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The Alaskan Sled Dog

A Genetic Breed Apart

BY RAYMOND MACDOUGALL, NHGRI

Heather Huson has a passion for sled dogs. She grew up participating in sled-dog racing, qualifying twice for the U.S. Olympics team and competing in the sport's world championship of sled-dog racing in 1995 and 2001.

Now the National Human Genome Research Institute (NHGRI) graduate student and University of Alaska at Fairbanks Ph.D. candidate has found another place for sled dogs: in her genetics research.

Huson is the lead author of a study on the genetic origins of sled dogs, a study whose authors also include Elaine Ostrander and other scientists from NHGRI's Cancer Genetics Branch as well as her university advisor. In their analysis of 199 Alaskan sled dogs and 681 purebred dogs belonging to 141 other breeds, the study found that Alaskan sled dogs represent a distinct genetic breed characterized by performance and behavior rather than appearance. The study was published in the online issue of the BioMed Central's open-access journal *BMC Genetics* (*BMC Genet* **11**:71, July 22, 2010).

"The Alaskan sled dog presents a case in which a genetically distinct breed of dog has been developed through the selection and breeding of individuals based solely on their athletic prowess," Huson said. "Interestingly, this continual out-crossing for athletic enhancement has still led to the Alaskan sled dog repeatedly producing its own unique genetic signature. Indeed, the

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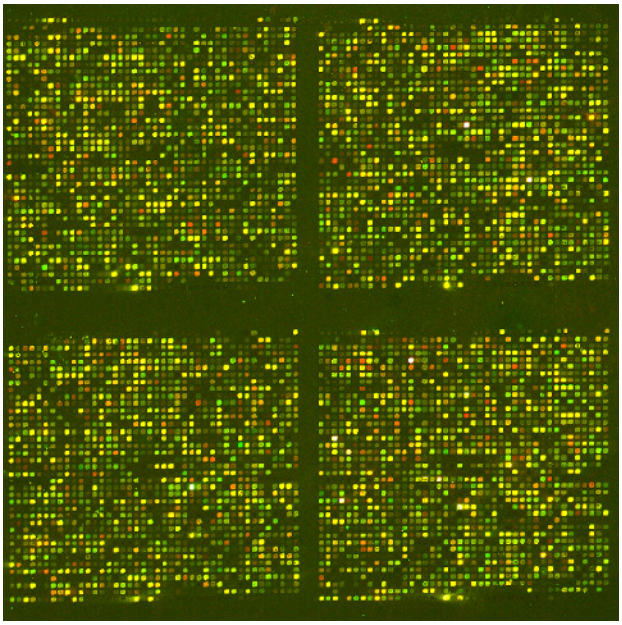
NIEHS Advances Predictive Genomics

And May Help Prevent Drug-Induced Liver Injury in the Process

BY THADDEUS SCHUG, NIEHS

Toxicogenomics pioneers at the National Institute of Environmental Health Sciences (NIEHS) are harnessing the power of microarrays and other gene-expression technologies to gain new insights into the mechanisms of toxicity and advance the discipline of predictive toxicology.



JUANITA MARTINEZ, ANGELINA RODRIGUEZ, U. OF NEW MEXICO

NIEHS scientists used microarrays to identify genetic indicators that could predict drug-induced liver injury. Each microarray is a small membrane or glass slide containing samples of many genes arranged in a regular pattern.

Take drug-induced liver injury (DILI) for instance. Although new drugs are rigorously tested as they are being developed, rare adverse effects—such as acute liver failure—might not become evident until after the drugs are approved. In fact, DILI is a major reason that drugs are withdrawn from the market, have their use restricted, or are required to wear a warning label. It is difficult to predict DILI or diagnose it in its early stages. Serum markers or liver biopsies are not true predictors and only detect liver injury once it's happened. And some people may be genetically predisposed to having an adverse reaction to certain drugs.

But NIEHS researchers may have found a better way to predict DILI, according to a study published in a special issue of *The Pharmacogenomics Journal*. Bioinformatician Pierre Bushel led a team of 23 investigators who used gene expression microarray technology to

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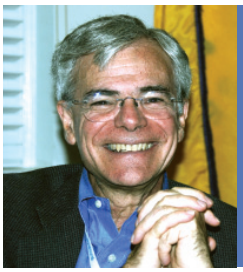


Communicating in Plain Language

BY MICHAEL GOTTESMAN, DDIR

Do you ever get the feeling that most people have no idea what you're talking about? Do you find yourself telling your neighbors you just work on cancer and leave it at that, when it's really Wnt signaling or something else equally esoteric? Who can fault us? We're scientists, not professional communicators, right? Well, yes and no.

Better communication skills can give taxpayers and Congress a better appreciation for your work . . .

Clearly our primary role as NIH scientists is to advance the NIH mission: to seek fundamental knowledge about the nature and behavior of living systems and apply that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. But as astronomer Carl Sagan would say, we, as scientists, also have a responsibility to share that knowledge. We are privileged to know as much as we do and to have such tools at our disposal. And as federal employees paid by tax dollars, we have the added responsibility of keeping the public informed about our research.

This isn't about dumbing down your research for a so-called uneducated lay audience. Better communication skills, as captured in the federally sponsored Plain Language Initiative, can give taxpayers and Congress a better appreciation for your work, which ultimately helps secure future funding.

Few of us can follow the arcane details and jargon of someone even in a closely related field; a paper or talk presented in plain language can educate and entertain colleagues. Plain language also can help spark collaborations among scientists who don't otherwise share the same esoteric language.

We are a rather smart crowd here. If you can learn science, you also can learn the principles of better communication. These principles include using shorter sentences and paragraphs, avoiding jargon and passive voice (write "We reviewed your application" not "The application was reviewed"), and organizing concepts logically.

And by all means, say what you mean without using more words than you have to. Use common everyday words ("allow" instead of "afford an opportunity").

Plain language long has been the domain of the NIH communications offices, for obvious reasons. But the times they are a-changing. In a world of vast misrepresentation of ideas, plain language has become everyone's responsibility.

In August the Office of Extramural Research (OER) sent a notice via e-mail to its staff about plain language. The reasoning, in part, was that our scientific review officers interact with grantees. Thus, they are in a valuable position to spread the concept of plain language to these scientists, whose grant applications are made public when funded. Others in the OER interact directly with elected officials, so their own use of plain language with these politicians can have a powerful effect on pro-science legislation.

As a winner of 2009 NIH plain language awards for my DDIR Web Board (ahem, a little self-promotion is perfectly legal in plain language) and for articles in *The NIH Catalyst*, I encourage you to familiarize yourself with some of the basic guidelines at http://execsec.od.nih.gov/plainlang and http://www.plainlanguage.gov. You may also enjoy taking the voluntary course at http://plainlanguage.nih.gov.

. . . which ultimately helps secure future funding.

As you find yourself no longer worried when speaking to neighbors and friends about your work, I hope you will be inspired to share your research results with our communication staff for broader dissemination. ●

NIH ABBREVIATIONS

CC: NIH Clinical Center
CIT: Center for Information Technology
FAES: Foundation for Advanced Education in the Sciences
FelCom: Fellows Committee
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCCAM: National Center for Complementary and Alternative Medicine
NCI: National Cancer Institute
NEI: National Eye Institute
NHGRI: National Human Genome Research Institute
NHLBI: National Heart, Lung, and Blood Institute
NIA: National Institute on Aging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAID: National Institute of Allergy and Infectious Diseases
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB: National Institute of Biomedical Imaging and Bioengineering
NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDA: National Institute on Drug Abuse
NIDCD: National Institute on Deafness and Other Communication Disorders
NIDCR: National Institute of Dental and Craniofacial Research
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
OD: Office of the Director
OITE: Office of Intramural Training and Education
OIR: Office of Intramural Research

INSTITUTE OF MEDICINE NEW MEMBERS

- Jeremy M. Berg, Ph.D., Director, NIGMS
- Linda S. Birnbaum, Ph.D., Director, NIEHS
- Ira H. Pastan, M.D., Chief, Laboratory of Cell Biology, Center for Cancer Research, NCI
- Thomas E. Wellems, M.D., Ph.D., Chief, Laboratory of Malaria and Vector Research, NIAID
- Carl Wu, Ph.D., Chief, Laboratory of Biochemistry and Molecular Biology, Center for Cancer Research, NCI

Bioinformatics at the NIH Library

BY REX ROBISON, NIH LIBRARY

"There's an angry mob outside," an events management coordinator told Medha Bhagwat as she was about to introduce the instructor for her bioinformatics class in a filled-to-capacity conference room several months ago. "You'd better show your face. People are demanding an explanation."

Medha Bhagwat's bioinformatics training sessions used to be held in small conference rooms, but they have become so popular that many are now held in larger auditoriums like Lipsett Amphitheater.

There were more than 50 anxious people outside the room, wondering why they weren't being allowed in. "When I walked out I took a deep breath," Bhagwat recalls. "I had to tell them I appreciated their coming, but there was no more room."

Now the NIH Library, which has trained some 1,300 researchers in its Bioinformatics Support Program since September 2009, knows to hold certain sessions in bigger auditoriums (such as Building 10's Lipsett Amphitheater, which seats 260).

Bioinformatics is the intersection of biology, computer science, and mathematics. It provides researchers with powerful tools to analyze a variety of data. Bhagwat, an informationist and bioinformatics specialist, used to work at the National Center for Biotechnology Information and started the NIH Library's program a year ago. She teaches courses in sequence analysis, genome browsers, identification of pathogenic mutations, and more. She also offers one-on-one consultations and online tutorials and sometimes invites outside trainers to give presentations about their products. The more advanced courses are held in the NIH Library's state-of-the-art training room, where students are provided laptops to try out exercises on their own. And, to help meet the demand, the NIH Library recently hired Lynn Young to provide more programming support for high-throughput data analysis, especially for microarray and next-generation sequencing data. Young was formerly at NCI-Frederick and CIT's Division of Computational Bioscience.

The library also provides bioinformatics software tools that are useful for retrieving and mining relevant literature, visualizing pathways, and identifying research targets, and it recently licensed software for next-generation sequence analysis. And there are two dedicated computers loaded with bioinformatics resources for NIH staff to use.

For more information about the NIH Library Bioinformatics Support Program, registering for free classes, getting accounts for licensed tools, and finding links to online tutorials, visit http://nihlibrary.nih.gov/ResearchTools/Pages/Bioinformatics.aspx. ●

A wordle, or word cloud, filled with comments about the NIH Library's bioinformatics training.

CLINICAL RESEARCH TRAINING AND MEDICAL EDUCATION

FDA Clinical Pharmacology Rotation

BY JUAN LERTORA, NIH CLINICAL CENTER

Clinical research trainees who want to get a first-hand look at how the Food and Drug Administration's (FDA) regulatory process works may want to consider applying for a Clinical Pharmacology Rotation at the FDA. The program, which has been ongoing since 2008, provides NIH clinical and translational investigators and clinical fellows with a short-term rotation at the FDA's Office of Clinical Pharmacology (OCP) in the Center for Drug Evaluation and Research (CDER).

The OCP's mission is to assure the safety and effectiveness of new drugs through the evaluation of clinical pharmacology and biopharmaceutical data in support of CDER's Investigational New Drug (IND), New Drug Application (NDA), and Biologics License Application (BLA) review programs. OCP ensures that regulatory policy and decision making are based on the best available science.

The four- to eight-week NIH-FDA program rotation, which takes place on the White Oak campus in Silver Spring, Md., includes tutorials on how to prepare an IND and on therapeutic, area-specific drug-development guidelines. Trainees may also review preclinical and clinical data on investigational drugs, participate in specialized therapeutic team meetings, contribute to IND 30-day safety reviews, and take part in meetings with sponsors. Trainees have plenty of opportunities to network.

In addition, sometime in 2011 there will be another rotation to consider at CDER's Office of New Drugs. Please note that these rotations are possible only if the respective NIH fellowship program directors grant permission. A signed confidentiality agreement is also required because of the proprietary nature of information discussed at the FDA meetings.

If you are interested, contact me (I'm the program director in the Office of Clinical Research Training and Medical Education, NIH Clinical Center) at lertoraj@cc.nih.gov or 301-496-9425. I will help you determine an area of interest, identify a proposed time frame for the FDA rotation, and find a mentor at the FDA-CDER-OCP. For more about CDER visit http://www.fda.gov/AboutFDA/CentersOffices/CDER; for more about OCP, visit http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm106189.htm. ●

FROM THE FELLOWS COMMITTEE

Bird's Eye View: Human Subjects Research Advisory Committee

BY KARA KUNTZ-MELCAVAGE, NINDS

As a postdoctoral fellow doing clinical research, I thought I understood institutional review boards (IRBs) and regulations that govern clinical research. I knew that protocols had to be carefully worded and that procedures had to be compliant with established standards. The guidelines seemed to squelch my creativity.

Then I was elected the FelCom liaison to the Human Subjects Research Advisory Committee (HSRAC). HSRAC advises the NIH Deputy Director for Intramural Research (DDIR) on policies and procedures regarding human subjects research. Attending HSRAC's bimonthly meetings broadened my understanding of the regulatory process and increased my appreciation for the IRBs' diligence in reviewing protocols. The discussions gave me insight into how policies emerge.

DDIR Michael Gottesman leads HSRAC, which includes chairpersons from each of NIH's 12 IRBs, the director of NIH's Clinical Center (CC), and the heads of the Office of Human Subjects Research and the CC's Department of Bioethics. The group's deliberations serve as the genesis for new policies that address emerging issues.

Recently, the HSRAC pondered the question,"If an investigator inadvertently learns that someone who donated DNA for breast cancer research is genetically predisposed to developing Huntington disease, should the investigator tell the donor?" Current protocols indicate whether genetic information will be disclosed to study participants, but a standard is needed for future, more encompassing, genomic research.

Investigators have begun using the Internet to recruit patients for clinical trials. HSRAC wants to be sure that patient confidentiality isn't compromised. New policies are developed as needed so investigators are assured that human subjects research offers more benefit than harm.

The next time you hear about a new policy involving human subjects research, rest assured that thoughtful discussions have preceded it. HSRAC policies enhance the integrity of research that occurs at NIH. For more information about the Office of Human Subjects Research and HSRAC visit http://ohsr.od.nih.gov/index.html. ●

GWAS: REPORTS OF ITS DEATH HAVE BEEN GREATLY EXAGGERATED

Statistical Genetic Analysis in the Genomic Era

BY ALEXANDER WILSON, PH.D., NHGRI, AND JOAN BAILEY-WILSON, PH.D., NHGRI

The reports of the death of the genome-wide association study (GWAS) and the failure of the GWAS to find cures for common disease are eerily reminiscent of the reports of the death of linkage analysis and family studies a decade ago. Linkage studies identified the breast-cancer-associated genes *BRCA1* and *BRCA2* and other clinically relevant variants. For GWAS, time will tell. GWAS results are simply candidate regions, regions considerably narrower than those identified with linkage analysis, but candidate regions nevertheless. We need to do more work to identify the true causal variants underlying these associations and to understand their biology.

We believe there are several reasons why GWAS remains an important tool. First, it has already identified thousands of candidate variants across a variety of diseases and traits. With some exceptions (for example, macular degeneration), these variants are not yet clinically relevant but may lead to important discoveries in medical science by identifying new biological pathways and interactions among genes.

Second, more sophisticated analyses and meta-analyses that allow for dominance effects and epistatic and gene-environment interactions may yield a deeper understanding of the effects of variants on disease risk. Third, the GWAS has only recently been applied to traits other than disease risk, such as drug response. And fourth, genes identified with common variants may be useful in finding new drug targets and understanding adverse drug reactions, because the loci that harbor common variants of small effect may be important regulatory loci and/or may contain many rare variants with larger effects.

Rather than slavishly follow the method or tool du jour, we need to understand that different methods and study designs have the ability to detect different things, and that multiple designs and multiple tools must be used to understand complex traits. A GWAS is, in the broadest sense, simply a test of association between a trait and a set of genotypic markers that span the genome. A GWAS has several elements: the density of the markers, ranging from single-nucleotide polymorphism (SNP) panels to whole-genome sequence variants; the type of ascertainment (population- or family-based); the study design (case-control or family studies); and the type of trait.

The term GWAS, and the recent focus that has excluded most other methods and study designs, now refers to population-based studies of unrelated individuals, with high-density SNP panels in case-control study designs. This change in the meaning has been driven by the genotyping technology available, the ease of obtaining population-based samples of unrelated individuals, the focus on categorical disease, and the computational speed and simplicity of the analysis. This study design has good power to detect association with common variants, but then only common variants are being considered. However, other GWAS study designs are possible and have good power in other situations.

SNPs, copy-number variants, and rare sequence variants, collectively referred to here as sequence variants, have two attributes: the frequency of the alleles of the variant and the size of the effect of the variant alleles. Although much debate has focused on common versus rare alleles, what is important is the size of the effect of the variant alleles and whether the effect is at the individual, family, or population level.

One variant for familial hypercholesterolemia, for example, has a large effect in the individual with two copies of the variant, less of an effect in relatives who carry only one copy of the variant, and almost no effect in the population because the variant is so rare. Rare variants with very large effects can be difficult to detect in population studies, particularly if there is genetic heterogeneity (different variants that cause phenotypically indistinguishable disease, such as *BRCA1*). Population-based GWAS studies are not well-powered to detect such effects but a family-based or familial-case versus control GWAS can be more powerful in this situation.

When the cost of whole-genome sequencing drops to that of today's high-density SNP panels, we will have the ability to identify all variants. Family studies will be useful to enrich samples for specific rare variants and identify sporadic variants. Sampling designs similar to that used by the ClinSeq study may become the norm. In ClinSeq, a population-based sample is used to identify sequence variants, but consent includes contacting relatives of the individual in the population study to further study the effect of the variants. As the field of genetics advances, we should design our studies with the most appropriate tools for the job, not just the tool du jour. ●

The authors (who are married to each other) have both published in the areas of segregation analysis, linkage analysis, genome-wide association studies, and most recently analysis of sequence data. For more about the GWAS debate, see the article "Revolution Postponed" by Stephen S. Hall in the October 2010 issue of Scientific American. *(*Sci Amer ***303****:60–67, 2010; doi:10.1038/scientificamerican1010-60)*

Research Briefs

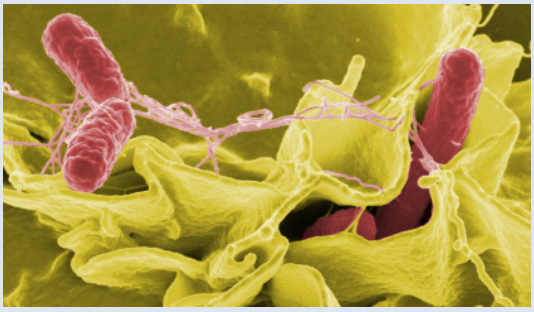
NIAMS, NIDCR, NIAID: CYTOKINES AND SEVERE AUTOIMMUNE DISEASE

NIH scientists have redefined the roles of several cytokines involved in the generation of immune cells implicated in severe autoimmune diseases, including rheumatoid arthritis, psoriasis, and multiple sclerosis. The study in mice showed that development of Th17 immune cells can occur without the presence of transforming growth factor (TGF)–beta, a mediator thought to be required for Th17 cell development. The study demonstrates that the interaction of three inflammatory cytokines—interleukin-6 (IL-6), IL-1-beta, and IL-23—is responsible for the creation of Th17 cells that are more active in promoting autoimmunity than Th17 cells generated with IL-6, IL-1-beta, and TGF-beta. These findings suggest a new model for Th17 generation and the existence of functionally different subtypes of Th17 cells. This study also provides a better understanding of the array of immune components involved in autoimmunity and suggests possibilities for new targeted therapies. (NIH authors: K. Ghoreschi, A. Laurence, X.P. Yang, J. Konkel, H.L. Ramos, L. Wei, T. Davidson, N. Bouladoux, J. Grainger, Q. Chen, Y. Kanno, W.T. Watford, H.W. Sun, G. Eberl, E. Shevach, Y. Belkaid, W. Chen, and J.J. O'Shea; *Nature* **467**:967–971, 2010)

NICHD: DEPRESSION HIGH AMONG VICTIMS OF SCHOOL CYBER BULLYING

Youth who are the targets of cyber bullying at school are at greater risk for depression than are the youth who bully them, according to a survey conducted by NICHD researchers. The new finding is in contrast to earlier studies of traditional bullying, which found that the highest depression scores were reported by another category of youth involved in bullying: so-called "bully-victims." Past studies on traditional bullying show that bully-victims—those who both bully others and are bullied themselves—are more likely to report feelings of depression than are other groups. Cyber bullying, or electronic aggression, involves aggressive behaviors communicated over a computer or a cell phone.

To conduct the study, the researchers analyzed data on 6th- through 10th-grade American students collected in the 2005/2006 Health Behavior in School-aged Children Study, an international study of adolescents in 43 countries (http://www.hbsc.org/overview.html). Compared with students who were not involved with bullying, adolescents who were bullies, bully-victims, or victims tended to score higher on measures of depression. (NICHD researchers: Jang Wang, Tonja Nansel, and Ronald Iannotti; *J Adol Health*, DOI:10.1016/j.jadohealth.2010.07.012.)



ROCKY MOUNTAIN LABS,NIAID

Color-enhanced scanning electron micrograph showing S*almonella Typhimurium* (red or dark) invading cultured human cells.

NHGRI: NIH RESEARCHERS IDENTIFY GENETIC ELEMENTS INFLUENCING THE RISK OF TYPE 2 DIABETES

A team led by researchers at NHGRI and including collaborators from two universities has captured the most comprehensive snapshot to date of DNA regions that regulate genes in human pancreatic islet cells, a subset of which produces insulin. The researchers used DNA sequencing technology to search the chromatin of islet cells for specific histone modifications and other signals marking regulatory DNA. Computational analysis of extensive sequence data identified different classes of regulatory DNA.

Among the results, the researchers detected about 18,000 promoters. Several hundred of these were previously unknown and were found to be highly active in the islet cells. The researchers also identified at least 34,000 distal regulatory elements, many of which were bunched together, suggesting they may cooperate to form regulatory modules. These modules may be unique to islets and likely play an important role in the maintenance of blood glucose concentrations.

The investigators also found that 50 single-nucleotide polymorphisms associated with islet-related traits or diseases are located within or very close to non-promoter regulatory elements. Variants associated with type 2 diabetes are present in six such elements that function to boost gene activity. These results suggest that regulatory elements may be involved in the molecular defects that contribute to type 2 diabetes. (NHGRI researchers: Michael L. Stitzel, Praveen Sethupathy, Daniel S. Pearson, Peter S. Chines, Michael R. Erdos, Stephen C.J. Parker, NISC Comparative Sequencing Program, Elliott H. Margulies, and Francis S. Collins; *Cell Metab* **12**:443–455, 2010)

NIAID: HOW SALMONELLA SPREADS

New findings by NIAID scientists could explain how Salmonella bacteria, a common cause of food poisoning, are efficiently spread in people. Researchers describe finding a reservoir of rapidly replicating Salmonella inside epithelial cells. These bacteria are pushed from the epithelial layer by a new mechanism that releases the Salmonella that infect other cells or are shed into the intestine. While much is known about the human infectious cycle of Salmonella, scientists have yet to determine how the bacteria escape the gut to spread infection. Epithelial cells line the outer and inner surfaces of the body, such as the skin and gut, and form a continuous protective tissue against infection. But Salmonella have learned how to live inside epithelial cells and use them for their benefit. Salmonella bacte-

ria protect themselves within membrane-bound compartments, called vacuoles, inside gut epithelial cells.

Using special high-resolution microscopes to view laboratory-grown human intestinal epithelial cells and laboratory mice infected with Salmonella, an NIAID team, in collaboration with researchers from the University of British Columbia (Vancouver), discovered a secondary population of Salmonella not confined within vacuoles, but instead moving freely inside the epithelial cells. These free-moving bacteria multiply more rapidly; have flagella that promote their movement; and exhibit a needlelike complex used to pierce cells and inject proteins.

The scientists observed that epithelial cells containing the hyper-replicating, invasive Salmonella are eventually pushed out of the intestinal tissue into the gut cavity, setting the Salmonella free. The process resembles the natural mechanism humans use to shed dying or dead epithelial cells from their gut. Salmonella may have hijacked this mechanism to facilitate their own escape.

The human immune system senses that these are not normal dying cells and triggers a response that includes release of interleukin-18, a cytokine that triggers an inflammatory cascade. Interleukin-18 is also prominent in chronic intestinal inflammation associated with autoimmune disorders, such as inflammatory bowel disease. The interleukin-18 release may provide an explanation for the acute intestinal inflammation associated with Salmonella infections. The scientists hope their research leads to a treatment that prevents the spread of infection. (NIAID researchers: Leigh A. Knodler, Jean Celli, Seth Winfree, Bryan Hansen, and Olivia Steele-Mortimer; *Proc Natl Acad Sci USA* **107**:17733–17738, 2010; DOI: 10.1073/pnas.1006098107) ●

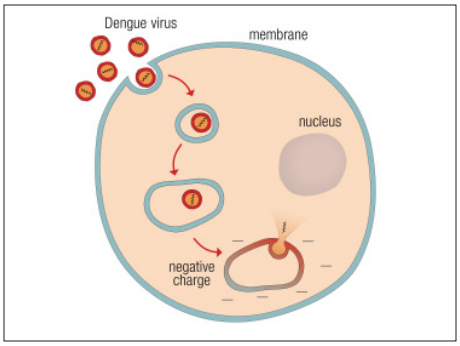
Getting the Better of the Dengue Virus

The mosquito-borne dengue virus may have met its match. NICHD researchers have discovered a key step in how the virus infects a cell, and NIAID scientists have developed vaccines, one of which is being tested in clinical trials.

The emerging infectious disease, which is transmitted by mosquitoes of the genus Aedes, occurs in tropical urban areas in at least 100 countries and has even been found in parts of Florida. According to the World Health Organization (WHO), 50 to 100 million infections occur annually, resulting in 22,000 deaths, mostly among children. Symptoms include a sudden high fever (as high as 104–105° Fahrenheit) followed in a few days by a rash, joint pain, and nausea. WHO estimates that 500,000 develop dengue hemorrhagic fever, which can cause high fever, pain, bleeding, a drop in blood pressure, and, in some cases, coma or death. There is no effective treatment for dengue other than to get bed rest, drink fluids, and take medicine to reduce the fever and minimize other symptoms.

Like many other viruses, dengue infects cells via endocytosis: It binds to the cell surface and then becomes enveloped by the cell membrane, which pinches into a pouchlike structure called an endosome. The virus waits inside the endosome until it has traveled deep within the cell; then, it fuses its membrane with the endosomal membrane and forms a pore through which it releases its genetic material. Once inside the fluid interior of the cell the virus begins to reproduce. Although scientists understand the fusion process with other viruses, little was known about how it works in dengue. Until now.

In recent experiments, NICHD researchers tagged dengue virus and cell membranes with fluorescent probes that glow when the virus and membranes fuse. They also exposed viral samples to artificial membranes to identify factors that allow fusion to occur. They were surprised to find that two conditions are essential for the dengue virus membrane to fuse with the endosome membrane: an acidic environment and a negatively charged endosome membrane, conditions that are only present once the endosome is deep within the cell. [*PLoS Pathog* DOI:10.1371/journal.ppat.1001131 (2010)]



NICHD

To infect a cell, the dengue virus (counterclockwise, from upper left), binds to the cell membrane. The virus is then enveloped in the membrane, which coalesces around the virus, forming an endosome. Deep inside the cell, the endosome membrane acquires a negative charge, which allows the virus to fuse with the endosomal membrane and release genetic material into the cell's interior.

"The confluence of acidity and a negative charge deep in the cell's interior ensures that the virus is safe within the endosome early in its journey, when it is most vulnerable, but can release its genome when it reaches its destination," explained Leonid Chernomordik, who led the team with Elena Zaitseva. "The findings will now enable us to test new ways to disrupt the fusion process and prevent infection."

Dengue vaccines are in the works, too. NIAID researchers Stephen Whitehead and Brian Murphy spent 10 years developing one that is in Phase 1 clinical trials at Johns Hopkins Bloomberg School of Public Health (Baltimore). With NIAID, NICHD, and other NIH scientists coming ever closer to having a better understanding of the virus's molecular dynamics, dengue may not stand a chance. ●

BIOSTATISTICS AT THE NIH

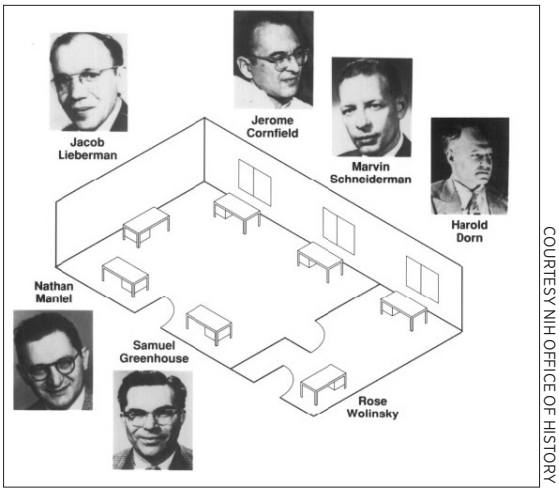
BY SEJAL PATEL, OFFICE OF NIH HISTORY

Biostatistics lies at the heart of just about every health investigation that takes place today. Investigators calculate sample sizes, ponder over confidence intervals, and pray for small *P*-values. NIH study sections and research journals alike expect investigators to use biostatistical methods in grant applications and papers. Most investigators would not think of proposing a study without at the very least consulting a biostatistician.

What investigators may not know is that NIH has played a pivotal role in the evolution of biostatistics, the application of statistics to analyze biological data and improve study designs. It all started in the late 1940s when Harold Dorn, who headed the U.S. Public Health Service's Division of Statistical Methods, recruited a talented team of statisticians—Nathan Mantel, Jerome Cornfield, Jacob Lieberman, Samuel Greenhouse, and Marvin Schneiderman—to the newly created Office of Biometry on the NIH campus. (The office soon became the Biometry Branch at the National Cancer Institute.)

When they came to NIH none had advanced degrees in statistics; most, however, had training during the war as operations researchers and so were adept at applying statistics to problem solving. For example, Schneiderman, when he worked for the U.S. Air Force, had helped to improve the productivity and efficiency of airplane engines by calculating the optimal time for the engines to be reconditioned.

With their training in applied statistics, problem solving, and population sampling, these biometrists excelled at optimizing methods for studying chronic diseases. They came to be known as the "gang of five," a loud, enthusiastic, argumentative group whose spirited debates could sometimes be heard in the Building One cafeteria. "Our luncheons were usually quiet and sociable, as long as we discussed subjects other than statistics. But when we raised statistical topics, almost always there were loud shouting matches without regard to the comfort of those around us," Greenhouse wrote in 1997. "At times, the arguments would carry over when we returned to the office and Dr. Dorn would stick his head through the doorway and innocently inquire what was going on." (*Stat Sci* **12**:82–87, 1997)



COURTESY NIH OFFICE OF HISTORY

Clockwise from bottom: The "gang of five" biostatisticians Samuel Greenhouse, Nathan Mantel, Jacob Lieberman, Jerome Cornfield, and Marvin Schneiderman and their fearless leader, Harold Dorn. The diagram represents where they worked: in Temporary Building 6, which used the concept of rooms without walls.

But as they engaged in research on statistical theory and methods, the design of experiments, applied probability, and applied mathematics, they were shaping the field of contemporary health research. In time, they developed an expertise in "the way in which one elicits the specific information from the investigator needed to find an optimum research design: the question, the nature of the measurements, the intervening factors that ought to be controlled, and so on," Greenhouse wrote.

The number of biostatisticians grew at NIH, and in 1949 biometry offices were established in each institute (a moment known as "the methodological big bang"). In 1953, NIH began funding university programs to produce more and better-qualified analytical statisticians for medical and health research. By 1960, more than 400 people had received NIH funding to pursue biostatistics training at either the masters or the doctorate level.

NIH Director James Shannon said in a 1959 speech that because of the rise in chronic disease, medical research "must include not only the physician but the whole array of university sciences; not only the individual patient but whole population groups; and that an essential and effective partner in the future is the sophisticated, biologically oriented mathematician."

The "gang of five" and other NIH biostatisticians left a lasting scientific legacy and designed some of the better-known methodological techniques still used by health investigators today. For instance, Cornfield's work estimating comparative rates from clinical data on cancer was considered one of the breakthroughs in biostatistics; his adaptation of multiple logistic regression analysis to health investigation is now a mainstay in risk-factor analysis. And Mantel's 1959 article on the Mantel-Haenszel test—"Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease"—was one of the most cited statistical articles for almost 20 years (*JNCI* **22**:719–748, 1959).

Shannon's comments from 1959 are as true now as they were then: "Biometry is now a powerful [language] in medical research, and for those who speak it well, it can open doors to new knowledge of health and disease." ●

Alaskan Sled Dogs

CONTINUED FROM PAGE 1

Alaskan sled dog breed proved to be more genetically distinct than breeds of similar heritage such as the Alaskan Malamute and Siberian Husky."

RICHARD SHAW

Heather Husan and her sled-dog team racing in Fairbanks, Alaska, in 2005.

Dogs have been used for pulling sleds in the Arctic region for hundreds of years. Over the past 50 years, sled-dog racing has become a high-performance sport that has influenced the kind of dog that is harnessed into a team. In the modern era, the working sled dog has been bred with fleet-footed breeds such as the English Pointer and the German Shorthaired Pointer to enhance the athletic performance desired, whether for sprints or long-distance sled races.

Consequently, the animals that Huson and others in her sport assemble as a team may look different from each other, with traces of Shepherd or Pointer or Husky. To look at Huson's sled-dog team, for example, the team that helped her capture first place in the 2004 Tok Race of Champions, you may suspect her dogs to not belong to the same breed. Some have short fur and others long fur, while some have a trace resemblance to Irish Setters and others to German Shepherds. But, depending on the type of race, its sprinting ability or race endurance that is the trait sought by mushers such as Huson. It helps if the animal has a strong work ethic as well.

In the study, Huson and her colleagues sampled sled dogs from eight kennels, rating them for speed, endurance, and work ethic, using established criteria specified for the distinct racing styles of sprint and distance. An assessment of work ethic was made by observing the tension of the tugline that attaches an individual dog's harness to the main team line. These attributes were correlated with genetic information taken from each dog and compared with likely ancestor breeds.

The new insights about performance and breed origin were derived from a DNA analysis of 96 markers in the canine genome. The researchers compared Alaskan sled dog DNA with data from 141 similarly genotyped purebred dog breeds. Their findings confirmed that the Alaskan sled dog has a unique molecular signature and that the genetic profile is sufficient for identifying dogs bred for sprint versus those bred for distance.

Moreover, the researchers could identify contributions from existing breeds to the Alaskan sled dog profile. The Alaskan Malamute and the Siberian Husky contribute enhanced endurance, the Pointer and the Saluki are associated with enhanced speed, and the Anatolian Shepherd demonstrates a positive influence on work ethic.

According to the study, this research has set the stage for mapping studies aimed at finding genes that are associated with athletic attributes integral to the Alaskan sled dog. Huson also notes that canine performance research, particularly on a high-performance breed such as the Alaskan sled dog, is instructive in gaining genomic insights about metabolic systems important for muscle rehabilitation, which could help people suffering from physically disabling diseases or traumatic injuries. ●

This story was adapted with permission and originally appeared on the NHGRI Web site at http://www.genome.gov/27540617.

NIHers Inducted into the American Academy of Arts and Sciences

Three NIHers were among those inducted into the American Academy of Arts and Sciences at a ceremony held in Cambridge, Mass., in October. The 230th class of Fellows includes 210 new Fellows and 18 Foreign Honorary Members who are leaders in research, scholarship, business, the arts, and public affairs.

The NIH inductees are **G. Marius Clore**, Chief, Protein Nuclear Magnetic Resonance Section, Laboratory of Chemical Physics, NIDDK; **Michael Marc Gottesman**, Deputy Director for Intramural Research and Chief, Laboratory of Cell Biology, NCI; and **Gary Jan Nabel**, Director, Vaccine Research Center, NIAID.

Founded in 1780, the American Academy of Arts and Sciences is an independent policy research center that conducts multidisciplinary studies of complex and emerging problems. Current Academy research focuses on science and technology policy; global security; social policy; the humanities and culture; and education. With headquarters in Cambridge, Mass., the Academy's work is advanced by its 4,600 elected members, who are leaders in the academic disciplines, the arts, business, and public affairs from around the world. All new members are listed at: http://www.amacad.org/news/a2z10.pdf.

Inductees sign the American Academy of Arts and Sciences Book of Members, a tradition dating back to 1780. Clockwise from top: G. Marius Clore, Michael Gottesman, and Gary Nabel. (Photos: Martha Stewart)

CONTINUED FROM PAGE 1

demonstrate that genomic indicators in the blood can predict drug-related liver injury long before it occurs (*The Pharmacogenomics J* **10**:267–277, 2010).

"There's a huge need to put better information in the hands of clinicians and genomics is an important tool for helping us reach that goal," said study co-author Richard Paules, who is a principal investigator in NIEHS's Laboratory of Toxicology and Pharmacology and director of the Microarray Core facility.

GENOMIC INDICATORS PREDICT A PHENOTYPE OF TOXICITY

To test the utility of genomic indicators for predicting very early stage DILI, the team used a MicroArray Quality Control (MAQC)-II project dataset that was generated by the NIEHS National Center for Toxicogenomics (NCT) and contributed by Paules. It consisted of gene-expression data from blood and liver tissue in rats. The researchers analyzed genomic indicators in the blood and found they could predict liver necrosis or hepatic cell death across a variety of chemical compounds that target the liver. They confirmed their predictions by examining liver samples in rats after they developed DILI.

The investigators compared results on two microarray platforms for profiling the liver data and predicted DILI with 92 percent accuracy. In a validation component of the study, they also showed that these genomic biomarkers were highly accurate in being able to predict liver injury caused by acetaminophen as well as by two non-therapeutic chemical compounds.

STEVE MCCAW

STEVE MCCAW

Pierre Bushel (left), head of the NIEHS's Microarray and Genome Informatics Group, used microarray technology to demonstrate that genomic indicators in the blood are good predictors of drug-induced liver injury. This spring the Society of Toxicology recognized Richard Paules (right) with the 2010 Leading Edge in Basic Science Award "for his work in the integration of genomics into the investigation of the molecular basis of injury and disease processes," describing him as "a visionary . . . who has diligently positioned NIEHS at the forefront of the field."

"Our results strongly support the claim that genomic indicators in the blood can serve as biomarkers of necrosis," said Bushel. The findings suggest that they could be used "for diagnostic testing of DILI in humans."

> The findings underscore the potential for using microarray gene expression technology to individually tailor drug treatments.

NIEHS has a long history of pioneering work in toxicogenomics, a field combining toxicology with genomics research. "While the challenges of developing signatures to utilize as clinical biomarkers of specific adverse effects are great, the prospects have never been brighter," said Paules. "We really hope to provide better science for better treatment of disease."

The study's findings underscore the potential for using microarray gene-expression technology to individually tailor drug-treatments and speed up the development of high-throughput drug screening assays.

MOVING FORWARD—THE SEQC PROJECT

The NIEHS-led study provides a proof of principle for the FDA-led MicroArray Quality Control (MAQC) project, which has been assessing bioinformatics for genome technologies in biomedical research. MAQC-II is developing best practices for using microarray-based technologies to predict toxicological and clinical endpoints.

Until recently, the potential of microarray analysis for addressing previously intractable problems—and uncovering novel potential targets for therapies—was hampered by studies with dissimilar or altogether contradictory results obtained using different microarray platforms to analyze identical RNA samples. In establishing best-practice guidelines, the MAQC-II project, which involves more than 200 scientists working in 36 teams, aims to establish a foundation for the reliable use of microarrays in clinical, research and regulatory settings and will be important as treatments are tailored to patients' individual needs.

A Decade of Toxicogenomics at NIEHS

In 2000, NIEHS established the National Center for Toxicogenomics (NCT) to promote the evolution and coordinated use of gene-expression technologies and to apply them to the assessment of toxicologic effects in humans.

The primary goal was to provide a worldwide reference system of genome-wide gene-expression data and to develop the Chemical Effects in Biological Systems (CEBS), a database that houses data—from academic, industrial, and governmental laboratories—of interest to environmental health scientists (http://www.niehs.nih.gov/research/resources/databases/cebs). A secondary goal was to expand the understanding of the mechanisms by which stressor-induced injury occurs.

NIEHS was also part of a Toxicogenomics Research Consortium (TRC) that worked under a National Institutes of Health cooperative agreement. TRC was a grant-supported consortium divided into two components—an independent component comprising individual research projects within the framework of a program project grant and a dependent component in which members of the consortium collaborated in the development of studies to bring definition to toxicogenomics.

NIEHS phased out NCT in 2006, but NIEHS researchers Richard Paules and Pierre Bushel continued their efforts to develop practical applications for toxicogenomics in drug discovery and the clinical setting. In 2007, Paules was senior author and Bushel was first author on a study published in *Proceedings of the National Academy of Sciences USA*, "Blood gene expression signatures predict exposure levels," conducted by a team of researchers from NIEHS and the University of North Carolina, Chapel Hill (UNC). (*Proc Natl Acad Sci USA* **104**: 18211–18216, 2007; doi: 10.1073/pnas.0706987104)

In those experiments, the researchers found that the signature gene lists were able to predict exposure to toxic versus nontoxic doses of acetaminophen with very high accuracy (88.9–95.8 percent); the more traditional predictors, of clinical chemistry, hematology, and pathology were only 65 to 80 percent accurate.

As part of the study, the NIEHS researchers compared the animal data with data from RNA in blood drawn from individuals who had been admitted to the UNC emergency room for acetaminophen overdose intoxication. When they compared the toxic blood samples with the samples from normal healthy volunteers, the researchers saw a striking difference.

These results support the hypothesis that gene-expression data from peripheral blood cells can provide valuable information about exposure levels well before liver damage is detected by classical parameters. It also supports the potential use of genomic markers in the blood as surrogates for clinical markers of potential acute liver damage.

The NIEHS report on using genomic indicators to predict DILI is one of 11 papers published by MAQC-II consortium researchers in the same special issue of *The Pharmacogenomics Journal* (*Pharmacogenomics J* **10**:245–374, 2010). Although the NIEHS-led team was successful in its use of microarrays to identify predictors for clinical endpoints, some of the other teams experienced difficulty. An editorial in the journal observed, "Quality control and appropriate bioinformatics processing will remain a challenge for any new high-throughput molecular technology."

As phase II of the MAQC project nears completion, FDA plans a third phase: MAQC-III, also called the Sequencing Quality Control (SEQC) project. The SEQC project will assess the technical performance of next-generation sequencing platforms by generating benchmark datasets with reference samples. The project will also evaluate the advantages and limitations of various bioinformatics strategies in RNA and DNA analyses.

Bushel, Paules, and several other NIH members (from NIEHS and the National Center for Biotechnology Information) were among many co-authors of the MAQC-II project summary report that was published this summer (*Nature Biotechnol* **28**: 827–841, 2010).

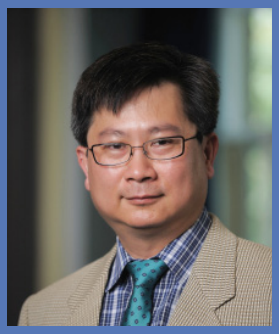
NIEHS will continue this partnership with the FDA and other agencies to extend the successes of MAQC-II and to look further into the quality and reproducibility of next-generation sequencing through SEQC.

"This is another example of how NIH and FDA are working together to advance translational and regulatory science," said NIEHS Director Linda Birnbaum. "I'm proud of the role NIEHS investigators played in this important undertaking." ●

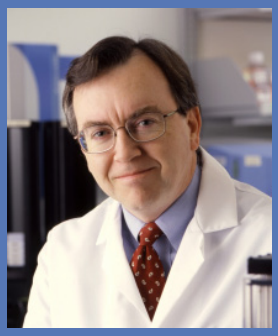
NIEHS: The mission of NIEHS, located in Research Triangle Park, N.C., is to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease. NIEHS traces its roots to 1966, when the U.S. Surgeon General announced the establishment of the Division of Environmental Health Sciences within the NIH. In 1969, the division was elevated to full NIH institute status. Since then, the NIEHS has evolved to its present status as a world leader in environmental health sciences with an impressive record of scientific accomplishments (see: http://www.niehs.nih.gov/about/research/index.cfm). For more information on NIEHS's intramural research, go to http://www.niehs.nih.gov/research/atniehs/index.cfm.

Recently Tenured

Silvia Bolland, NIAID


Chi-Hon Lee, NICHD

Mark Lewandoski, NCI-Frederick


Francis J. McMahon, NIMH

William Prinz, NIDDK

SILVIA BOLLAND, PH.D., NIAID

Senior Investigator; Chief, Autoimmunity and Functional Genomics Section, Laboratory of Immunogenetics

Education: University of the Basque Country at Lejona, Spain (B.A. in biology); University of Cantabria at Santander, Spain (Ph.D. in molecular biology)

Training: Postdoctoral fellow at Harvard University (Cambridge, Mass.) and at Rockefeller University (New York)

Came to NIH: In September 2001

Outside interests: Spending time with three-year-old daughter

Research Interests: Our group is interested in the role of antiviral innate immune pathways in autoimmune disease susceptibility. We use mouse models of the systemic autoimmune disease lupus to identify genetic and environmental factors affecting autoimmunity. A mouse deficient in the immunoglobulin G (IgG) Fc receptor (an immunoglobulin-binding receptor that inhibits antibody production and inflammatory responses) was the starting point in the analysis of genetic modifiers of lupus disease. These mice develop a spontaneous disease that resembles lupus in humans.

We discovered that a gene dose increase of the viral RNA-sensor toll-like receptor gene *TLR7* can accelerate or even initiate systemic autoimmune and inflammatory pathology. Both *TLR7* and the gene for the IgG Fc receptor have since been validated as susceptibility genes for lupus in mouse models and in human patients. We are studying potential ways of spontaneous activation of *TLR7* and other viral-RNA sensor pathways and their effect on autoreactive and chronic inflammatory responses. This work will help us understand cellular mechanisms that induce these pathologies and identify new genes that can be used as therapeutic targets.

CHI-HON LEE, M.D., PH.D., NICHD

Senior Investigator; Head, Section on Neuronal Connectivity

Education: China Medical College, Taiwan (M.D.); Rockefeller University, New York (Ph.D.)

Training: Postdoctoral, University of California, Los Angeles; Residency, Cancer Therapy Center, Veteran General Hospital, Taiwan

Before coming to NIH: Postdoctoral fellow at the University of California, Los Angeles

Came to NIH: In June 2002

Outside interests: Playing piano

Research Interests: I am interested in understanding how neurons make complex interconnections during development and how the assembled neural circuits extract visual information to guide animal behaviors. We have been taking a knockout approach: If silencing a class of neurons prevents animals from discriminating different colors, then these neurons are probably participating in color vision.

We use the fruit fly's visual system as a model because of the power of Drosophila genetics. We have identified several evolutionarily conserved adhesion or signaling receptors that are required for assembling neurons into columns and layers in flies and vertebrates. We have mapped the connections of different classes of visual neurons and assigned their functions. We found that the fly's visual system wiring diagram is similar to its vertebrate counterpart. What we learn will help us understand how brains develop and work in general.

MARK B. LEWANDOSKI, PH.D., NCI-FREDERICK

Senior Investigator; Head, Genetics of Vertebrate Development Section, Cancer and Developmental Biology Laboratory, Center for Cancer Research

Education: Rutgers University, New Brunswick, N.J. (B.A. in microbiology and English literature); New York University Medical Center, New York (Ph.D. in microbiology)

Training: Postdoctoral research as an American Cancer Society Fellow at the University of California, San Francisco (UCSF)

Shyam Sharan, NCI-Frederick

Carlos A. Zarate, NIMH

Before coming to NIH: Continued as a research anatomist at UCSF
Came to NIH: In 1999 and established the Genetics of Vertebrate Development Section
Outside interests: Reading, playing the piano and various synthesizers

Research Interests: We use mouse genetics to understand how cell-to-cell signaling controls development. By doing molecular analysis of embryonic mutants, we construct a model of the normal developmental process. It's exciting when our complex genetic manipulations rescue the initial defect. Our insights contribute to an understanding of how misinterpreted, pathologically reactivated, or ignored signaling causes disease and cancer.

Our long-standing interest is in fibroblast growth factors (FGFs), and we've studied how the pathway they stimulate interfaces with wingless proteins (WNTs) and bone morphogenetic proteins (BMPs). We focus on two embryonic processes: limb development and somitogenesis. Although limb development has been studied for about 50 years, basic questions of how pattern is generated remain unanswered. Recently, we have determined that BMPs regulate FGF signals in the early limb bud by regulating a family of genes called *Sprouty*, which encode FGF signaling antagonists. During somitogenesis, mesodermal segments are generated along the body axis and eventually generate muscle, skin, and the vertebral column. Through conditional and combinatorial loss- and gain-of-function genetics, we've determined the roles of FGF and WNT signaling in a molecular clock that, through a feedback mechanism, causes rhythmic gene expression required for somitogenesis.

FRANCIS J. MCMAHON, M.D., NIMH
Senior Investigator and Chief, Genetic Basis of Mood and Anxiety Disorders Section
Education: University of Pennsylvania, Philadelphia (B.S. biology); Johns Hopkins University School of Medicine, Baltimore (M.D.)
Training: Johns Hopkins University School of Medicine (residency in adult psychiatry; postdoctoral fellowship in psychiatric genetics)
Before coming to NIH: Faculty, Johns Hopkins University School of Medicine; associate professor of psychiatry and medical director of the Electroconvulsive Therapy Clinic, University of Chicago
Came to NIH: In 2002 to establish a new genetics unit at NIMH
Outside interests: Birdwatching, bicycling, travel

Research Interests: We are identifying genes that contribute to the risk for mood and anxiety disorders so that better methods of diagnosis and treatment can be developed. We are trying to identify genes that contribute to bipolar disorder, major depression, and panic disorder. We use a combination of genome-wide association, copy-number variation, and large-scale sequencing methods. We are also conducting pharmacogenetic studies to identify genetic markers that predict individual differences in treatment outcomes with antidepressants or lithium. Our work may provide insights into therapeutic mechanisms and help develop personalized treatment approaches in psychiatry. Finally, we are carrying out genetic-association studies of neuroimaging phenotypes that are candidate endophenotypes for mood and anxiety disorders.

WILLIAM PRINZ, PH.D., NIDDK
Senior Investigator, Cell Biology Section
Education: Vassar College, Poughkeepsie, N.Y. (B.A. in biochemistry); Harvard Medical School, Boston (Ph.D. in microbiology)
Training: Department of Cell Biology, Harvard Medical School (Boston)
Came to NIH: In September 2001
Outside interests: Running, hiking, traveling

Research Interests: Understanding organelle biogenesis is a central problem in cell biology; defects in this process are associated with many diseases. Though a good deal has been learned about how proteins are targeted to various organelles, less is known about other aspects of organelle biogenesis including how lipid composition, shape, and intracellular distribution of organelles are determined. My laboratory studies these questions using a yeast model organism, *Saccharomyces cerevisiae*.

We have two projects in the lab. The first focuses on how cells regulate the intracellular distribution of lipids in membranes and, in particular, the role of nonvesicular lipid trafficking in organelle biogenesis and lipid metabolism. In a second project, we are studying how the characteristic shape of an organelle is generated and how this shape contributes to optimal organelle function. We study how the endoplasmic reticulum is shaped and how maintaining its shape affects its function.

CONTINUED

Recently Tenured

CONTINUED FROM PAGE 13

SHYAM K. SHARAN, PH.D., NCI-FREDERICK

Senior Investigator; Head, Genetics of Cancer Susceptibility Section, Mouse Cancer Genetics Program

Education: University of Delhi, India (B.Sc. in botany; M.Sc. in genetics); Case Western Reserve University, Cleveland (Ph.D. in genetics)

Training: Postdoctoral fellow, Howard Hughes Medical Institute, Baylor College of Medicine (Houston)

First came to NIH: In October 1999

Outside interests: Spending time with family

Research Interests: My laboratory does functional analysis of the human breast cancer susceptibility genes, *BRCA1* and *BRCA2*. Women who inherit a mutation in one of these genes have up to an 80 percent risk of developing breast cancer by age 70. Sequence-based genetic tests are available to identify individuals who are at risk.

We developed a mouse embryonic stem cell–based assay to understand the functional significance of more than 2,000 variants identified in these genes. The assay takes advantage of the fact that the products of these two genes participate in DNA repair and cause cancer when their repair ability is disrupted. We are using these embryonic stem cells to uncover novel functions of *BRCA1* and *BRCA2*. We are also dissecting these genes using humanized mouse models—existing *Brca1* and *Brca2* knockout mice and bacterial artificial chromosomes containing human *BRCA1* and *BRCA2* genes.

In delineating the biological function of *BRCA1* and *BRCA2*, we will better understand how mutations that are scattered throughout these genes lead to cancer. We also hope to identify potential targets and design inhibitors that would either retard or inhibit the aberrant path towards carcinogenesis.

CARLOS A. ZARATE, M.D., NIMH

Chief, Experimental Therapeutics and Pathophysiology Branch, Division of Intramural Research Program

Education: Faculty of Medicine, Catholic University of Cordoba, Argentina (M.D.)

Training: Adult psychiatry residency, Massachusetts Mental Health Center/Veterans Affairs Medical Center (Brockton); clinical psychopharmacology fellowship, McLean Hospital (Belmont, Mass.); fellowships in psychiatry, Harvard Medical School (Boston)

Before coming to NIH: Associate professor of psychiatry and Chief of the Bipolar and Psychotic Disorders Program, University of Massachusetts Medical School (Worcester)

Came to NIH: In January 2001

Outside interests: Family, tennis

Research interests: We are investigating the pathophysiology of mood disorders and developing novel therapeutics to treat them. For several years there have been no significant gains in discovering new molecular targets for their treatment. One of the major limitations of existing antidepressant therapies is that it may take weeks to months for them to work.

We are identifying novel therapeutics that take effect within hours or days. For example, we have demonstrated that ketamine, an *N*-methyl-D-aspartate receptor antagonist, produces antidepressant action within hours in patients who have treatment-resistant major depressive disorder and bipolar depression. Efforts are under way to develop ketamine-like compounds and other glutamatergic modulators. In addition, we are using neuroimaging and electrophysiological technologies in an attempt to identify predictors of treatment response. ●

If you were tenured in the past year or so, The NIH Catalyst *will be in touch about doing an article on you.*

DEMYSTIFYING MEDICINE 2011

Tuesdays 4:00–6:00 p.m.
Ground Floor Auditorium, Building 50
(See registration details on page 15)

January 11: "Sleep: Mechanisms, Disorders and Circadian Rhythm"; D. Dinges (U. Penn.), M. Menaker (U. of Virginia)

January 18: "*Helicobacter pylori*: . . . Peptic Ulcers and Cancer"; S. Czinn (U. of Maryland), S. Merrell (USUHS)

January 25: "Staphylococcus"; F. DeLeo (NIAID), A. Freeman (NIAID)

February 1: "Estrogens: Mood and Postpartum Depression"; P. Schmidt (NIMH), A. DeCherney (NICHD)

February 8: "Malaria"; P. Duffy (NIAID), G. Heppner (U.S. Army, Walter Reed Army Institute of Research)

February 15: "VZV: A Case of Shingles"; A.Marques (NIAID), J. Cohen (NIAID)

February 22: "Chronic Fatigue Syndrome: Is There a Virus?"; S. Lo (FDA), Fred Gill (NIDDK), H. Alter (NIDDK)

March 1: "Multiple Sclerosis: An Autoimmune Dilemma"; B. Bielekova (NINDS), J. Ohayon (NINDS)

March 8: "Inflammation: Mechanisms and Diseases"; J. Gallin (CC)

March 15: "Diabetes: Mechanisms and Fatty Liver"; R. Malek (NIDDK), Y. Rotman (NIDDK)

March 22: "HIV/AIDS: . . . New Treatments"; C. Lane (NIAID), J. Coffin (NCI)

March 29: "Hypersocial, Hyperverbal Kids (Williams Disease)"; K. Berman (NIMH)

April 5: "Cardiovascular Disease in the Eras of Imaging and Stem Cells"; R. Balaban (NHLBI), M. Boehm (NHLBI)

April 12: "Hepatocellular Carcinoma: Mechanisms and Stem Cells"; S. Thorgeirsson (NCI), I. Avitar (NCI)

April 19: "Prostate Cancer"; W. Dahut (NCI), K. Kelly (NCI)

April 26: "Cushing's Syndrome: Adrenocortical Hormone Regulation and Function"; L. Nieman (NICHD), G. Hager (NCI)

May 3: "Hearing: Mechanisms and Loss"; J.Niparko (Johns Hopkins, Baltimore), T. Friedman (NIDCD), J. Battey (NIDCD)

May 10: "Alzheimer's Disease"; M. Mattson (NIMH), L. Ryan (NIMH)

May 17: Finale; speakers to be named

"DEMYSTIFYING MEDICINE" RETURNS

Want help bridging the gap between advances in biology and their application to major human diseases? You might want to consider attending the 19-week "Demystifying Medicine" course, which starts on Tuesday, January 11, 2011. The weekly course includes presentations about patients, pathology, diagnosis, and therapy in the context of major disease problems and current research. Although it's primarily directed toward Ph.D. students, fellows, and staff, the course is also of interest to medical students and clinicians. Those seeking academic credit may register with FAES (http://faes.org). Those not seeking academic credit should register through the course e-mail list. For details visit http://demystifyingmedicine.od.nih.gov or contact Win Arias at ariasi@mail.nih.gov. (See lecture dates and topics in column at left.) If you would like a DVD of the 2009–2010 session, e-mail your request and mailing address to Priyanka Basa at basap@faes.od.nih.gov or you can pick one up at the information desk at the NIH Library (Building 10).

COMING SOON: NEXT CLASS OF PRATS

Deadline: January 28, 2011

Applications are now being accepted for the Pharmacology Research Associate (PRAT) Program. The PRAT Program is a competitive postdoctoral fellowship program intended for individuals with backgrounds in the basic or clinical sciences who wish to obtain advanced experience in an area of pharmacology, or for those with a pharmacology background who want to gain experience in new fields. The program supports three years of training in NIH or FDA laboratories in fields such as molecular pharmacology, signal-transduction mechanisms, drug metabolism, immunopharmacology, chemistry and drug design, structural biology, endocrinology, bioinformatics, and neuroscience. Candidates apply in conjunction with an identified preceptor, who may be any tenured or tenure-track scientist at NIH or FDA. For more information or application materials, visit http://www.nigms.nih.gov/Training/PRAT.htm, contact the PRAT program assistant at 301-594-3583, or e-mail prat@nigms.nih.gov. The deadline for applications is January 28, 2011, for positions starting in fall 2011.

ODS CALL FOR CO-FUNDING

The NIH Office of Dietary Supplements (ODS) will fund intramural research projects that can be carried out in a short time with limited resources. Priority will be given to young scientists accepted into the NIH Intramural Tenure-Track Program and Senior Staff Fellows. Support is available for a variety of projects including pilot or feasibility studies; collection of preliminary data; secondary data analysis of existing data; small, self-contained research projects; and development of new research technology. The support is not renewable and is limited to one year of funding, not to exceed $100,000. ODS supports preclinical, clinical, behavioral, and epidemiological research in which the primary emphasis is the investigation of dietary supplements and/or their ingredients. The following deadlines (and funding notifications) apply: Jan 26, 2011 (notification by Feb 18, 2011); May 4, 2011 (notification by May 27, 2011); August 3, 2011 (notification by August 26, 2011). For more information contact Rebecca Costello at costellb@od.nih.gov or 301-435-3605, or visit the ODS Web site at http://ods.od.nih.gov.

BRIDGING SCIENCE, TREATMENT, AND PUBLIC EDUCATION OF ANXIETY DISORDERS

Friday, November 19, 2010, 1:30–4:00 p.m.
Conf. Rooms D and E, Neuroscience Center
6001 Executive Boulevard, Rockville, Md.

National Public Radio's Diane Rehm will moderate "Bridging Science, Treatment, and Public Education of Anxiety Disorders," a tribute to the life and work of the late psychotherapist Jerilyn Ross, who was a leading expert on anxiety disorders. Featured speakers include some of the most renowned researchers in the field today—Ron Kessler, Elizabeth Phelps (New York University, New York), Danny Pine (NIMH), Kerry Ressler (Harvard Medical School, Boston), and Blair Simpson (Columbia University/New York State Psychiatric Institute, New York). Registration is not required but seating is limited. If you plan to attend, send a message to rossymposium@mail.nih.gov. For additional details, contact Ann Graham at Agraham@mail.nih.gov. Note: The location is subject to change.

TRANSLATIONAL SCIENCE: LESSONS FROM THE PUBLIC AND PRIVATE SECTORS

Monday, December 13, 2010, 3:00–4:00 p.m.
Lipsett Amphitheater (Building 10)

Richard Klausner, M.D., managing partner of the Column Group (San Francisco, Calif.) and former NCI director, will present a lecture entitled "Translational Science: Lessons from the Public and Private Sectors." The event will not be videocast. For more information, contact Karen Kochersberger at kochersbergerks@mail.nih.gov or 301-228-4027.

PROMISE FOR THE FUTURE

NCCAM's Second Annual Stephen E. Straus Distinguished Lecture
Wednesday, December 15, 2010
9:00–10:00 a.m.
Lipsett Amphitheater (Building 10)

In a lecture entitled "Promise for the Future in Yesterday's Remedies: Traditional Therapies to Modern Medicine," Vikas Sukhatme, M.D., Ph.D. (Harvard Medical School, Boston), will discuss scientifically promising, affordable, and immediately available medical treatments related to traditional medicine. The event will be videocast live on the Web (http://videocast.nih.gov). For more information, visit http://nccam.nih.gov/news/events/lectures.

To submit items for Announcements, e-mail catalyst@nih.gov or call 301–402–1449. Deadlines: December 1 for Jan–Feb issue, Feb 1 for March–April issue, April 1, for May–June issue, etc.

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CATALYTIC REACTIONS?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation or confession that scientists might appreciate and that would be fit to print in the space to the right, why not send it via e-mail: catalyst@nih.gov; fax: 301-402-4303; or mail: *The NIH Catalyst*, Building 1, Room 333.

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

IN FUTURE ISSUES:

- MALARIA RESEARCH
- RESEARCH FESTIVAL
- ZEBRAFISH FACILITY

LABORATORY CONFESSIONS

The National Institute of Food Procurement

BY NAME WITHHELD

The annual NIH Research Festival this past October got me thinking about new ways to spur trans-NIH collaborations. I do appreciate current efforts, such as the scientific interest groups, shared resources, funding mechanisms such as the NIH Director's Challenge Innovation Award Program, and even *The NIH Catalyst* itself. Our goal is to get outside of our labs physically and mentally.

But when I learned that free lunch tickets for the Research Festival were gone a few nanoseconds after they were announced via e-mail, I started wondering: Is the way to a researcher's heart through his or her stomach? If not lunches, then cookies and fruit seem to draw the crowds to even the most esoteric talks.

I'm a grown man. I make a good salary. And yet I found myself lured to the festival poster sessions for nothing more than a free brownie. A good 500 people had similar motivation in hiking across campus. What we need, therefore, is an office or even a center to provide food at research events.

Clearly there are ethical concerns. But one must remember this is about collaborations. Why should food be different from other shared resources such as the magnetic resonance imaging facility if, in the end, it brings us together and fosters collaboration? If that logic doesn't fly, then we need to hire a team of 65-year-old mothers. Maybe Italian mothers or Jewish mothers or Chinese mothers. Even skilled fathers. I'm not picky. We simply need people experienced in feeding, say, 50 people each with a big ol' pot of something delicious. Place a few of these "chefs" outside Masur Auditorium and we'd fill it every time. Right when you walk in: meeting programs to the left and meatballs to the right. How simple is that?

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

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

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