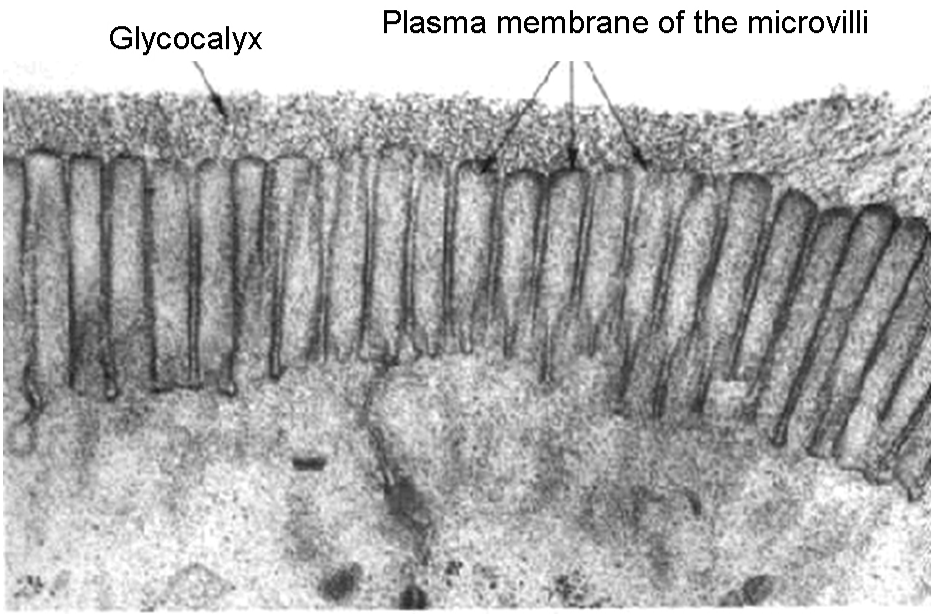
By John Cipollo, Center for Biologic Evaluation and Research, Food and Drug Administration

Not long ago, glycoconjugates—carbohydrates chemically linked to other chemical entities—were considered unimportant extras that served little or no purpose in biological processes. But a casual glance at the cross-section of an intestinal brush border cell (so named for its brushlike, microvilli-covered surface) quickly calls this wisdom into question. The glycocalyx, or sugary coat that surrounds the cell, is several hundred times as thick as the all-important plasma membrane. Why would Nature expend so much energy to synthesize something so large and complex for no reason? The short answer is she does not.

The glycocalyx and other glycoconjugates play complex roles. In the intestine, glycoconjugates provide a physical barrier and molecular sieve that is constantly being renewed. The interaction of the glycocalyx and gut bacteria is fundamental to normal and pathogenic processes. The varied structures of the glycocalyx and associated glycoconjugates present regionally specific receptors that ensure conditions for colonization that are ideal for healthy microflora but not for enteric pathogens.

Research in the glycosciences has grown considerably since 1965. Scientists have discovered major glycosylation systems and have learned that glycoconjugates are involved in many biological processes including cell-cell interactions, growth and malignancy, protein stability, and host-pathogen interactions. These findings have implications for such areas as vaccine development, the mechanisms of cancer, immune responses, tissue development, and cell-cycle control. But often the investigators in these areas are not experts in the glycosciences. Clearly, there is a need to bring these scientists and the experts together.

The NIH Glycobiology Special Interest Group (GSIG) has launched efforts to bring such groups together and foster growth in the glycosciences in the National Capital Area. GSIG's activities include an annual FDA-NIH Glycosciences Research Day, a Special Topics in the Glycosciences Seminar Series, and the participation of more than 30 training laboratories at the NIH Institutes, FDA, and local universities.



The glycocalyx, or sugary coat, is several hundred times as thick as the plasma membrane in these intestinal brush cells (so named for their brushlike, microvilli-covered surface). This scanning electron microscope image is used with permission: Danton H. O'Day, University of Toronto at Mississauga.

NIH-FDA Glycosciences Research Day: Held annually in May, this event was attended by more than 200 people in each of the past two years and featured dozens of posters and oral presentations. Glycosciences leaders from NIH institutes, FDA, local universities, and across the nation gave talks on such topics as glycoconjugates in vaccine development, lectins and adhesions in disease, the role of glycans in development and disease, and glycosylation and glycan structure and function. Program information for 2008 and 2009 can be found at http://meetings.nigms.nih.gov/?ID=3546 and http://meetings.nigms.nih.gov/?ID=6185, respectively.

Special Topics in the Glycosciences Seminar Series: These lectures highlighting the work of various laboratories are being incorporated into curricula for the overall training program. A list of past and upcoming lectures can be found at the GSIG website.

Participating labs: The NIH and FDA have more than 60 laboratories, and neighboring universities have nearly as many, doing glycosciences research. In addition, more than 30 laboratories at NIH, FDA, and local universities train undergraduates, graduate students, and postdoctoral fellows in the glycosciences. A list of participating laboratories can be found at the GSIG website.

All those interested in the glycosciences are encouraged to participate in the group's activities. For more information and to join, go to the GSIG website: http://sigs.nih.gov/GBIG. If you would like your laboratory to be considered as a glycosciences training laboratory, contact Pamela Marino (marinop@nigms.nih.gov) or John Cipollo (john.cipollo@fda.hhs.gov). ■

Bone Marrow Stromal Cell Transplantation Center Celebrates Its First Year

By Pamela Robey, National Institute of Dental and Craniofacial Research

Clinical investigators and other researchers who want to use human bone-marrow stromal cells (BMSCs) to reconstruct bones and joints and to nurse other tissues back to health are in luck. The Bone Marrow Stromal Cell Transplantation Center (BMSCTC), established in October 2008 as a trans-NIH "Manhattan Project," is harvesting and growing clinical-grade BMSCs to treat patients with skeletal and nonskeletal diseases and disorders. The center can also help NIH investigators develop clinical protocols and prepare investigational new drug submissions to the Food and Drug Administration.

BMSCs, also known as mesenchymal stem cells, can regenerate bone and associated tissues as well as exhibit immunomodulatory effects, which are likely due to the secretion of high levels of cytokines and growth factors. These BMSCs are being used worldwide in several small clinical trials to treat a variety of diseases and injuries.

Operating out of the Clinical Center's Department of Transfusion Medicine, the BMSCTC has developed procedures to grow clinical-grade human BMSCs using ex vivo expansion methods. The first products will be generated in cell factories using fetal bovine serum; later ones will be grown in bioreactors. BMSCTC's Cell Processing Lab (CPL)—David Stroncek, Marianna Sabatino, and Jiaqiang Ren—is using several assays to test products to ensure that they maintain their biological properties.

For most clinical applications, allogeneic cells (from different, but matched, individuals) will be used, but for bone regeneration and certain other cases, autologous cells (from the same individual) will be generated. Third-party donor-screening procedures, similar to ones used by the National Marrow Donor Program, will be applied. A cell bank will be established and clinical investigators across the campus are creating protocols to treat graft-versus-host disease, inflammatory bowel disease, and ischemic heart disease. At least one clinical trial will be under way soon.

A steering committee—co-coordinated by senior investigators Harvey G. Klein, in the Department of Transfusion Medicine, and Pamela Gehron Robey, in the National Institute of Dental and Craniofacial Research—monitors the BMSCTC activities. The committee meets quarterly with users to discuss progress in product development, potential clinical applications, preclinical animal model testing, and plans for the future development of the center. Anyone is welcome to attend.

The BMSCTC's oversight and steering committees have recently approved the release of human BMSCs—those generated by the CPL during the research and development phase of the project as well as leftovers from clinical procedures—to NIH investigators for use in basic and preclinical studies. Cells can be requested by completing a form, available on the website, and forwarding it to either Harvey Klein or Pamela Robey for steering committee review.

For more information, visit http://sigs.nih.gov/bmsctc. ■

New: Wnt Working Group

The Wnt Working Group is now a scientific interest group and hopes to foster collaborations via broader interactions within the NIH intramural program. The group consists of scientists from the NIH campus in Bethesda, the NCI facility at Frederick, and the local extramural community. Participants come from labs devoted to Wnt research as well as labs in which Wnt signaling is a narrower, perhaps transient interest.

We meet every few months to present our unpublished research in a confidential setting intended to give timely feedback and encourage collaboration. Typically we have two seminar speakers at each session. Speakers are often postdoctoral fellows. Occasionally, we also have seminars from invited outside speakers. Meetings alternate between the Bethesda and Frederick campuses.

For more information or to join, contact moderators Jeffrey Rubin (RubinJ@mail.nih.gov) or Terry Yamaguchi (yamagute@mail.nih.gov). The website is at http://sigs.nih.gov/wnt. ■

Scientific Interest Groups

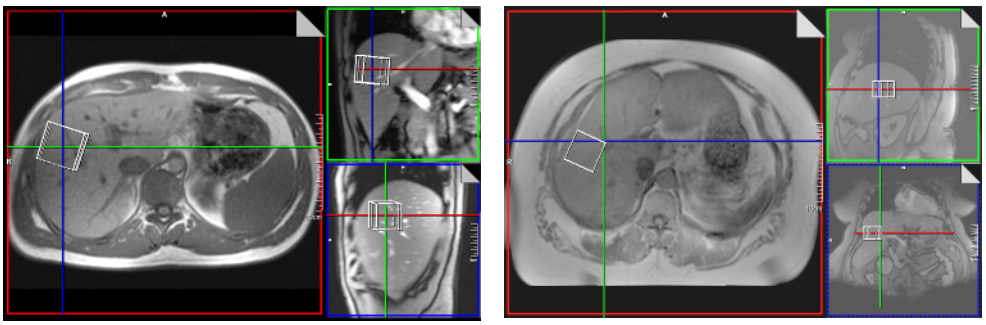
NIH Inter-Institute Interest Groups are assemblies of scientists with common research interests. These groups are divided into seven broad, process-oriented parent groups, or faculties, and more than 100 smaller, more focused groups centered on particular research models, subjects, or techniques. The latter groups are initiated and run by scientists in the Intramural and Extramural Research Programs at NIH.

The interest groups sponsor symposia, poster sessions, and lectures; offer mentoring and career guidance for junior scientists; help researchers share the latest techniques and information; act as informal advisors to the Deputy Director of Intramural Research (DDIR); provide advice for the annual NIH Research Festival; and serve as hosts for the Wednesday Afternoon Lecture Series. Many of these groups are cosponsored by neighboring academic and government institutions and welcome interested non-NIH scientists. Information about group activities or new groups is published in the *NIH Catalyst* and on the DDIR's Bulletin Board. (The latter is available only to NIH staff.) Some central coordination for the groups is provided by the Office of Intramural Research (OIR).

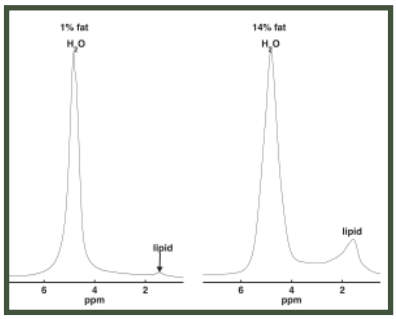
For a complete list of Scientific Interest Groups go to: http://www.nih.gov/sigs/sigs.html. In addition, the August issue of *The NIH Catalyst* (http://www.nih.gov/catalyst) published an annual directory of interest groups.

To create a SIG, contact the OIR Communications Director Christopher Wanjek (wanjek@od.nih.gov). ■

Imaging
continued from page 1



Liver MRIs of two subjects: 175-pound male (left) and 325-pound female (right). While significantly more fat (shown as white) can be seen around the organs in the obese patient, the focus is on the fat within the liver, revealed by spectroscopy (cross-section indicated by white box on left in each image). The same technique applied in muscle can even differentiate the types of fat and metabolites as well as the location, intra- or extracellular, which holds great promise in understanding metabolism and the lipid-disease connection. Images: Courtesy of R. Ouwerkerk.



A spectrum of a cross section of liver tissue quantifies the amount of fat (or lipid) relative to water. The fat is higher in the obese patient (right).

that can accommodate patients up to 500 pounds.

The imaging aspect of the protocols ventures into uncharted territory, said CC staff radiologist Ahmed Gharib, who's leading the effort. His team must wrestle with how to create crisp images while probing across relatively large volumes of fat, with the added complication that these obese patients may be physically limited in the positions they can maintain in the scanner.

Ultimately, the protocols might not only yield insights in the fields of metabolism and endocrinology but also set a new standard for imaging obese patients in general, an emerging concern because over two-thirds of the U.S. population is overweight or obese.

All Fat Not Created Equal

Obesity experts have known for years that type and distribution of fat matter most in the onset of metabolic changes and progression of disease. Adipose tissue, after all, is an endocrine organ that produces metabolic hormones such as leptin and cytokines such as tumor necrosis factor–∂, an immune cell regulator.

Recent research has suggested that liver, cardiac, intramuscular, and visceral fat and even the depth of subcutaneous fat all play unique and overlapping roles. For example, excess visceral adipose tissue, colloquially known as belly fat, is associated with cardiovascular disease. Excess intrahepatic fat, or liver fat, may be a key biomarker for the onset of insulin resistance and diabetes.

The reversibility of insulin resistance and cardiovascular disease—through diet, fat reduction, and bariatric surgery to reduce stomach capacity—also points out the role that various types of adipose tissue and their chemical signaling must play in metabolism and energy regulation.

"What we have set out to do is to understand on the individual level what are the critical mechanisms, or regulators, of metabolism and insulin resistance," said Kong Chen, a metabolism expert in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), who is leading several protocols in the Clinical Center's Metabolic Clinical Research Unit. "Imaging is critically important for us to separate out where the fat is."

But teasing out these differences——understanding, for example, why a morbidly obese individual is not diabetic while someone with far less body fat is——has proven difficult.

Traditional methods for assessing fat, such as hydrostatic weighing (weighing underwater), the Bod Pod (a computerized, egg-shaped chamber used for determining lean body mass), and dual-energy X-ray absorptiometry scanning (an imaging test that measures bone density), cannot quantify the amount of visceral fat, let alone differentiate intramuscular and liver fat.

An MRI scan can make such distinctions. In one protocol, Chen is collaborating with extramural colleagues at Vanderbilt University (Nashville, Tenn.) to study the metabolic changes in patients who have undergone bariatric surgery. He pointed to new images of one of the first obese patients to be scanned at NIH in the study. They clearly show the fat in and around her liver and the extent of intramuscular fat in her thigh.

"People have done this with normal-weight individuals, but the challenge has always been, can we study obese individuals," Chen said. The answer, judging by Chen's excitement as he viewed his first scan, is yes.

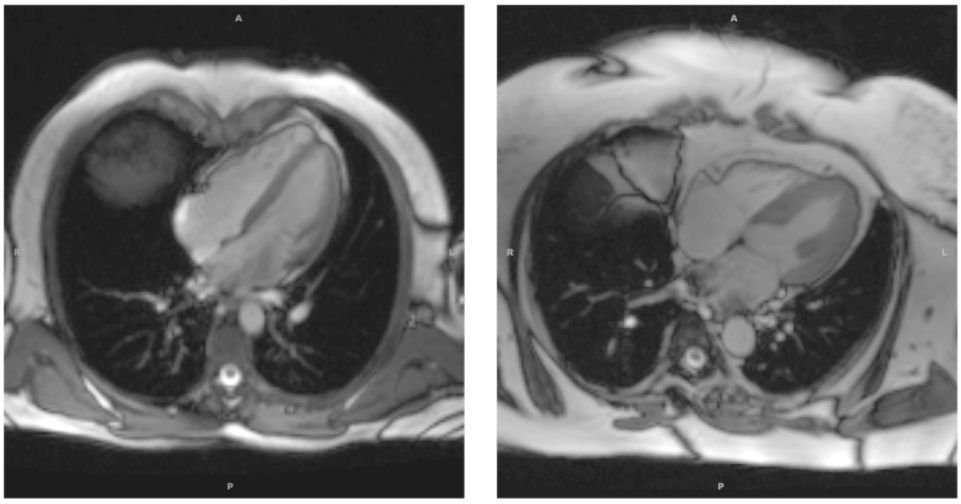
Physical Limitations

The sheer difficulty of imaging obese patients has long stymied researchers. There's the physical limitation of the machine. Most MRI scanners have a 55- to 60-cm (21.7 to 23.6 inches) bore diameter, which isn't large enough to accommodate some obese patients. The new NIDDK-CC scanner, the Siemens MAGNETOM Verio 3T, has a 70-cm (27.6 inches) bore size.

Then there are the physical limitations of the patients themselves. Many morbidly obese patients can only lie a certain way or cannot maintain a still position for an hour, a typical duration needed for some imaging. Or, they may have a rapid heartbeat or be unable to hold their breath—a technique, like holding still for a photograph, to get a crisp image—making cardiac imaging difficult.

Yet MRI, more than other techniques, holds the greatest promise for imaging obese patients, Gharib said. Ultrasound images are distorted by fat tissue, particularly at the higher frequencies needed for sharp imaging. Positron-emission tomography scans, used mainly for tumor imaging, also suffer from high scattering in soft fat tissues and have the added difficulty that the highest safe isotope dose is still too low for suitable image quality. Computed tomography (CT) scans are limited by the amount of radiation needed to penetrate these large patients to acquire high-quality images.

Gharib and his mostly NIDDK-based team—Ronald Ouwerkerk, Khaled Z. Abd-Elmoniem, Jatin Matta, Julie Heroux, and Nancy Muldoon (CC)—are up for the challenge. In fact, Gharib, with his primary expertise in cardiac imaging, has overcome



Heart MRIs of two female subjects, 125 pounds (left) and 374 pounds (right). Significantly more fat (shown as white here) can be seen around the chest cavity and atop the heart itself in the obese patient, who would be too large for standard-size MRI machines. Images: Courtesy of A. Gharib.

similar imaging roadblocks in recent years.

In 2006 he helped a team led by Steve Holland and Alexandra Freeman of the National Institute of Allergy and Infectious Diseases (NIAID) identify, for the first time, coronary artery aneurysms in two patients with Job's syndrome, an immune disorder. The challenge was performing an MRI scan of the heart without the aid of beta blockers to slow the heartbeat. An article about this from lead author Jennifer Ling of NIAID appeared in 2007 in the journal *Clinical Immunology*. (*Clin Immunol* **122:**255–258, 2007).

MRI and CT scans of a beating heart, in general, are tricky to capture, akin to "imaging spaghetti on a trampoline," says Roderic Pettigrew, director of the National Institute of Biomedical Imaging and Bioengineering and, in his role as chief of NIDDK's Section on Integrative Cardiovascular Imaging, a leader or collaborator on many of Gharib's projects.

Job's syndrome patients can't take beta blockers to slow their heartbeat because most of them have advanced lung disease, traditionally viewed as a contraindication to beta blockers. So to get around this, Gharib needed to decrease the MRI-acquisition window, or shutter speed, to accommodate a rapid heart rate. He may need to do the same for his obese patients.

Similarly, Gharib won an NIH Bench-to-Bedside award in 2008 and three more in 2009, with many collaborators, in which he must work with patients who are compromised by human immunodeficiency virus, kidney disease, or mutations in STAT3, a gene often associated with untreatable cancer. Once again, he will need to be able to perform imaging often without using beta blockers or breath-holding. He must use respiratory-navigation methods that allow for free-breathing acquisitions.

Tweaking the Machine

Gharib has only the most basic game plan for the moment for the obesity protocols, for each obese patient and each type of organ scan presents unique challenges. He hopes to first perform scans of the liver and heart and, if feasible, given the fat distribution, the muscle. In his arsenal are several types of CT and MRI scanners, each uniquely suited to providing one piece to the imaging puzzle.

Even scans of normal-weight individuals with heart disease or diabetes can provide a stepping-stone to imaging obese patients. Elsewhere researchers have used 1.5T MRI on obese patients, and Gharib hopes to learn from this experience as well.

NIDDK purchased and installed the Siemens Verio 3T this summer in the Clinical Center's MRI unit. Gharib described his initial tests as "taking a new car for a spin," and he now hopes to "look under the hood." The "hood" would be the very controls of MRI. With Ouwerkerk and Abd-Elmoniem, both physicists, Gharib hopes to tweak the scanning parameters to get the most and best information in the shortest possible scan time.

Fat-containing tissues are easy to identify and usually appear white in the scan, but relatively small amounts in the liver or muscles, between about 1 and 20 percent, need to be accurately determined for this project. Such refinement is possible only with special MRI techniques for imaging fat and water separately and with MR spectroscopy for measuring fat and water in a small volume inside an organ, requiring precise optimization of magnetic field homogeneity. The researchers must adjust these variables patient by patient to maximize signal relative to noise and achieve more accuracy.

Yet with refinement come new possibilities. Gharib's long-standing goal is to provide options to other researchers that they never realized they had.

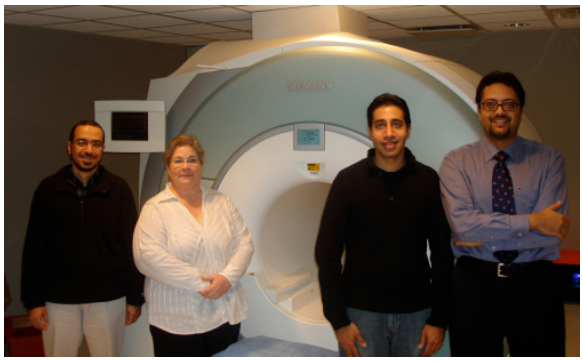
Noninvasive Biopsy

Monica Skarulis, chief of NIDDK's Clinical Endocrine Section in the Clinical Endocrinology Branch, leads a new protocol that will use MR spectroscopy to quantify fat in the liver, skeletal muscle, and heart, which is easier and safer than performing a biopsy. She is interested in how fat deposition in these tissues affects metabolism in a broad range of patients, even thin, healthy ones.

Skarulis' work exemplifies the noninvasive aspect of an MRI in providing not just "surface" imagery of things under the surface—that is, images of organs and vessels with their fatty deposits—but also subcellular details.

As Chen puts it: "We now are able to look at, with higher resolution and in vivo, not only where the fat is statically but also its dynamic change with time, for example, pre– and post–bariatric surgery. . . . We're even talking about the level [at which] we may study how the mitochondria [function] in the near future—noninvasively! That's exciting!"

When the CC's Metabolic Clinical Research Unit opened in 2007, Skarulis described it as "providing an unfair advantage" to intramural researchers. The new MRI scanner and, more important, the broad skills embodied by Gharib's team will help ensure unfair play for some time to come. ■



Other member's of Gharib's imaging team standing before the Siemens MAGNETOM Verio 3T MRI, left to right: Khaled Abd-Elmoniem, Nancy Muldoon, Jatin Matta, and Ahmed Gharib.

Biospecimens
continued from page 1

Cryoport used to transport biospecimens

collected and stored under varying conditions, with varying amounts of patient information and no standard for informed consent. "This is a nation of biobank fruit baskets," said Compton. "Everybody does everything differently, and they don't really know what they have in their bank."

Once this problem was publicly pinpointed, a flurry of exploratory committees and infrastructure assessments followed. When the dust settled in 2003, NCI had developed its National Biospecimens Network Blueprint, which laid the foundations for caHUB. In 2005, the OBBR was formed to develop guidelines and standards, promote biospecimens research, and explore the possibility of a national biobank. OBBR received this year an allocation of $60 million from the American Recovery and Reinvestment Act (ARRA) to create caHUB.

For an idea of the impact these fruit basket biobanks have on research, look at the early history of the Cancer Genome Atlas (TCGA), an ambitious project that's beginning to map the genetic alterations responsible for cancer. In 2006, a pilot study for TCGA needed 500 samples each of ovarian, brain, and lung cancers of a sufficient size and specimen quality to provide molecules for 10 different genomic analyses. These were large demands, but an early estimate stated that they could find the requisite samples at four to six sites.

Just a few months later, it became clear that the sites from which they were collecting had nowhere near the necessary quality or quantity of samples. One site with 12,000 samples in its database, turned out to have only 120 appropriate samples after a detailed inventory, and of these all but 18 failed the TCGA specifications due to low tumor-cell counts or poor molecular quality. Other centers faced similarly astronomical dropout rates because samples didn't meet requirements.

TCGA subsequently expanded its efforts to find the needed samples; now it collects tissues from 54 different cancer centers. The project has delivered very promising results, including one of the most comprehensive datasets on brain cancer and ovarian cancer to date.

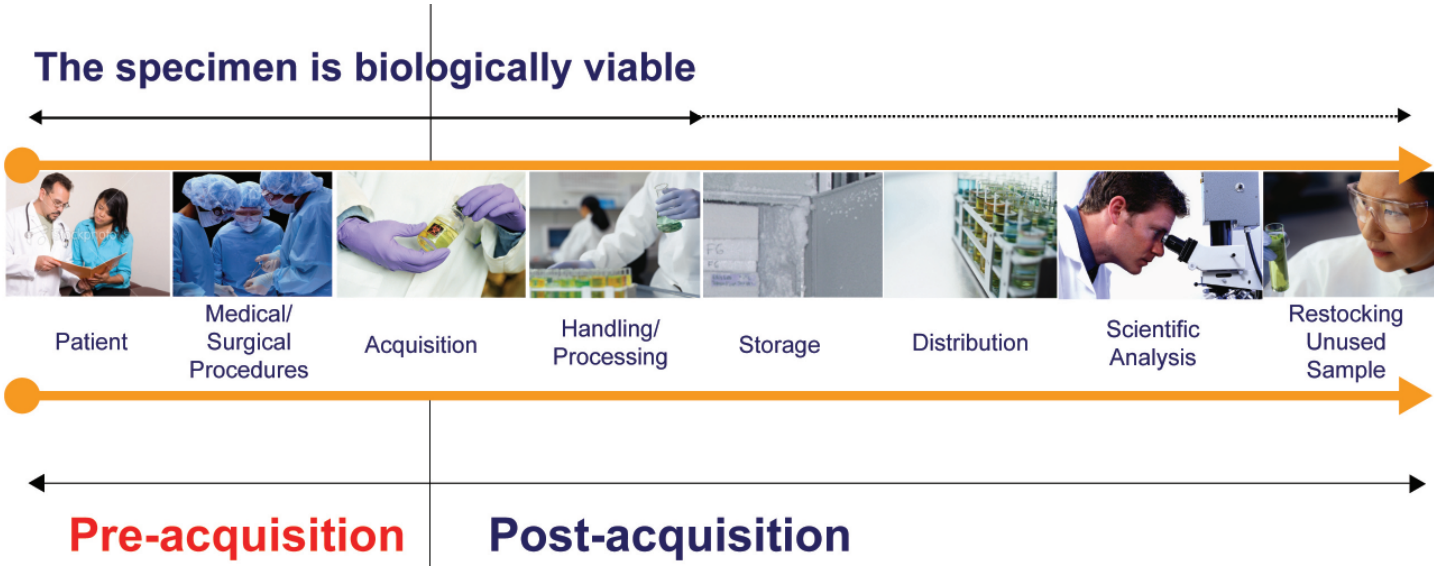
Such a lack of biospecimen standardization doesn't just make research less convenient; it can also confound results and lead to false conclusions. For example, in 1987, the protein HER2 was associated with breast cancer; in 1999 a drug was developed to target HER2 in patients who tested positive for it; and in 2002 it was shown that the test was inaccurate 13 to 18 percent of the time, meaning that a relatively large fraction of the patient population was either receiving or being denied the treatment in error. In going back and trying to understand what went wrong in understanding HER2, a researcher at the University of Utah found that in the original studies, poor sample handling confounded the results and misled investigators.

Finding the specimens to fill caHUB isn't going to be an easy process, or a cheap one. Most of the money going into the project will be used to solicit and train institutions to become biospecimen-collection sites, following caHUB's stringent guidelines.

Many of the sites that have demonstrated interest are off-campus institutions associated with the NCI Community Cancer Centers Program (NCCCP), interested in donating specimens in order to further the understanding of cancer. Although the Clinical Center would conceivably be a convenient place to find samples, most cancers seen at NIH have already undergone multiple rounds of treatment, which changes their chemical profile in ways that are still not understood.

Standardized labeling systems have been developed to properly identify slides containing biospecimens.

Meanwhile, healthy tissue specimens will



be coming to caHUB from rapid autopsies in a system built up in part around the organ-donor program.

The hope for caHUB is that each of these specimens will be of excellent quality: collected and stored using the same standardized procedure as all the other specimens, annotated with a complete patient history, and obtained in strict adherence to standards for informed consent.

The caHUB inventory is also set to be searchable online by any interested parties, though physical access to specimens will be trickier. Researchers from NIH institutes, academia, or industry who would like samples will need to go through a two-tier application process to determine whether their research is appropriate and important enough to merit access to caHUB's resources.

The OBBR and other groups involved in this project have high hopes for caHUB's impact on biomedical research. *Time* magazine has ranked the national biobank as number 8 on its 2009 list of "10 Ideas Changing the World Right Now."

A central biobank would make research involving human tissue radically simpler by making reliable tissue samples easier to acquire, and would open the door for studies on large populations of cancers that would be otherwise impossible. Those in charge of the biobank hope that it could change the focus of research at NIH.

In October 2008, NCI's Office of Market Research and Evaluation surveyed 727 extramural cancer researchers about the availability of biospecimens for their research. The results were shocking: 70 percent complained that they weren't always able to access the number of biospecimens they needed, and 80 percent said that those they could access weren't always of sufficient quality. Even more distressing, up to 60 percent of the researchers sometimes questioned the validity of their work because of the quality of available biospecimens. More than 80 percent had limited the scope of their research at times because they knew they wouldn't be able to find appropriate specimens.

Preparing biospecimens for molecular analysis extraction.

"It would be great to always have 'high-quality biospecimens,' but we often have to make do with what we have," said one of the queried researchers. The study paints a picture of cancer research stunted by poor access to standardized biospecimens.

"We can't do the most innovative science in this country if this is the kind of infrastructure we've got," said Compton. "We are limited in our ability to do transformative research."

A major step in the OBBR mission is trying to define standard methods by which biospecimens are collected, processed, and stored. The Biospecimens Research Network (BRN) is working on this problem, trying to understand the effects of collection procedures on the genomic and proteomic profile of a specimen.

A lack of biospecimen standardization doesn't just make research less convenient; it can also confound results and lead to false conclusions.

"We think of them as reagents but they are actually complex biological entities that can change their molecular profile until they're stabilized," cautioned Helen Moore, head of the BRN. Any step in the process from tissue removal to tissue fixation can potentially affect the sample's makeup in ways that the BRN is trying to understand.

Avoiding such artifacts is a particularly difficult goal because even a specific kind of tissue can be collected by varying means. Take renal carcinoma, an example highlighted by NCI's Gennady Bratslavsky at the 2009 BRN Symposium. In laparoscopic surgery for the tumor, blood flow is cut well before the tumor's removal, leaving it at body temperature but ischemic for an extended time. In open surgery, the tumor gets disconnected from the blood supply, removed, and frozen much more quickly. Bratslavsky's lab is trying to understand the impact of ischemia time when evaluating renal tumor samples for potential biomarkers.

Findings from groups like Bratslavsky's are being collected in the Biospecimen Research Database (BRD), which is searchable online at the BRN website.

The work that the BRN is doing to understand biospecimens is only the tip of the iceberg in the standardization problem. "It's an infrastructure problem," Moore said. She added that it would take more than just an understanding of biospecimens to change the collection field.

Carolyn Compton at the National Cancer Institute is helping to shape a national biobank project.

The BRN and others have compiled lists of recommendations for researchers collecting biospecimens. The NCI's "Best Practices for Biospecimen Resources," finalized in 2007 and updated this year for release in early 2010, outlines detailed principles by which to set up collection procedures in any institution dealing with biospecimens. On campus, the "2008 Guidelines for Human Biospecimen Storage and Tracking within the NIH Intramural Research Program" is the main handbook for researchers working with human tissue, and the Biospecimens Interest Group provides a forum for researchers to share findings at their monthly meetings and on their LISTSERV electronic mailing list.

Unfortunately, enforcing these standards is almost impossible. A project like caHUB can set up contracts to ensure the quality of samples coming into it, but smaller biorepositories have a much harder time controlling the samples coming in, and there's almost no accounting for the contents of lab-owned biorepositories.

The National Heart, Lung, and Blood Institute's (NHLBI) Biologic Specimen Repository, active since 1975, is the oldest of the institute-level biorepositories funded by NIH. It has been instrumental in understanding the spread of human immunodeficiency virus and hepatitis C, and today it holds 4.5 million samples of serum, plasma, whole blood, white blood cells, and other frozen specimens.

That repository is one of many that have started the complex process of assessing already frozen specimens, some of which

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Biospecimens
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have been frozen for over three decades. This assessment presents challenges ranging from understanding informed consent guidelines dating back to the late 1970s to finding ways to stick a plastic label onto a frozen glass vial.

And that's just the beginning. Applying standards to the specimens coming into the repository has turned out to be just as challenging. "People ask how hard it can be to put your blood in a tube and stick it in a freezer, but when you do it 40,000 times it gets pretty difficult," said Elizabeth Wagner, project head of NHLBI's biorepository. Specimens are coming from dozens of different sources, including researchers, physicians, and transfusion medicine centers. Checking that each of these sources is collecting and storing its samples appropriately is necessary to assure biospecimen quality.

"The entire operation would have to take place within an ethical and legal framework," Compton said. "That's an easy sentence to utter, but quite complicated to achieve." The biobank, for all its exciting promise, will need to be set up carefully to protect the privacy and interests of donors.

Informed consent is the key to this ethical framework: Any patient who donates specimens needs to understand what is going to happen with the tissue once it is placed within the biobank. This will take a lot of patient education, but is invaluable in the process of finding specimens. "Without the patient's consent and understanding and full participation in the process of research, we will never change medicine for the better," said Compton.

Privacy is also a huge issue for the biobank because patients are donating not only their tissues but also their detailed medical histories. Although their histories will be stripped of their names, it's impossible to completely anonymize a sample that includes a patient's DNA, so linking a sample to a history can allow someone to link a person with a specific condition. The biobank aims to avoid these problems with strong security measures such as using barcodes to label samples, so that they can't be identified without a computer, and using multiple layers of password protection to secure their database.

The response from NIH researchers has been overwhelmingly positive. The first BRN Symposium in 2008 had to shut down registration a month early because its 300 available spaces got snatched up quicker than anyone would have thought.

Rubenstein, a main contact for the Biospecimens Interest Group, is also excited about the interest in biospecimens research on campus. "I was stunned to see there was such a tremendous outpouring of enthusiasm," she said.

Some researchers are worried, though, that the demanding standards for biospecimens will hamper science instead of furthering it. "If research is painful to do," worried one hesitant hematologist, "researchers will leave."

Paul Plotz, a seasoned physician-scientist at National Institute of Arthritis and Musculoskeletal and Skin Diseases raised a very different concern. The biobank, while conceivably indispensable, ignores the way that scores of NIH scientists have successfully done research for decades: using samples taken from their own patients. There's no way that caHUB, or any biobank, could include the kind of detailed knowledge that doctors have about their patients. In Plotz's office, he waved a hand at a shelf of green journals. "My wretched, wonderful notebooks…bring a patient to life for me in a moment," something that the patient information in a biobank could never do for its users. Plotz sees the biobank as disregarding the way that translational research has traditionally been done at NIH.

The devotees of the biobank counter that the NIH is changing the kind of research it does and making research more efficient. The caHUB and other bioreposi-tories don't threaten the physician-scientist, but rather help her to get her hands on the samples she needs to do her research and work towards the development of treatments.

As NCI attempts to set up the first national biobank for the United States, biobanks in Iceland, Canada, Sweden, Australia, the United Kingdom, and the European Union are already up and running and helping researchers to understand diseases. Because these nations have nationalized health-care systems, they can allow centralized access to biospecimens and control of collection procedures. They have the added incentive that an understanding of their national health will save their health-care system money.

The caHUB project and biospecimen standardization initiatives on campus have the potential to put the United States on the biobank map within the next year. It has taken longer to set up than other national biobanks, but the pieces are in place; all that's left is to find the willing tissue donors. NIH, along with the rest of the biomedical community in the United States, has the technologies to benefit immensely from a powerful biospecimens resource and stands poised at the brink of immense breakthroughs. ■

(All photos for this article were provided by NCI)

Biospecimens Interest Group

The NIH Biospecimens Interest Group formed in 2008 as an educational and tutorial vehicle for disseminating information, best practices, regulations, and ethical and legal information on the topic of biospecimens. The group's events, held two or three times a year, have proven to be quite popular; the September 16 lecture on "Mystery Diagnosis: The Undiagnosed Disease Program" filled the Masur Auditorium (in Building 10) to near capacity. Membership now exceeds several hundred, with participation from at least a dozen institutes and centers as well as external organizations and universities.

The Biospecimens Interest Group hopes to elicit expertise from across NIH and the community as it journeys toward its ultimate vision of providing connectivity to various biorepositories and biospecimens around the world, especially those containing rare and difficult-to-obtain biospecimens. The group is sponsored by the NIH Office of Rare Diseases Research (ORDR) and the National Cancer Institute's Office of Biorepositories and Biospecimens Research (OBBR). The website is at http://sigs.nih.gov/biospecimens. Moderators are Yaffa Rubinstein (ORDR) and Helen Moore (OBBR).

The ORDR has a special interest in this effort because many of the difficulties associated with biospecimens for common diseases are more challenging and daunting with rare diseases, with fewer patients scattered over large geographical areas and few repositories specialized in the banking of rare disease biospecimens. ORDR works closely with OBBR on several projects associated with biospecimens, such as establishing a common biorepositories locator and database. ORDR also participates in OBBR initiatives concerning the development of best practices for biospecimens collection, handling, and distribution.

—Christopher Wanjek

2009-2010 Wednesday Afternoon Lecture Series (WALS)

Don't miss WALS, which features presentations by research "All Stars." For details visit http://wals.od.nih.gov. To request copies of the 2009-2010 WALS poster, which has the whole schedule, e-mail Sarah Freeman (sarah.freeman@nih.gov). Lectures are held from 3:00 to 4:00 p.m. in the Masur Auditorium, Building 10. All lectures are available via live videocast at http://videocast.nih.gov and are archived one week after the lecture.

November 18, 2009
Dan Kastner: "Fevers, Genes, & Histories: Adventures in the Genomics of Inflammation"

December 2, 2009
Tobias Meyer: "Shotgun siRNA Perturbation to Dissect Growth Factor Triggered Proliferation and Migration Signaling Systems"

December 3, 2009 (Thursday)
Juan Bonaficino: "Sorting It All Out: Signal-mediated Protein Trafficking in the Endosomal-Lysosomal System"

December 9, 2009
Gerard Karsenty: "The Novel Physiology of Bone"

December 16, 2009
Rebecca Richards-Kortum: "From Cell Phones to Cell Biology: High Tech, Low Cost Solutions for Global Health"

January 6, 2010
John Rich: "Wrong Place, Wrong Time: Understanding Trauma and Violence in the Lives of Young Black Men"

January 13, 2010
George Rose: "Protein Folding: Seeing Is Deceiving"

January 20, 2010
Carol Robinson: "From Rare Gases to Ribosomes"

January 27, 2010
Art Horwich: "Molecular Chaperones in Protein Folding and Neurodegeneration"

February 3, 2010
Ellen Rothenberg: "Stem Cell to T Cell: Molecular Anatomy of Commitment"

February 10, 2010
Fred Gage: "Neural Plasticity and Diversity in the Adult Mammalian Brain"

February 17, 2010
Helen Mayberg: "Tuning Depression Circuits Using Deep Brain Stimulation"

February 24, 2010
Michael Dustin: "Creating Super-regulatory T Lymphocytes"

March 3, 2010
Susan Taylor: "Dynamics of PKA Signaling"

March 10, 2010
Jeffrey Ravetch: "The Paradox of Immunity"

March 17, 2010
Carol Barnes: "Memory and the Aging Brain"

March 18, 2010 (Thursday)
Julio Montaner: "Closing the Implementation Gap to Stop HIV/AIDS"

March 24, 2010
Maria Grazia Roncarolo: "Role of Regulatory T Cells in Tolerance: Implication in Human Diseases"

March 31, 2010
David Altshuler: "Genomic Variation and the Inherited Basis of Common Disease"

April 7, 2010
Judy Cho: "Genetics after Genome-wide Association Studies: Inflammatory Bowel Disease"

April 14, 2010
Catherine Costello: "Proteins as Chameleons: The Good, the Bad and the Ugly"

April 21, 2010
Ronald Breaker: "Ancient RNA Relics and Modern Drug Discovery"

April 28, 2010
Sandra Schmid: "Protecting Your Borders: Regulated Entry into the Cell"

May 5, 2010
Joseph Takahashi: "Clock Genes and Clock Cells: A New View"

May 12, 2010
Julie Buring: "What Do We Do When Studies Disagree?"

May 19, 2010
Michael Karin: "Control of Tumor Promotion and Metastatic Progression by Inflammatory Signaling"

May 26, 2010
Daniel Haber: "Interrogating Circulating Tumor Cells to Direct Targeted Cancer Therapies"

June 2, 2010
Bruce Spiegelman: "Transcriptional Control of Adipogenesis and Systemic Energy Homeostasis"

June 9, 2010
Yuan Chang: "A New Virus as a Culprit in Human Cancer"

June 16, 2010
Rafi Ahmed: "Memory CD8 T-Cell Differentiation"

June 23, 2010
Karen Duff: "It Takes Tau to Tangle : Plaques, Tangles and Neurodegenerative Disease"

June 30, 2010
Joan Steitz: "Regulating the Activity of MicroRNAs in Vertebrate Cells"

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Kyungjae Myung
National Human Genome Research Institute
"Evolutionary Conserved Pathways Suppress Genomic Instability"

December 18, 2009
Will Prinz
National Institute of Diabetes and Digestive and Kidney Diseases
"Intracellular Lipid Trafficking and Organelle Biogenesis"

January 15, 2010
Silvia Bolland
National Institute of Allergy and Infectious Diseases
"Role of Viral RNA Recognition Pathways in Autoimmune Disease Susceptibility"

February 19, 2010
Maria Morasso
National Institute of Arthritis and Musculoskeletal and Skin Diseases
"Unraveling the Basics of Rare Ectodermal Disorders"

March 19, 2010
John Isaac
National Institute of Neurological Disorders and Stroke
"Construction of Neocortical Circuits: How Sensory Experiences Build Layer 4"

April 16, 2010
Raffit Hassan
National Cancer Institute
"Targeted Immunotherapy for Treatment of Malignant Mesothelioma"

May 21, 2010
Richard Siegel
National Institute of Arthritis and Musculoskeletal and Skin Diseases
"TNF Family Cytokines: From Molecule to Malady and Back Again"

June 18, 2010
Yasmine Belkaid
National Institute of Allergy and Infectious Diseases
"Control of Treg Induction and Function by Microbes"

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

In Future Issues...

- FAES
- BTRIS
- Prions

Janet Stephens

Maybe you heard: President Barack Obama visited NIH on September 30, 2009, touring a laboratory at the Clinical Center, getting briefed on scientific research being conducted at NIH, and delivering an address to congratulate NIHers for their "extraordinary work" and for distributing the first $5 billion of a $10.4 billion American Recovery and Reinvestment Act appropriation. From left to right: NIH Director Francis Collins; Marston Linehan, head of the Urologic Oncology Branch in the National Cancer Institute; President Obama; and Kathleen Sebelius, Secretary of the U.S. Department of Health and Human Services.

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

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