FOSTERING COMMUNICATION AND COLLABORATION

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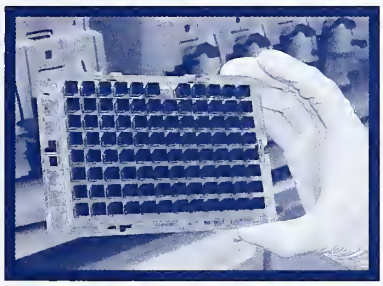
Heart Study Moves to the IRP

FRAMINGHAM, MARYLAND?

by Christopher Wanjek

In 1948, as death rates from cardiovascular disease continued their gradual yet steadfast rise from decades prior and were more than a little worrisome, the National Heart Institute established a novel study in the historic town of Framingham, Mass.



Christopher Wanjek

***Modern probes of the heart**: The NHLBI Genomics Core can study the gene expression profile of 96 samples at once on one plate. Facility director Nalina Raghavachari holds one such plate*

Little was known then about the general causes of heart disease and stroke. The Framingham Heart Study, a longitudinal study originally composed of 5,209 Framingham adult residents, ultimately established most of the risk factors that are now embedded in the vernacular: high blood pressure, high blood cholesterol, smoking, obesity, diabetes, and physical inactivity.

To embark on a long-term study of thousands of people who had no overt symptoms of cardiovascular disease was an ambitious project not without its share of criticism. Early peer-reviewed papers from the Framingham research team mostly justified the epidemiological ap-

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Another Roadmap 'Pathway'

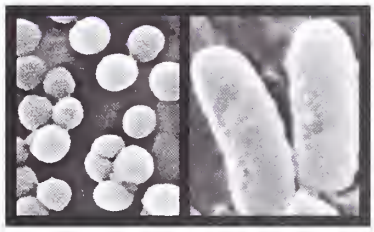
THE HUMAN MICROBIOME PROJECT TO INVENTORY THE 'OTHERS' INHABITING OUR BODIES

by Markus Elsner

More than 90 percent of the cells in the human body belong to the bacteria, fungi, and other microorganisms that colonize our gut, skin, mouth, and other body surfaces, a fact that would probably shock most people to learn but has long been recognized by scientists.

However, notwithstanding that much is known of the diverse roles of microbial communities in a wide range of body functions—from the development of the immune system to the control of body weight and even behavior—the inventory of the kinds and numbers of microbes that live in and on the human body is surprisingly incomplete.

Julie Segre



Two of the multitude of inhabitants on human skin and other surfaces

To remedy this knowledge gap, NIH in December 2007 launched an ambitious $115 million project to map the human microbiome, that is, to identify the species and numbers of microbes that colonize the human body as well as to characterize their protein and metabolic profile.

The NIH Human Microbiome Project (HMP), now among the "new pathways to discovery" of the NIH Roadmap, was introduced to the wider NIH community in a recent talk by Julie Segre, head of the epithelial biology section and senior investigator in the Genetics and Molecular Biology Branch, NHGRI.

Segre discussed her own pilot studies on the microbes that inhabit human skin and tied her work into the larger efforts to decipher the complete human microbiome.

Traditionally, microbiology has relied on culturing and describing individual bacterial species, but only about 1 percent of all microbes can be grown in laboratory cultures. The picture that emerges from culture-based studies, therefore, is at best semiquantitative and heavily skewed toward microbes that grow easily in the laboratory environment.

To obtain a more balanced estimate of the bacterial population on human skin, Segre and her colleagues chose to characterize the diversity in the sequence of genes common to all prokaryotes. They selected the *16S rRNA* gene, which forms a part of the bacterial ribosome that translates the genetic information into proteins. This gene is ideally suited for such an undertaking, Segre observed, because it is present in all bacteria and contains not

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From the Deputy Director for Intramural Research

NIH Director's Intramural Challenge Awards

Michael Gottesman

By the time you read this, my office will have announced a request for applications for a new source of intramural funding: the NIH Director's Intramural Challenge Awards.

Dr. Zerhouni has provided $1.5 million in new intramural funds to stimulate highly innovative, potentially high-impact research.

The awards seek to bring together researchers from multiple institutes and centers (ICs), who will take advantage of the strengths and unique aspects of the NIH intramural program.

This year the funds will support projects related to the three existing trans-NIH initiatives—the Center for Human Immunology, Autoimmunity, and Inflammation (CHI), the Imaging Initiative (Molecules to Cells), and the Systems Biology Initiative (Molecular Networks).

Funds will be awarded in mid-July, and must be spent by September 30, 2008.

Beginning October 1, 2008, we will expand the program.

First, we will solicit ideas for additional programmatic topics, and new areas of interest will be selected. The intent here is to broaden the trans-NIH initiatives beyond Immunology, Systems Biology, and Imaging to new areas of potential trans-NIH cooperation.

We will cast a wide net among all of our investigators for subject areas that are well-matched to the talents, environment, and resources in the intramural program.

The scientific directors will choose the topics from among the nominations received from our faculty. Then, senior investigators and investigators can apply for funds, with approval of their scientific directors, to support projects related to one of the newly selected topics, or to one of the three current trans-NIH initiatives.

Awards will be made for up to two years of funding, and can be used to support personnel, equipment, and/or supplies.

Requests should be in the range of $50,000–$200,000 per year. Preference will be given to proposals that bring together two or more ICs, but the major emphasis will be on highly innovative, potentially high-impact research.

Our hope is that your scientific directors will use this opportunity to invest in projects that would have been difficult to support without these new funds.

In reviewing the current budget situation, it has become clear that declining budgets have taken their toll on NIH intramural equipment and supply funds, and many of our laboratories are having trouble purchasing cutting-edge equipment and expensive reagents.

For work that can create new fields or make paradigm-shifting contributions to existing fields—and that takes advantage of trans-NIH collaborations—we hope that these NIH Director's Intramural Challenge Awards can make a difference.

The Office of Intramural Research is in the process of creating a website that lists other sources of trans-NIH funds that are competitive and bring new resources into your IC and your lab, including the Intramural AIDS Targeted Anti-Viral Program, the NIAID Biodefense Program, the Clinical Center Bench-to-Bedside Program, and several NIH training and education programs. We'll let you know when this website is activated.

As always, your comments on these new initiatives are welcome.

—Michael Gottesman
Deputy Director for Intramural Research

COMMENTARY

Needed: A Structured Top-notch Program at NIH For the Aspiring Physician-Scientist

Fran Pollner

Bolanle Famakin

Training options for the physician aspiring to become an independent bench scientist is a topic that needs to be addressed for clinical fellows who are physicians pursuing basic science research at NIH. (For the record, "clinical fellows" fall into two categories: those enrolled in an ACGME-accredited clinical fellowship with some time allotted to research in the second and third years and those who have completed such a fellowship elsewhere and have come to NIH specifically to obtain training in basic science research.)

Currently, physicians who want to perform patient-oriented research can obtain a Masters in Clinical Research. However, there is a surprising dearth of options for the physician who has not gone the traditional M.D.-Ph.D. route and wants to pursue basic science research after a medical residency and fellowship.

Right now, the quality and relevance of training for clinical fellows who have come to NIH to gain experience in basic research depends largely on the mentor's investment in the fellow's objectives.

With no time-defined structured program that flexibly accommodates the physician's research objectives, there is no guarantee he or she will acquire the desired research expertise or the tools to creatively ask and answer complex questions.

Physicians interested in pursuing a Ph.D. at this stage should be able to do so without having to take the same classes as a traditional Ph.D. student fresh out of undergrad, that is, participating in the Graduate Partnerships Program (GPP). And should a physician choose to pursue a Ph.D. through the GPP—a highly structured, full-time program—there is no provision for seeing patients on a limited basis in conjunction with coursework and basic research training.

NIH, with interested degree-granting institutions on board, can provide a program that enables the physician to pursue focused medical specialty–research—a program with targeted relevant coursework, some structured mentoring, time to see patients, and a Ph.D. offered at the end of a defined period of time.

Physicians who have completed their medical training can bring much more to basic science research, especially translational research, if given the opportunity to pursue Ph.D.-like basic research training at the end of their formal medical training. A physician at this point in training has defined scientific interests centered on a chosen subspecialty. This situation contrasts with the traditional M.D.-Ph.D. route: A student completes dissertation research without having chosen a medical specialty and therefore is not poised to formulate research questions relevant to a given medical field or disease process from the perspective of a health provider.

It is also more efficient to have physicians pursue basic science research training after they have completed all formal medical training and before they have secured a tenure-track position. During this transitional period, physicians can also still see patients on a limited basis and hence have the opportunity to pursue basic research questions bidirectionally—from bench to bedside and from bedside to bench. This route may also be more attractive to physicians interested in bench science than is the typical M.D.-Ph.D. pathway, which entails a lengthy period of up to nine years of consecutive training.

As things now stand, physicians interested in basic science research pursue this training largely on an ad hoc basis, diminishing their potential to contribute effectively to the translational research mission of NIH. They are also less able to compete with Ph.D. postdocs, who have up to nine years of bench training—four during their graduate training and up to five as postdocs—and who tend to receive most of the translational awards, for instance, the new K99/R00 awards.

Maintaining the status quo means that NIH will remain a place where the dreams of physicians with an interest in pursuing basic science research go largely unfulfilled.

This is an enormous loss that defies adequate assessment because these physicians tend to go quietly into the world of patient care—and as a result the field of translational medicine to bridge the gap between bench and bedside continues to advance at a snail's pace.

—Bolanle (Bola) Famakin
Clinical Fellow
Stroke Branch, NINDS

***Ed.response:** Ten years ago, NICHD physician-scientist Tracey Rouault worked with a group of NIH scientists to propose a program to bring physician-scientists into NIH labs. Some ICs have begun to do that, but there is not an NIH-wide program. She wrote at that time: "Much has been written about the shortage of MD researchers. We argue that the NIH intramural program is uniquely qualified to address this critical issue. The NIH intramural program was critical in providing MD researchers to medical centers in the 1950s-1980s, and we can play that role again if we design a modern research fellowship program." The time has come to craft such a program.*

—Michael Gottesman
Deputy Director for Intramural Research

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Framingham, Maryland?

Associate director Christopher O'Donnell

proach to studying heart disease.

But by the late 1950s, the study was bearing fruit, as researchers began to see the effects of high blood pressure and cigarette smoking on the hearts of their subjects, who returned every two years for a detailed examination.

Dozens of landmark papers followed. Framingham, the city, soon became synonymous with the study. In 1971, the study enrolled a second-generation cohort—5,124 of the original participants' adult children and their spouses. Then the grandchildren joined in 2002. Throughout this period the study enjoyed the continuous support of NIH extramural funding.

Beating Stronger Every Day

Sixty years and nearly 2,000 journal articles later, the NHLBI's Framingham research team has joined the NIH intramural program. The study is still within NHLBI, only now it has reinvented itself once again. Indeed, the Framingham Heart Study remains as innovative and promising as it was a half-century ago.

The impetus for the move was to "leverage 60 years of data collected at Framingham" with intramural resources, such as in gene-expression profiling and bioinformatics," in order "to make the investment all the more cost effective," said Daniel Levy, who joined the study in 1984 and became its director in 1995.

Levy has numerous projects under consideration that can best be done in-house. Entering a feasibility stage this June is a study to correlate gene expression with phenotypes and 500,000 genotyped SNPs in Framingham participants, using microarrays (perhaps better described as "macroarrays")—a 96-sample peg plate instead of the standard chip. NHLBI has the core facility to undertake this project in the Clinical Center.

The new Framingham projects will combine the intramural program's expertise in microarrays and the tools for comprehensive statistical analysis—all housed in an open-door environment with multiple institutes and smart colleagues investigating related fields, such as metabolic disorders and cancer.

"We're looking for new biology," said Peter Munson, head of the Mathematical and Statistical Computing Laboratory within CIT's Division of Computational Bioscience, who shifted his attention to the Framingham project a year ago to develop data-analysis software. Munson describes Framingham's new focus as "a melding of good, old-fashioned science and people with lots of technical know-how."

Genome of the Heart

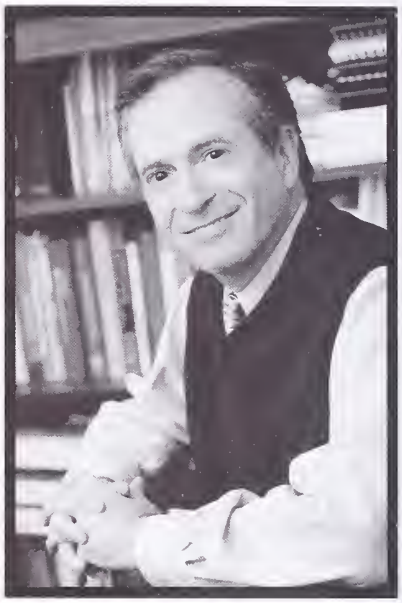
Framingham hinted at its new direction in recent years with several large-scale genotyping projects, such as a genome-wide scan of nearly 100,000 SNPs from 1,345 study subjects, using the Affymetrix 100K Genechip.

That study, published as a series of 17 papers in September 2007, included one paper exploring associations between the SNPs and four major cardiovascular disease outcomes: major atherosclerotic CVD, major coronary heart disease, atrial fibrillation, and congestive heart failure. Although there were no blockbuster results for those traits, intriguing findings emerged, most notably the replicated associations of chromosome 9p21 with major CVD.

Digging deeper, NHLBI launched the Framingham SNP Health Association Resource (SHARe) project in early 2007, under the leadership of Christopher O'Donnell, Framingham's associate director and SHARe's scientific director.

They upped the ante, too, with the goal of genotyping approximately 550,000 SNPs in more than 9,000 participants from three generations, encompassing more than 900 families.

Stored within NCBI's dbGaP and, as its acronym signals, open to scientists worldwide (beginning in October 2008), the SHARe database will contain all previous Framingham SNP and microsatellite genotyping, as well as extensive phenotype information from the three-generation cohort: quantitative measures such as systolic blood pressure, total and HDL cholesterol, fasting glucose, and cigarette use; anthropomorphic measures such as body mass index; biomarkers such as fibrinogen and C-reactive proteins; and electrocardiography measures such as the QT interval.



Framingham Heart Study director Daniel Levy

SHARe contains the 500K-SNP data and may possibly house much more.

Using the SHARe resource, O'Donnell hopes to discover new genes underlying coronary heart disease and subclinical atherosclerosis detected by computed tomography and other imaging measures.

Christopher Wanjek

Core scientists: *(left to right) facility director Nalini Raghavachari, technologist KimberlyWoodhouse, and research biologist Poching Liu*

Levy hopes to discover genes involved in hypertension and altered vascular function. The project might relate common genetic variation to alterations in gene expression as a means to get one step closer to understanding functional changes in human DNA.

"The focus is on discovering new genomic and genetic risk factors to identify the specific genetic sequences underlying associations seen previously and to test how these new genetic risk factors

might be used to predict and prevent cardiovascular disease," said O'Donnell, who joined the Framingham Heart Study in 1996 and, like Levy, joined the intramural program in 2007 as a tenured investigator in NHLBI who maintains his base in Massachusetts.

"[Framingham] is a study that reflects the real world," he said, and SHARe brings that study to the world by allowing scientists to compare genes within the Framingham study and between similar heart studies.

New Expressions

The next level, as Levy sees it, is discovering biomarkers and related therapeutics via a "phenomic" analysis of gene expression—to link proteins and metabolites to risk factors.

Enter the Genomics Core, a facility on the 8th floor of the CC to study gene expression, initiated by Eric Billings, head of Bioinformatics and Systems Biology in NHLBI's Intramural Research Program, and now under the direction of Nalini Raghavachari.

This facility has automated the sample-preparation protocol, allowing for a tremendous increase in capacity while reducing noise to a 15 percent coefficient of variation. A robot can manipulate an "array of arrays," processing 96 samples at once, reducing batch effects, and exerting exogenous controls.

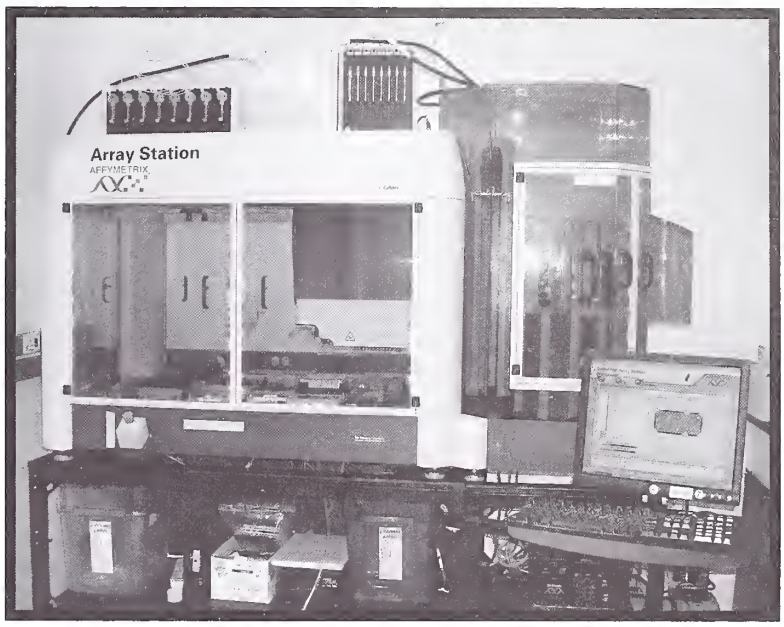
Beginning this summer for about two months, the Genomics Core will become an assembly line to study Framingham samples. The feasibility aspect is to assess which types of biological samples would be most useful in this mRNA analysis. Handling the sheer number of samples once the project moves forward—estimated to be at least 7,000 samples—is less of a concern, although this is the largest project by far that the Genomics Core has undertaken.

The Genomics Core processes about 1,000 samples a year; its largest single project has been a heart study for NHLBI Director Elizabeth Nabel involving 200 samples. "This blows away anything we've done before," said Mark Gladwin, former chief of NHLBI's Vascular Medicine Branch, who coordinated this and other projects between NHLBI and the CC.

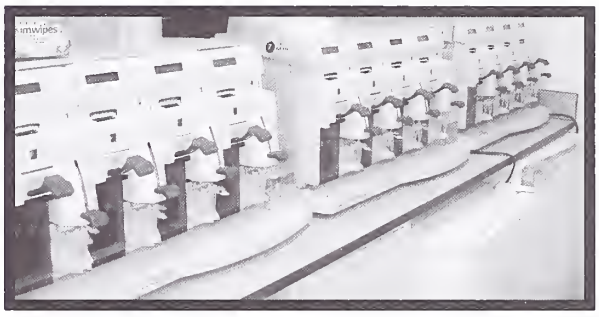
Levy speaks eagerly of the enormous research potential for Framingham within the intramural program, anticipating biomarker discoveries that are proteomic, metabolomic, and lipomic. He's enthused about combining genetic and genomic information and applying systems biology approaches on a population level, as well as about the possibility of internal collaborations and recruiting high-quality fellows.

Genome-wide association studies have proven themselves successful for diabetes and several inflammatory diseases," but the Framingham study can go far beyond that," said O'Donnell.

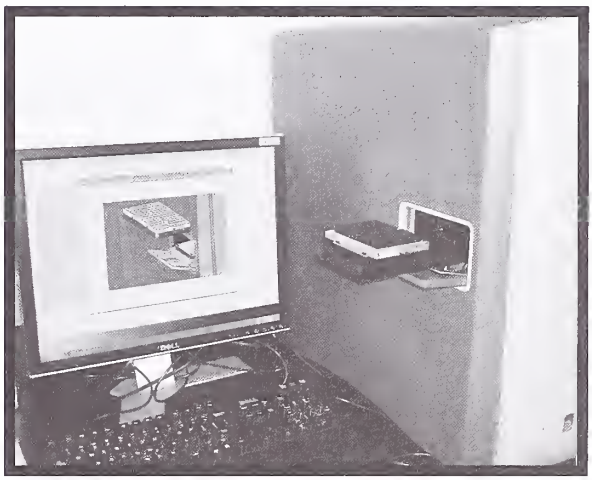
"I'm optimistic this will yield a lot of fruit." ■



The Gene Chip Array Station robot can process and analyze 96 RNA samples at once within a few hours



Affymetrix fluidic stations, which can wash and stain gene chips in an automated manner, are used in the Genomics Core to maximize efficiency



The 96-sample plate that has been hybridized to 96 different RNA samples, washed and stained with fluorescent dye is scanned by the laser scanner to detect expressed genes in the samples

photos by Christopher Wanjek

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Human Microbiome Project

Julie Segre

only regions that hardly vary between different bacterial species but also others that exhibit substantial variety in their sequences. The variable regions can be used to identify bacteria species, whereas the conserved regions are amenable to easy DNA amplification using polymerase chain reaction (PCR) techniques.

In her pilot study, Segre and her team took samples from five patients with no apparent skin disorders at the NIH Clinical Center, amplified their *16S rRNA*, and determined the resulting DNA sequences. The samples were taken from the right and the left inner elbows to explore the variability of the bacterial communities in seemingly equivalent portions of the skin.

The first lesson emerging from this and other studies is that the human body is populated by representatives of only a few of the main divisions of the bacterial kingdom. Of the 70 known bacterial phyla, only four dominate the human microbiome. About 90 percent of the bacteria in Segre's samples were members of a single phylum, the proteobacteria—and in most patients, a single genus, the Pseudomonas bacteria, contributed about half of all microorganisms identified. [At *Catalyst* deadline, these studies were pending publication in *Genome Research*.]

How different are the bacterial communities on different parts of the skin, and how much do they vary from person to person? The samples collected from the same person showed only insignificant variation, and four of the five patients had virtually indistinguishable microbial communities. Unlike the others, the skin of the fifth patient was colonized by staphylococci, but no clinical symptoms of diseases associated with staphylococci infection were observed.

Segre compared her data from the inner-elbow samples with those collected from the inner forearm by Martin Blaser and his group at New York University and found enormous differences. While Pseudomonas dominated the inner-elbow skin, this genus of bacteria was virtually absent from the skin of the forearm, where Actinobacteria dominate.

The volunteers in both studies showed no noticeable abnormalities of the skin, and the results suggest that different parts of the skin have highly adapted and specialized groups of bacteria. Nevertheless, the number of samples collected is much too small to draw definitive conclusions, Segre observed.

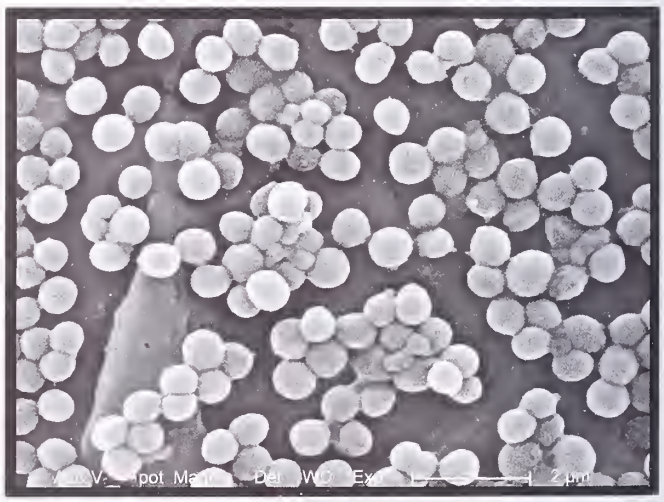
An immediate question arising from these observations is whether there is a connection between the appearance of human diseases and the composition of the bacterial flora. Many human skin diseases show most of their symptoms in distinct areas of the skin. For example, atopic dermatitis, a common allergic skin hypersensitivity responsible for 10–20 percent of all visits to dermatologists in the United States, typically affects the inside of the elbow, while psoriasis, with its sore, itchy patches of thick red skin and silvery scales, which affects 2–3 percent of the population, is mainly seen on the outer elbow.

"The skin is really an ecosystem," Segre explained. "There are niches of the skin, oily regions, moist regions, acidic regions. They all have the same human DNA . . . but may provide a different environment for different microbes to grow."

Yet, the role of the bacterial communities in these diseases is not yet defined, but is potentially significant. In a mouse model for atopic dermatitis, Segre obtained preliminary data that the bacterial communities living on the skin of affected versus unaffected littermates are dramatically different.

Over the past few years, several research groups around the world have also used the *16S rRNA* technique to characterize the bacterial communities

Janice Haney Carr, CDC, published in the Public Health Image Library



Janice Haney Carr, CDC, published in the Public Health Imagage Library

Scanning electron microscopy images of Pseudomonas aeruginosa *(left) and* Staphylococcus aureus*, examples of the types of bacteria found on human skin*

of the mouth, colon, vagina, stomach, and esophagus. Taken together, these studies show that, depending on the location, between 20 and 80 percent of the bacterial species had not previously been described. Remarkably little had been known about even some dominant species, including the second most common genus to emerge in Segre's study, the Janthinobacteria.

There were marked differences in the bacterial composition of the different organs—not surprising, considering the differences in their respective environments, such as the availability of nutrients, water, and oxygen.

Overall thus far, only a limited number of subjects have been sampled and only a few studies have followed the development of the microbiome over time. "What happens during puberty, for example?" asks Segre.

The first phase of the HMP aims to establish whether there is a core human microbiome. Samples from 250 volunteers will be taken at five different sites (nose, gut, vagina, skin, and mouth) and the bacterial species identified using the *16S rRNA* technique. The sampling will be done at the Washington University School of Medicine in St. Louis and the Baylor College of Medicine in Houston, Texas.

The initial investigations will focus on describing the normal bacterial population of healthy human beings, the diversity within and between individuals, and the role of genetic and environmental factors in determining the composition of the bacterial communities. It will also address technical issues, such as developing methods to reproducibly take samples from the different locations.

In Segre's study, for instance, various methods for obtaining skin samples (by punching out a section of the skin or by swapping or scraping the surface of the skin) yielded equivalent results for four of the patients, but the Staphylococcus colonization of the fifth patient would have been missed in the scraping and the punch biopsy.

Segre noted that the volunteers from rural and urban regions will be selected to encompass a wide variety of lifestyles and racial and ethnic backgrounds in order to get a glimpse of the breadth of variations that can be expected in the human microbiome. At the same time, it is unlikely that a sample of only 250 human beings will be large enough to exhaustively explore those influences. The first results from these studies are expected within 12 to 18 months.

Other questions include how many sequences are needed to obtain a complete picture or comparison of different sequencing methods.

The second phase of HMP investigations is expected to follow how differences in the microbiome correlate with lifestyle, diet, and, especially, diseases and treatment of disease in more detail. Even now, preliminary projects outside the HMP, such as the previously mentioned work on atopic dermatitis, explore the feasibility of correlative studies.

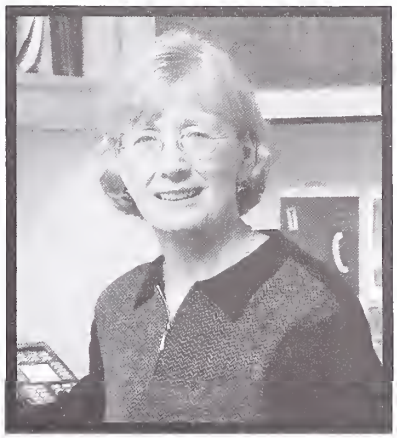
The initial phase of the HMP will contain 10 so-called demonstration projects that will explore possible connections between microbial colonization and human disease. After a year, the five most promising projects will be selected and supplied with additional scale-up funds, said Jane Peterson, associate director, NHGRI Division of Extramural Research, and HMP project leader.

Ultimately, the HMP aims to move beyond the description of species to develop a map of genes and proteins in microbial communities, describing the flow of metabolites and energy among the microorganisms and between the microorganisms and human cells. The first step in this direction is the sequencing of reference genomes of 1,000 bacterial species.

The project started in 2007 with the awarding of $8.2 million for the sequencing of the first 200 genomes to four sequencing centers at the Baylor College of Medicine, the Washington University School of Medicine, the Broad Institute of MIT-Harvard in Cambridge, Mass., and the J. Craig Venter Institute in Rockville, Md.

In 2009, another $30.5 million will be awarded in up to five competitive four-year grants to sequence 400 additional reference genomes and to further characterize the genetic complexity of the human microbiome. Other funding by NHGRI and international efforts will complete the full reference set of genomes.

Maria Giovanni, HMP project leader for NIAID, emphasized that the genomic information created in this part of the project will be an invaluable scientific resource comparable to the sequencing of the human genome completed in 2003.



Jane Peterson

Markus Elsner

"The scientific community will have rapid access and use the datasets and reagents generated by the HMP to ask more questions and develop research projects," Giovanni said.

A major focus will be to develop a data coordination center to organize the large amounts of data that will be stored at the National Center for Biotechnology Information. The databases will be freely accessible to all scientists around the world.

The sequencing effort is anticipated to produce results quickly. Due to the development of new technologies triggered by the HMP and the cooperative nature of the project, Giovanni expects that the first 600–1,000 genomes will be sequenced within two to three years.

Participants in the HMP expect their results to quickly find their way from the laboratory bench to the hospital bed. "This is a new frontier for health," says Peterson. And Segre adds, "this has the potential to really change the point of contact care for patients." ■

COOL METHODS

The Beginners' Guide to 508 Compliance, or How to Make Your Website More Accessible to *Everybody* in Eight Easy Steps

Section 508 of the Rehabilitation Act requires federal agencies to make their electronic and information technologies accessible to people with disabilities. Here's a primer on website compliance with 508 guidelines.

First off, remember that Section 508 isn't just about making websites more accessible for blind people. The guidelines make websites more accessible to people with disabilities ranging from colorblindness to paralysis, epilepsy, hearing impairment, and even a slow dial-up Internet connection. The goal is to make all the information on your website available in the simplest format, so that interaction with your site can be as flexible as possible.

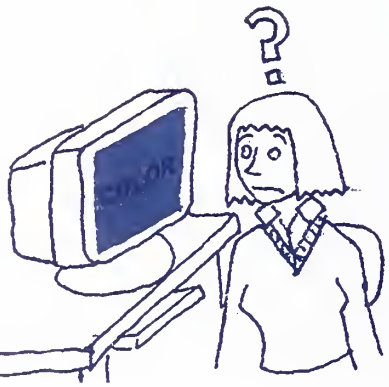
That said, one of the most important considerations to make in adapting your website is how it will interact with a screen reader. A screen reader is an assistive technology that translates information on a website into speech, Braille, or another format in an orderly fashion to help people with visual impairment or learning disabilities. One of your main tasks in reaching 508 compliance is cooperating with the screen reader to make your website as understandable as possible.

Step 1: Get friendly with the alt tag

Researcher, this is an alt tag. Alt tag, this is a well-informed researcher. When you're putting an image in a website, you should always use the alt tag to include a detailed caption for the image so that a screen reader can describe it to users with visual impairment.

You should also make sure to include a "null" alt tag in images that are part of your site's layout but don't carry important information. In html, you can do this by including the phrase alt= "" in your img tag. Including a null alt text in these images allows a screen reader to skip over them without adding confusing narration.

Step 2: Make yourself colorblind



While there's nothing wrong with adding color to your website to give it a little bit of pizzazz, be conscious of the fact that not everybody sees color the same way. For people with colorblindness, colored text might fade into a colored background. The best way to avoid this type of problem is to keep your contrast high.

And try to avoid using color to designate a section heading. Screen readers break up web pages by using a different voice for headings, but only identify larger font sizes or formatting changes like bold or underline as designators. You can use color in a section heading, but be sure to also designate the heading in some other way, too.

Step 3: Video killed the radiologist

Videos are one of the trickier subjects in accessibility. In some cases, it's easiest to just provide a text-only version of the content. Short of that, though, you can make videos accessible by providing captioning for both actions and dialogue. And remember that audio files always need to be accompanied by a transcript.

text and cartoons by Eric Schaffer, OIR communications intern

Step 4: The subtle difference between a table and a pile

When someone uses a reader to access a data table, they depend on the row headers and column headers of the table to make sense of its content. In html you can add headers using the <th> tag at the beginning of each row and column. Without row and column headers, the table becomes a jumble of data that's nearly indecipherable for people with visual impairment.

Step 5: Save the strobe lights for Studio 54

Do you remember that controversy around a Pokémon episode that was banned in the USA because the flashing lights were dangerous to kids with epilepsy? Flickering animations are still dangerous on the Internet, so avoid strobing and flashing in your website. Plus, nobody really needs to see that video of the mitosis breakdance anyway.

Step 6: Adobe Acrobat isn't always right

You've run the accessibility check on your PDF documents, and they come out clear, but that's not always enough! There's a simple checklist on the HHS website that you should run through before posting your PDF documents:
<http://www.hhs.gov/web/policies/checklistpdf.html>.

Step 7: Life without style sheets

While a style sheet is useful for making your website look

nice, make sure that your website doesn't rely too heavily on it. Take a look at your website without the style sheet. Does it still make sense? Try to make sure that the page is organized logically so that it doesn't need the style sheet to put elements in the right order.

Step 8: If all else fails…

Provide a text-only version of your website. This is by far the best way to make your site accessible to people using a screen reader. The best way to include the text-only option is to make a link that says "text only" at the top of a page in the same color as the website's background, so that anybody who isn't using a reader can't see it.

COMMENTARY

The Dual Challenges Presented by Dual-Use Research

by Henry Metzger
<metzgerh@arb.niams.nih.gov>

This essay is intended to open a dialogue for a plan of action for evaluating dual-use research both before it is undertaken and before publication.

An investigator decides to develop a vaccine against a select toxin known for its resistance to conventional denaturing conditions. After purifying the toxin in the usual way, he adds a rather simple step and finds that on testing in mice, the oral LD_{50} is 0.1 percent that reported in the literature!

This result, taken from a real occurrence, is a typical example of "dual-use research"—that is, research that may generate valuable scientific knowledge but that could also be deliberately used to create serious harm to the public health or the environment.

Whether the investigator should publish this finding is the dual challenge presented by dual-use research results. On the one hand, it is important to publicize the findings so that others can make use of the new knowledge to our mutual benefit; on the other hand, one wishes to avoid dissemination of information that could easily be used by someone to create havoc.

That advances in biotechnology require only relatively simple resources to be misused for destructive purposes has long been recognized, but the terrorist activities of September 11, 2001, and the deliberate dissemination of anthrax spores shortly thereafter magnified this concern within both the scientific community and the public at large.

A keyword search for "bioterrorism" within the PubMed database fails to yield a single hit before 1996, but in 2002, the peak year, almost 900 citations are listed. In parallel, potential dual-use research results such as those listed in Table 1 have appeared on the front pages and in op-eds of the nation's most influential newspapers, and they have raised controversies about their publication in the halls of Congress.

Table 1. Recent Examples Of Published "Contentious Research"

- Extending the host range of *Listeria monocytogenes* by rational protein design (human to mouse, 2007)
- Comparison of immune response to a virulence gene from vaccinia and smallpox (2002)
- Total synthesis of poliovirus genome (2002)
- Enhanced virulence of mousepox virus–IL-4 construct (2001)

Academies of science in the United States, the United Kingdom, and elsewhere have organized conferences on the subject; an in-depth monograph on the subject by the U.S. National Research Council (*Biotechnology Research in an Age of Terrorism,* 2004) has been particularly influential. Professional societies—in particular, the American Society for Microbiology and FASEB—have promoted discussions of the issues, and the U.S. government responded by creating a National Science Advisory Board on Biosecurity in 2004.

The Board's membership includes representatives of government security agencies, health agencies—including, of course, the NIH—and academia and industry. Its "Proposed Framework for Oversight of Dual Use Life Science Research: Strategies for Minimizing the Potential Misuse of Research Information" was issued for public comment in June 2007. Special emphasis has been directed towards those areas of research that are of most obvious concern such as those listed in Table 2.

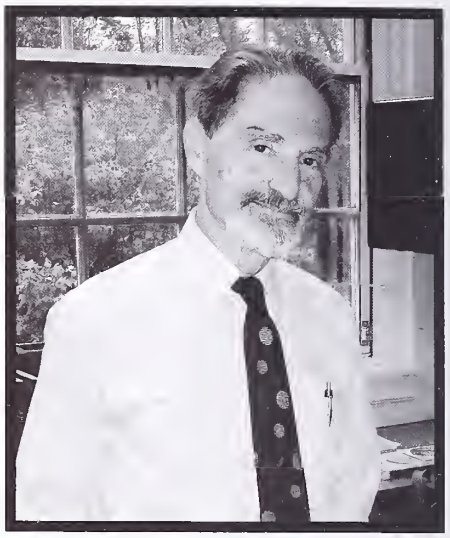
The importance of international co-operation for dealing with the challenge of dual-use research is self-evident. A second "Forum on Biosecurity," attended by 31 countries and sponsored by eight international organizations, was held March 31–April 2, 2008, in Budapest.

The agenda and PowerPoint presentations can be accessed at **<http://www7.nationalacademies.org/biosecurity/2nd%20International%20Forum%20on%20Biosecurity.html>**.

Table 2. Principal Types Of Research Results That Raise Dual-Use Concerns

Findings that:

- Enhance the harmful consequences of a biological agent or toxin
- Disrupt immunity or the effectiveness of an immunization without clinical and/or agricultural justification
- Confer upon a biological agent or toxin resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitate its ability to evade detection methodologies
- Increase the stability, transmissibility, or ability to disseminate a biological agent or toxin
- Alter the host range or tropism of a biological agent or toxin
- Enhance the susceptibility of a host population
- Generate a novel pathogenic agent or toxin or reconstitute an eradicated or extinct biological agent



Fran Pollner

Henry Metzger

All those considering this subject have emphasized the foremost importance of educating members of the research community about the dual-use research dilemma, recognizing that, as with recombinant DNA research, the scientific community itself is in the best position to properly balance the advantages of open unfettered research and communication of its results and the need to protect the public from harm.

Table 3 lists the annual number of deaths from various causes over the five-year period from 2002 to 2006. It would be a tragedy if by self- or government-imposed censorship occasioned by the threat of misuse, research directed towards the biological, behavioral, and social factors responsible for the major causes of death and morbidity were to be constrained.

The best way to avoid that scenario is for the scientific community to provide credible evidence that it is willing and able to deal responsibly with the public's legitimate concerns. ■

Table 3. World Mortality Statistics

Cause	Incidence Per Year (2002–2006)
Communicable diseases and maternal, perinatal, and nutritional conditions	18,400,000
Noncommunicable diseases	33,500,000
Injuries (intentional and nonintentional)	5,200,000
Bioterrorism	1

The Passing of a Musical Tradition: April Coda for the NIH Chamber Music Series

by Henry Metzger
Scientist Emeritus

Forty years ago at the NIH, the world-famous ensemble Virtuosi di Roma presented an all-Vivaldi program to an appreciative crowd of scientists and local residents.

This was the first of a series of chamber music concerts initiated by the late NIMH scientist Giulio Cantoni (see <http://www.nih.gov/catalyst/2006/06.03.01/page7.html>) and supported by the Foundation for Advanced Education in the Sciences (FAES)—a series that ended on April 6 this year with a performance by baritone Wolfgang Holzmair and violinist Russell Ryan.

In those years before the opening of the John F. Kennedy Center for the Performing Arts in 1971, world-class chamber music performances were in short supply in the Washington metropolitan area. Giulio, a native of Italy transplanted to what was then the sleepy town of Bethesda, had a passion for classical music.

With the help of Paola Saffiotti in Italy—who represented famous and aspiring musicians and whose husband, Umberto, had been recruited to the NCI—Giulio set off to share his passion with the NIH community.

Giulio and Paola's goal was to present both well-known artists at the peak of their careers and promising junior performers. Their first full season, in 1968-1969, included concerts by such musical luminaries as pianist Mieczyslaw Horszowski, violinist Isaac Stern, and flutist Jean-Pierre Rampal; over the ensuing seasons the concerts included outstanding instrumentalists and vocalists from almost every European country as well as from Japan.

For many performers, the NIH concerts constituted either their American or Washington debut, and this list includes Maurizio Pollini (1971), Radu Lapu (1974), Viktoria Mullova (1987) and Ignat Solzhenitsyn (1992). The concerts were held mostly on Sunday afternoons in the Clinical Center's Masur Auditorium.

After the initiation of the campus security regulations after the events of September 11, 2001, the concerts had to be moved off campus. This move, as well as a variety of other factors, led to a gradual but continuing decline in attendance, particularly of NIH personnel. With the deteriorating financial balance, the concerts required increasing support from the FAES, further precipitating its demise.

In the last few years as Giulio's health deteriorated, Paola had to assume most of the organizational work—and all of it for the last two seasons after Giulio's death in July 2006. Paola herself now can no longer keep the series vibrant. It should be noted that the Cantoni and Saffiotti efforts have been entirely without pay.

The end of the Sunday afternoon series, albeit a sad passing, does not leave a vacuum of professional musical offerings at NIH. The Manchester String Quartet presents free concerts in the Masur Auditorium from 12:30 to 1:30 p.m. on most first Mondays of the month, October through May.

Giulio Cantoni

An unusual feature of the Manchester Quartet's popular offering is that it is an integrated series with detailed program notes; each concert is introduced by informative comments by the quartet's leader, cellist Glenn Garlick.

The Merck Foundation has supported this series, but that support will end after the completion of its 20th season in 2008–2009. Thereafter, the FAES has pledged to continue the series. Of course, no series of classical music, often now simply called "great music," can survive without an audience. Help keep the NIH hills alive with the sound of music. ■

Translational Research Interest Group: Bench to Bedside and Back

The purpose of the Translational Research Interest Group (TRIG) is to bring together physician-scientists and basic scientists, particularly intramural investigators, to discuss efficient ways of accelerating the application of biomedical discoveries to clinical practice for the benefit of patients. Conversely, it is also aimed at promoting the translation of clinical observations to the development of improved preclinical strategies and of disease models.

The first meeting of the TRIG will be held on May 29, 2008, 10:00 a.m.–12:00 noon, at the Natcher Conference Center (Building 45), Balcony A. A tentative meeting agenda follows:

- Introduction of TRIG
- Discussion of future events to facilitate bridging the gap between laboratory research and clinical applications at NIH, for example, making clinical specimens and other resources available to NIH intramural scientists
- Coordination of all translational research activities, including facilitation of collaborations between intramural scientists and NIH grantees
- Introduction of the Clinical Translational Science Award Program
- Discussion of other proposed items
- Signing up to serve on a steering committee composed of NIH staff only

NIH intramural scientists and extramural scientists are invited to become members of the TRIG at <http://www.nih.gov/sigs/sigs.html>. The invitation to join the TRIG is extended to staff at the Food and Drug Administration and other federal government agencies, and to scientists from the extramural research community outside of government. An e-mail message will be sent to encourage a new member to complete subscription to the NIH ListServ. TRIG events will be announced through this ListServ.

For additional information, contact Min Song, NCI, at <**songm@mail.nih.gov**>.

Trainees Pack Natcher for Career Symposium

by Caroline Small
OITE communications intern

Animated speakers and an eager crowd of more than 800 NIH trainees defined the first annual NIH Career Symposium, held April 9 at the Natcher Conference Center.

Keynote speaker Peter Fiske, author and CEO of of a California-based technology company, set the tone—serious and playful—in describing the significance of having the letters "Ph.D." follow one's name.

These letters, Fiske said, reflect an educational process that has conferred on degree holders (the postdocs and graduate students in the audience) an assortment of highly valued transferable skills and character traits that are advantageous in any chosen career field—and, he added, having a Ph.D. means that people think "you are a lot smarter than we know you actually are."

Throughout the day, Fiske and other panelists echoed the sentiment that Ph.D. candidates often sell themselves short. They urged trainees to value their skills and abilities and make them shine in their true lights on CVs and any other job-seeking description of oneself.

Another recurring theme was the need to make oneself available to new options and be ready for opportunities when they arise. "It is the prepared people that have all the lucky things happen to them," said Sharon Milgram, director of the Office of Intramural Training and Education, encapsulating OITE's goal for the event. Her office, which co-hosted the symposium, encourages trainees to learn how best to prepare for a scientific career, including how to gracefully transition from one to another position, as well as to anticipate and achieve the skills necessary to move on to one's desired destination. OITE staff and private consultants were on hand to discuss personal and career development.

More than 70 speakers from private consulting firms, government agencies, educational institutions, and biotechnology companies participated in 15 panel discussions.

The great strength of the event was the range of speakers—in fields represented, degrees held, and positions attained. Some were a few years into their career of choice; others had more than 30 years of experience.

Each panel was followed by a social period of information exchange and networking, and many panel participants were eager to speak with trainees after the event.

Some of the 800-plus attendees during a break from the symposium

Some of the most popular sessions focused on how to get jobs in academia and industry—jobs that involve heavy bench work. But bench research, Milgram observed, is not the only path to advancing scientific excellence, education, and development in the modern world. Beyond technical ability, she observed, scientists need to master the skills needed to be team players, leaders, mentors, and professionals.

The larger-than-expected crowd, most of whom stayed for most of the day, reflects the event's success. Many speakers expressed interest in participating again next year. Milgram declared the day "a huge step forward" in providing solid and comprehensive career development services.

Co-sponsors of the event were the Foundation for Advanced Education in the Sciences, the Fellows Committee, and the Graduate Student Counsel. ■

NCBI visiting fellow Manoj Tyagi (left) enjoying a post-talk encounter with keynoter Peter Fiske

Speaker Patricia Phelps, University of North Carolina School of Medicine, Chapel Hill (left), touching base with Anthony Bount, a UNC -GPP student

Lori Conlan, director of the Office of Postdoctoral Services, OITE (left) speaking at length with a postdoc

photos by Bill Branson

Introducing the Assistant Clinical Investigator

by Craig Woodside

Clinical and scientific directors at NIH have created a new professional designation, the assistant clinical investigator, to help fill the gap between clinical fellowship and tenure-track while also better recognizing clinical investigators.

This new position aims to provide clinical clinical investigators with advanced mentoring, independent resources, and more time to enlarge their talents and research accomplishments on the road , should they aspire to take it, to the tenure track.

It is "not designed to hold them at NIH forever," noted Lynette Nieman, an NICHD senior investigator and chair of the Careers Working Group of the Advisory Board for Clinical Research. Rather, it is viewed as the intramural equivalent of a newly appointed assistant professor in the extramural program, many of whom have K23 grant support.

This new designation did not materialize out of nowhere, said Richard Wyatt, executive director of the Office of Intramural Research. The idea for such a slot dates back to the 1997 Straus Report, (see <**http://www.nih.gov/catalyst/back/97.05/p2.html**> for the Executive Summary), which stated that clinical research might be "no longer such a desirable career choice," due to the slow production of results compared with basic research. This language, in turn, influenced the 2004 Benz-Goldstein report, with the more pointed recommendation:

"Staff clinicians whose major focus is clinical research should be treated like other tenure-track scientists, recruited through an open search, and provided with independent research resources.... Perhaps a separate designation, such as clinical investigator, would be appropriate for these individuals. The non-tenured staff clinician designation should be reserved for those who truly function primarily in a service role."

The use of this designation is at the discretion of the institutes, and one institute may opt to use it more heavily than another. Interested clinical researchers— for example, clinical fellows or staff clinicians—should contact their branch chief to learn the nuances of the position in their institutes and centers (ICs), Wyatt said.

The position is described in the intramural sourcebook:

<**http://www1.od.nih.gov/oir/sourcebook/prof-desig/AsstClinInv.htm**>.

A standard competitive recruitment mechanism may be used to attract both intramural and extramural candidates for these positions, Nieman said.

Assistant clinical investigators will have a three-year appointment with the possibility of up to two one-year extensions. Though the slot can be a valuable steppingstone to the tenure track, its principal objective is to stimulate careers in clinical research, according to Nieman, CC Director John Gallin, Deputy Director for Intramural Research Michael Gottesman, IC scientific directors, and many others within the Intramural Research Program.

Staff clinicians serve important roles in the clinical research process. In some cases, they may be eligible for an Assistant Clinical Investigator designation, but other options may also be possible, Wyatt said.

As the Straus Report points out, without clinical researchers, it would be very difficult for the NIH to fulfill the second part of its mission—the "pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability. . . .

"[NIH's] massive intellectual and capital resources, its singular focus on research rather than on service obligations, teaching, or profit, and its sustained support by an enlightened nation should permit the NIH to harbor an atmosphere of dynamic scholarship and incomparable clinical research productivity even as clinical research continues to erode elsewhere."

"The assistant clinical investigator position is a critical step in mentoring and enabling clinical research careers at the NIH," said Gottesman. "I strongly encourage its widespread use." ■

Staff Scientist/Staff Clinician Town Hall Meeting

The NIH Staff Scientist/Staff Clinician (SS/SC) Organization was conceived in 2004 with the intention of providing representation for the more than 1,000 staff scientists and staff clinicians dispersed across the 22 NIH institutes and centers (ICs) with intramural research programs.

The organization will hold its first Town Hall Meeting on **Friday, May 30, 2008,** from 9:30 to 11:30 a.m. in the Lipsett Auditorium, NIH Clinical Center.

The meeting is open to all members of the NIH community, with videoconferencing available at the following locations: Frederick, Md. (Bldg. 549, Boardroom), Baltimore (BRC, Rm. 03C219), Rocky Mountain Labs, Hamilton, Mont. (Bldg. 11 conference room), and Research Triangle Park, N.C. (Executive Conference Room).

After introductory remarks by Michael Gottesman, deputy director for intramural research, the SS/SC Council of Representatives, composed of one to two members from each IC, will present an overview of the activities of the past year, including ratification of the organization's constitution and bylaws.

Council members and a diverse panel of individuals from across NIH will then discuss key issues facing staff scientists and clinicians. Questions for the panel discussion can be submitted prior to the meeting at

<NIH_SSSC_REPS-l@list.nih.gov>.

To find out more about the organization, visit the website:

<http://www.nih.gov/sigs/sssc>

or e-mail

<sssc@nih.gov> or <mailto:difilipm@mail.nih.gov>.

Trans-NIH Systems Biology Meeting

A trans-NIH systems biology meeting will be held at Natcher on **June 26–27, 2008,** sponsored in part by the Office of Intramural Research and organized by Rafael Daniel Camerini-Otero (NIDDK), David Levens (NCI), Alan Michelson (NHLBI), and others.

Day 1 features talks by 16 individuals who were instrumental in establishing a systems biology program at their host institution.

Day 2 is a half-day meeting for the speakers and a smaller group of NIH scientists.

All are invited to attend the first day or listen via webcast. A poster and schedule will be distributed in early June. ■

On Tenure Track

Joseph Hibbeln

Joseph Hibbeln, a psychiatrist and lipid biochemist by training, describes himself as an investigator attempting to translate basic neuroscience on the omega-3 essential fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) into direct clinical applications. He is acting chief of the Section on Nutritional Neuroscience, Laboratory of Membrane Biochemistry and Biophysics, NIAAA.

Eleven years after originating a hypothesis that omega-3 deficiencies increase the risk of depression, violence, and suicide, Hibbeln co-authored omega-3 treatment recommendations for the American Psychiatric Association in 2006.

His work also forms the core of a 2008 United Kingdom Parliamentary Inquiry Report that recommends increasing omega-3 intake in school children, pregnant women, patients with major mental disorders, and prison populations.

Hibbeln's collaborative clinical trials with investigators in Kuopio, Finland; Dublin, Ireland; the Brooklyn, N.Y., VA; Columbia University in New York; the University of Arizona; and the University of Cincinnati have demonstrated the efficacy of omega-3s in reducing suicidal thinking and depression among Irish subjects with a history of deliberate self-harm, reducing anger and anxiety among polysubstance abusers, treating depression during and after pregnancy, and reducing the severity of bipolar symptoms in children.

He theorizes that adequate intakes of DHA, in particular, might reduce the violence, depression, and anxiety common among alcoholics, whose brain stores of DHA are depleted. Underlying mechanisms appear to include serotinergic and dopaminergic depletion, increased neural vulnerability to apoptosis, excessive transcription of corticotropin-releasing hormone, and accompanying dysregulation of the hypothalamic-pituitary-adrenal axis, he said.

During fetal development, the nervous system is especially vulnerable to omega-3 deficiencies caused by limiting seafood intake during pregnancy. Thus, Hibbeln tested the efficacy of the 2004 EPA/FDA advisory for fertile or pregnant women to consume less than 12 ounces of seafood a week. He sought to determine whether the risk from nutritional deficiency from avoiding seafood was greater than the risk of exposure to trace levels of methylmercury.

Hibbeln traveled frequently from NIH to collaborate with investigators at the University of Bristol. He found that when maternal consumption of seafood was at or below the limits of the 2004 advisory, the children were more likely to have low verbal IQ and suboptimal behavioral and social development. Paradoxically, the advisory was intended to reduce these harms.

Hibbeln has reported links between increasing rates of homicide, violence, and major depression potentially attributable to changes in the U.S. and international food supply. Such changes include lower consumption of seafood and higher consumption of competing omega-6 essential fatty acids from seed oils.

In calculating intakes based on RDA criteria, Hibbeln estimated the proportion of cardiovascular disease, stroke, premature mortality, and burden of mental illnesses potentially attributable to this reversible nutritional deficiency.

Hibbeln said he hopes "to nurture the field" with extensive collaborations, especially internationally, and is translating his epidemiological studies into clinical trials to reduce violence among prisoners in the Delaware prison system and, at NIH, is designing metabolic diets to selectively lower omega-6 intake.

He is developing protocols to prevent and treat depression, suicide, and posttraumatic stress disorder among military personnel by restoring nutritional adequacy.

—Caroline Small
OITE communications intern

Eric Schaffer

Mihaela Serpe

Mihaela Serpe is the newest investigator in the Laboratory of Gene Regulation and Development at NICHD, where she works at untangling the molecular mechanisms of cellular signaling that guide the embryonic and later development of fruit flies.

Serpe started out as a biochemist at the University of Bucharest, but developed a passion for signaling while earning her Ph.D. at SUNY-Buffalo in stress sensing and cellular response to stress. That passion took her to the University of Minnesota-HHMI, where she started to examine the ways cells encode and interpret signals about their location in the developing embryo.

"I became fearless," she says of her time in Minnesota, where she started to work with fruit flies and sometimes did experiments in worms, frogs, and zebrafish to better understand the class of signaling molecules known as transforming growth factor–beta (TGF–β).

The TGF-β superfamily of growth and differentiation factors is one of the largest classes of signaling molecules. TGF-βs control many biological processes including patterning, from deciding which side of an embryo is dorsal to finessing the crossveins in a fly's wing.

Serpe's work aims at understanding the intricate regulation of these factors by a handful of secreted molecules, such as Crossveinless-2 (Cv-2), which recently attracted her attention by its ability to both facilitate and impede the action of some TGF-β signals—the bone morphogenetic proteina (BMPs).

In a 2008 paper, she showed that Cv-2 binds to BMPs, to the cell surface, and to the BMP receptor and can either antagonize BMPs or guide them to receptors.

To understand how molecules like Cv-

2 can modulate BMP gradients and shape the fly wing, Serpe has teamed up with computer scientists at the University of Minnesota to create mathematical models. Through constant comparison between the wet bench data and computational models, she's been able to hunt more effectively for the mechanisms of signal interactions.

It's this precise refinement in the developmental message that fires Serpe's passion for cellular communication. "The style of the language" is her main focus, "rather than the letters used," she says. For her, it's in the subtle shadings of the proteins repertoire that medical applications begin to be seen.

She envisions the development of efficient therapies, including the speedy repair and strengthening of damaged bones, arising from an understanding of the molecular mechanisms responsible for localizing and stabilizing BMP signaling in fruit flies.

—Eric Schaffer
OIR communications intern

Vasculopathy Workshop

A workshop on Vasculopathy in Sickle Cell Disease will be held **August 27–28, 2008**, at the Natcher Conference Center.

For more information, visit **<www.sicklecellmeeting.net <http://www.sicklecellmeeting.net/>** or contact Sue Dilli at 443.451.7252 or at **<sue@strategicresults.com>**.

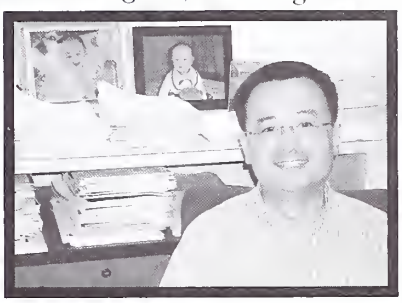
New Price List

The NCI Animal Production Program has implemented a price increase. The new Price List is effective May 5, 2008, and can be found at the website: **<http://web.ncifcrf.gov/research/animal_production_program>**

For more information, contact Linda Blumenauer at 301-846-1153 or at **<blumenauerl@ncifcrf.gov>**.

Recently Tenured

Jun Shen *received his Ph.D. in 1995 from the University of Wisconsin at Madison. He did postdoctoral work at Yale University in New Haven, Conn, and was a research assistant professor at New York University and a senior staff investigator at the Nathan Kline Institute in Orangeburg, N.Y., before joining NIMH as an investigator in 2002. He is currently a senior investigator in the Mood and Anxiety Disorders Program, NIMH.*



Fran Pollner

Jun Shen

My group studies brain chemistry using, primarily, in vivo magnetic resonance spectroscopy (MRS) and imaging. In vivo MRS allows noninvasive detection of metabolic events and neurotransmission in the living human brain. It offers a unique window into brain chemistry by providing valuable biomarkers for various brain disorders. We develop in vivo MRS and spectroscopic imaging techniques and apply them to brain studies.

Whereas proton MRS measures static concentration of important brain chemicals (for example, GABA, the major inhibitory neurotransmitter in the CNS), ^{13}C MRS allows determination of dynamic metabolic fluxes by introducing exogenous ^{13}C-labeled substrates. For example, the flux between neuronal glutamate and astroglial glutamine (an indicator of presynaptic glutamate release) can be determined by measuring the kinetics of ^{13}C label incorporation into glutamate and glutamine from ^{13}C-labeled glucose or the glia-specific substrate acetate.

Converging evidence suggests that hyperglutamatergic activity and GABAergic dysfunction play important roles in the neurobiology and treatment of depression and other mood disorders. For instance, we found abnormal GABA levels in the prefrontal cortex of patients with major depressive disorder but normal levels in depressed patients in remission.

To understand the interactions between GABAergic and glutamatergic systems, we first studied the effect of altered brain GABA level on focal excitability of rat brain. Using proton MRS to measure GABA and functional magnetic resonance imaging to measure neuronal activation, we found that GABA level is negatively correlated with the extent of functional neuronal activation. Next, we used ^{13}C MRS to measure the flux from neuronal glutamate to astroglial glutamine and back in the rat brain, infusing ^{13}C-labeled glucose in the first instance and ^{13}C-labeled acetate in the second. In both cases, we found that increased brain GABA level attenuates the trafficking of neurotransmitter glutamate between glutamatergic neurons and astroglia. The results of our animal studies provide a glutamatergic mechanism of action for GABA-elevating drugs that may contribute to their mood-stabilizing effects.

The quantification of GABA synthesis and glial uptake of neurotransmitter GABA has been controversial due to rapid post-mortem GABA anabolism. We developed the first in vivo 11.7 Tesla MRS techniques using a vertical 89-mm bore magnet. 11.7 Tesla is still the highest field strength at which in vivo MRS of brain has been successfully attempted and enables spectral separation between ^{13}C-labeled GABA and glutamate in the proton spectra.

Using our 11.7 Tesla MRS methods, we performed the first in vivo measurement of GABA turnover from ^{13}C-labeled glucose and acetate. Our results demonstrate that neuronal glucose, not glial glutamine, is the major metabolic precursor of GABA and that the intercompartmental GABA-glutamine cycle is a minor flux for clearance of released neurotransmitter GABA.

In addition to measuring static concentrations and dynamic fluxes, MRS has also been used to measure the activity of certain enzymes in vivo using magnetization transfer. The phenomenon of in vivo enzyme-specific magnetization transfer was discovered for creatine kinase and ATP exchange reactions in the late 1970s using ^{31}P MRS. Since then, no new enzyme-specific magnetization transfer effects had been found in vivo until our recent discovery of magnetization transfer effect catalyzed by aspartate aminotransferase, lactate dehydrogenase, malate dehydrogenase, and carbonic anhydrase.

Our discoveries have extended the scope of in vivo ^{13}C MRS to include enzyme activities. We hope that by using hyperpolarized ^{13}C imaging techniques we can generate in vivo enzyme activity images. ■

Catalytic Reactions?

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

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

In Future Issues...

- Web Copyright Do's and Don'ts
- Collaboration and the Ombudsman
- Interest Group Directory

Fran Pollner

Canada geese seem to have adopted NIH as their natural habitat. They ambulate everywhere on campus these days—singly, in couples, in groups, expecting and receiving right-of-way. And they have an uncanny way of turning the environment to their own purposes without doing damage—for instance, the day after a downpour a little while ago that left an impressive puddle between Building 1 and Building 2, a goose took up residence in the center of what had clearly been transformed into its own personal lake and lounged there surveying the passersby (and preventing them from stepping into the puddle—a win-win situation).

It was a sight worthy of a camera, but I was in too much of a hurry to retrieve the Catalyst camera from the office, though it was only steps away. So the photo above will grace this back cover instead. It's a closer representation of leave-taking, anyway,—which is what I'm doing (the other could perhaps have depicted my adapting to the post of Catalyst managing editor nearly 12 years ago).

I've enjoyed my strolls around campus.

—Fran Pollner

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