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Research Festival

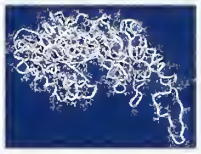
EPIGENETICS: THE SOUNDS OF SILENCE

by Karen Ross

"...not everything that is inherited is genetic."

—Boris Ephrussi
geneticist and embryologist (1901–1979)

Munira Basrai, of the NCI Genetics Branch, opened the Research Festival symposium on "Epigenetics and Cell Cycle Control: From DNA Replication to Cancer Therapy" with the above quote from Boris Ephrussi, whose insights presaged the elucidation of epigenetics.



German Cancer Research Center
Structural model of a methyltransferase enzyme

Epigenetics is the study of DNA modifications that persist during cell division but that do not change the DNA sequence itself. NCI's Shiv Grewal, Mirit Aladjem, and David Schrump discussed ways in which epigenetic phenomena control gene expression, the timing of DNA replication, and the potential of cells to form tumors.

Grewal, of the Laboratory of Molecular Cell Biology, explained how gene expression is turned off, or silenced, in particular regions of the genome of fission yeast. Silencing occurs, he said, when specific proteins bind to the DNA, converting it into a form called heterochromatin.

How does the cell know which parts of the genome should be silenced? The answer, at least in some cases, Grewal said, lies in the RNAi pathway, a system that has lately come to the fore with its increasing use by researchers to knock out the function of genes of their choice in

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Research Festival

PEERING INTO THE INFECTIOUS FUTURE OF EMERGING INFECTIOUS DISEASES

by Aarthi Ashok

Aarthi Ashok

On the Front Lines in the Labs: *(left to right) Tony Fauci, José Ribeiro, Kanta Subbarao, and Bruce Chesebro*

"The war against infectious diseases has been won."

—Surgeon General William H. Stewart
testifying before the U.S. Congress in 1967

Quoting the former surgeon general, NIAID Director Tony Fauci set the stage for the Research Festival symposium on 21st-century challenges in infectious disease research.

He did not have to belabor the folly of Stewart's declaration—the fact that infectious diseases were the second leading cause of death worldwide in 2002 was enough.

In his introductory overview of emerging and re-emerging infectious diseases, Fauci said that:

- Prevention of HIV infection—about 3 million people globally were newly infected in 2003—remains the most difficult challenge in the HIV arena today, particularly with regard to the development of an HIV vaccine.
- The sequencing of the genomes of the most lethal malarial parasite and its mosquito vector offers fresh approaches for overcoming malaria, currently the cause of 1.5–2.5 million deaths annually.
- The threat of an influenza pandemic is "significant." Infections of humans with lethal H5N1 avian influenza have been detected in Asia since 1997 and, together with a pervasive lack of immunity to the H5N1 strain in the population and shifts in influenza antigenicity, add to the complexity of this public health issue.
- West Nile virus, a classic re-emerging microbe, is currently endemic in the United States but likely to spread to the Caribbean and South America in coming years. On the positive side is the development by the NIAID Laboratory of Infectious Diseases of a chimeric West Nile virus vaccine with a dengue virus backbone.
- The anthrax attacks of 2001, which generated fear and disruption of routine activities, also led to a large increase in NIH biodefense spending—from $291.1 million in 2002 to an estimated $1.6 billion in 2004—and the expansion of NIH research facilities, including the construction on campus of a biosafety

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Supporting High-Risk, High-Impact Research In the NIH Intramural Research Program

Michael Gottesman

Those of you who heard my keynote talk* at the NIH Research Festival know what my bottom line was: The greatest successes of the NIH intramural research program (IRP) in the past came from recruiting highly creative scientists and giving them the freedom and environment in which to explore important problems in biomedical research.

The future of the IRP (and the U.S. biomedical research effort overall) depends on ensuring that the current and next generations of IRP scientists have the freedom they need to be innovative.

In recent discussions with the NIH director, the Board of Scientific Directors (SDs), and the chairs of our Boards of Scientific Counselors (BSC), there was unanimous agreement that the IRP must continue to be a vital, creative research program, willing to take high scientific risks in hopes of enormous scientific payoffs.

Much time was spent at a retreat of the SDs this summer brainstorming ways to make it easier for our research staff to tackle difficult problems with no assurance of success. We identified three barriers that currently make adventurous research all too difficult in the IRP:

(1) The product-oriented nature of the review process by our BSCs

(2) The understandable conservatism of our scientists and scientific leadership at times of constrained resources

(3) A tenure-track system that may penalize highly innovative early career scientists whose research risks do not pay off

The SDs recommended that we address each of these problems in turn, through a series of discussions by their board and appropriate subcommittees, with follow-up when I meet in the spring with the BSC chairs. Our long-term goal is to rewrite the instructions to the BSC members so that they can help us support higher-risk, higher-impact research in the IRP. We want tenure-track review processes that do not penalize the most creative early career scientists.

I would like to stimulate discussion about our ideas thus far. The first idea relates to current BSC processes, which largely reward products—such as discoveries, patents, and papers. The BSC could also help us identify highly creative projects that might take more time than usual but if brought to fruition would have very high impact. We could also meet with colleagues in academia and industry to get their tips on how to reward and encourage creativity.

The current primarily retrospective review that recognizes past successes is certainly a good way to encourage more innovative research. But we need also to add a way to evaluate innovative approaches and ideas—experiments that are brilliant in conception—but do not always result in traditionally successful outcomes. Successful outcome ought not be the only measure of the value of the research. This change would permit our most innovative scientists to continue to explore new ideas, even if they have not been particularly productive over a previous four-year period. We have students and postdoctoral fellows whose careers depend on some measureable scientific output; so, whatever else we do, we must continue to do enough "bread and butter" science to support these careers.

Our long-term goal is to rewrite the instructions to the BSC members so that they can help us support higher-risk, higher-impact research in the IRP. We want tenure-track review processes that do not penalize the most creative early career scientists.

Another idea on the table is that the SDs themselves take more responsibility for recognizing and encouraging innovative research. This means making merit-based decisions about assignment of resources so that our most creative scientists are given the resources they need to conduct their research. Across-the-board approaches to resource allocation or limitation, although less likely to result in complaints from the scientific staff, may not be in the best interest of novel science.

In the matter of tenure-track constraints on innovation, a special subcommittee of SDs has been established to think about creating a climate for tenure-track investigators that is more conducive to taking chances.

As it now stands, at a period in their scientific careers when they are most likely to produce truly creative work, early career scientists are under the greatest pressure to achieve specific goals.** Striving to meet these goals may limit out-of-the-box thinking and research for some individuals.

Some ideas are percolating about how to avoid penalizing our tenure-track investigators who take scientific risks, but I would be interested to hear more from the entire NIH community.

The good news is that there is general agreement from NIH leaders and advisors who help oversee our research that the IRP is the best place to conduct high-risk, high-impact research; we now need to work together to develop policies and processes that embrace this goal. ■

*To hear the keynote address, go to **<http://videocast.nih.gov>**; click on ***Past Events*** and then on ***special***; from there, navigate to the September 28 event.

See the criteria for tenure in the NIH Sourcebook: **<http://www1.od.nih.gov/oir/sourcebook/prof-desig/tenurecriteria.htm>.

Peering into the Infectious Future

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photos by Aarthi Ashok

Peering into the infectious future: *(left to right) NIAID's José Ribeiro, Kanta Subbarao, and Bruce Chesebro*

level 3 building, that will accelerate the development of countermeasures to an array of infectious agents.

Fauci ended with a cautionary thought taken from the book *The Restless Tide* by former NIAID director Richard Krause: Microbes will continue to bombard the shores of mankind and, try as they may, neither of the adversaries—humans or pathogens—will fully eliminate the other.

Insect Vectors: Transgenic Solutions?

It has long been clear that the eradication of infectious diseases transmitted by insect vectors requires intervention at the level of the vector itself.

Not only are there more than 15,000 species of insect vectors on the globe, said José Ribeiro, head of the Vector Biology Section, NIAID, but they are "r-selected" species whose large numbers of offspring give rise to enormous genetic diversity in the population and hence adaptability to a rapidly changing environment.

International commerce has abetted the spread of insect vectors. One example, he said, was the importation into the United States in the 1980s of rubber tires from Malaysia that harbored the eggs of the West Nile–associated mosquito species *Ochlerotatus japonicus* and *Aedes albopictus*.

On a more local level, changing habitats through the movement of people into suburbs has broken the fragile balance of the environment and imposed a greater risk of zoonotic diseases such as Lyme disease.

Recent achievements, however, rival these challenges, Ribeiro said. He cited the sequencing of a mosquito genome, the expanded knowledge of insect population genetics, and the unprecedented ability to compile large amounts of geographical and biological data through the use of geographical information systems.

The most significant advance, he said, is probably the characterization of the vector genes that affect host selection, habitat choice, blood feeding, and parasite susceptibility.

He projected that although several ethical dilemmas remain regarding the creation of transgenic mosquitoes, this type of research over perhaps the next 20 years could lead to novel approaches in the control of vector-borne illnesses.

Animal Models of SARS

In 2003, the World Health Organization identified 8,000 cases of severe acute respiratory syndrome (SARS) across the globe; 774 people died before the outbreak ended in July 2004.

Kanta Subbarao, a senior investigator in the Laboratory of Infectious Diseases, NIAID, has worked extensively on the development of animal models of SARS. She aims to clarify the pathogenesis of the disease and evaluate vaccine candidates.

"We wanted to explore a range of animal species, as their susceptibilities may vary," she said. She described results in intranasally inoculated mice and golden Syrian hamsters and intratracheally inoculated African green monkeys, rhesus monkeys, and cynomolgus monkeys.

None of the animals tested developed clinical signs of disease, but virus was detected in the respiratory tract of mice, hamsters, and African green monkeys, and serology showed that they were indeed infected.

The animals were protected from replication of virus after subsequent viral challenge by antibody production.

Hyperimmune serum from infected animals could be used to protect naïve animals, clearly defining the role of antibodies in preventing virus replication, Subbarao noted.

The African green monkey was found to be the most permissive model among the three species of nonhuman primates tested, she reported, but because the course of infection in these monkeys is significantly different from that in humans, she urged caution in their use for the evaluation of vaccine efficacies.

Several SARS vaccines are currently being evaluated in this animal model, including inactivated subunit DNA and live attenuated forms, and the prospects look promising, Subbarao said.

Another aspect of SARS infection requiring targeted research is that old age (over 60) appears to be a significant risk factor in disease progression.

To better understand the pathogenesis of SARS in the elderly, Subbarao's group has created an older mouse model, which shows a dramatically different response to SARS infection and progression.

"We are very interested in investigating this model further," Subbarao said, implying there is reason for optimism.

Prion Diseases: Are Prions Infectious?

Prions have been described as the agent of transmissible spongiform encephalopathies (TSE), but not all investigators are convinced, said Bruce Chesebro, chief of the Laboratory of Persistent Viral Diseases at NIAID's Rocky Mountain Laboratories in Hamilton, Mont. He placed himself in this group of skeptics.

Prion protein diseases belong to a class of protein-folding diseases, which also include Alzheimer's, type 2 diabetes, and cystic fibrosis, in which the accumulation of misfolded proteins disrupts the function of various organs.

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Poster Session

Plumbing the Cell Biology of Lou Gehrig's Disease, Atherosclerosis, and Lysosomal Membrane Proteins

by Aarthi Ashok

More than 300 posters, placed under 25 different scientific umbrellas, were presented during the Research Festival. Below are reports on three of the posters from the cell biology session.

Mutant Proteins in ALS

Aarthi Ashok

Luca Di Noto, NHLBI

Luca Di Noto, Laboratory of Biochemistry, NHLBI; Principal Investigator: Rodney Levine

Susceptibility of mutant superoxide dismutase to degradation by the proteasome and correlation with amyotrophic lateral sclerosis

Lou Gehrig's disease, or amyotrophic lateral sclerosis (ALS), results in loss of motility due to neuronal degeneration and is the most common motor neuron disease in adults.

The familial form of ALS (fALS), which constitutes about 10 percent of all ALS cases, has been linked to more than 100 mutations in the *sod1* gene that encodes copper/zinc superoxide dismutase (SOD1).

Previous studies have shown that mutations of the ALS type decrease the half-life of the mutant protein in vivo. Di Noto and colleagues hypothesized that the cell's multicatalytic protease, the 20S proteasome, may be responsible for the degradation of SOD1 with fALS-type mutations.

To test this hypothesis, they used purified 20S proteasomes from rat liver to examine the degradative susceptibility of the "apo" or metal-free forms of both normal and fALS mutation-bearing SOD1 proteins.

Quantification of degradation by reverse-phase chromatography and mass spectroscopy led them to conclude that some SOD1 mutant proteins were better substrates for the proteasome than the normal protein.

Further, because the cleavage sites were unaltered in these mutants, the differences between the normal and mutant forms were clearly quantitative.

When they looked at the temperatures at which each of the mutant proteins became completely unfolded (melting temperature), they noticed that some of the mutant SOD1 proteins had lower thermal stability than their normal counterpart, and this lower stability had a linear correlation with proteasomal degradation.

The unfolding of proteins at or near their melting temperature should lead to the exposure of the buried hydrophobic residues, and hydrophobic patches on proteins have been proposed as signals for proteasomal recognition and degradation. Using the fluorescent dye ANS, which binds hydrophobic patches, Di Noto noted that an increase in surface hydrophobicity correlated with increased degradation.

To drive home the point that thermal stability governs proteasomal susceptibility, Di Noto reduced an intramolecular disulfide bond in the normal protein that caused its melting temperature to decrease dramatically.

He then showed that this reduced form was a better substrate for proteasomal degradation than the normal unreduced form.

Taken together, the data point to the absence of metal ions, increased thermal instability, and surface hydrophobicity as the susceptibility factors for proteasomal degradation.

Di Noto suggests that the accumulation of toxic degradation products due to the increased turnover of the mutant SOD1 proteins may be toxic to neurons and thereby result in fALS.

Many degenerative diseases are hypothesized to occur as a result of the accumulation or aggregation of mutant protein.

Based on their studies, Di Noto and colleagues propose an alternative mechanism whereby rapid turnover of mutant proteins into toxic degradation products underlies the pathology of the disease.

PRIONS

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However, prion diseases differ in that they are transmissible.

Creutzfeldt-Jakob disease (CJD), a prion disease that has a familial, sporadic, and infectious form (vCJD), has gained much notoriety in recent years due to the link between vCJD and mad cow disease and the suggestion of a possible trans-species spread.

Chesebro agrees with the delineation of the prion protein, PrP^c, as the protein that misfolds in these diseases to a form known as PrP^{sc}. But he disagrees that the evidence unequivocally defines this protein as the infectious agent itself.

Several animal models designed to mimic the familial form of CJD with a mutation in the gene encoding PrP^c show evidence of brain diseases but no infectivity. The infectious agent—a virus—may remain to be identified, Chesebro said.

The misfolding of PrP^c in that case would serve as the necessary susceptibility factor.

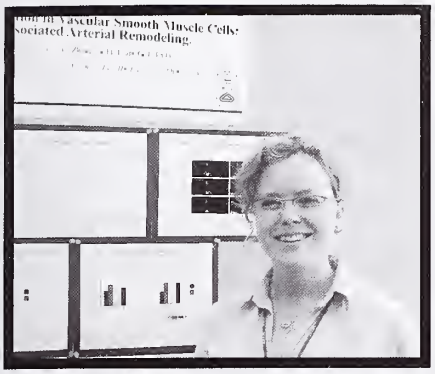
Better vCJD screening strategies are also needed, Chesebro added, noting that current tests are only sensitive enough to detect infection at the late preclinical stages—at about 30 months of age in cattle—whereas the majority of cattle are slaughtered between 14 and 16 months of age.

Chesebro's group has created a mouse infected with a hamster variant of prion disease protein that has shown no clinical signs of disease for two years.

There is evidence, however, that the agent is becoming better able to infect mice.

This carrier of infectivity may serve as a great model for understanding the adaptability of the prion disease agent and its cross-species spread to humans, Chesebro suggested. ■

Arterial Aging



Aarthi Ashok

Gaia Spinetti, NIA

Gaia Spinetti, Laboratory of Cardiovascular Science, NIA; Principal Investigator: Edward Lakatta.
MCP-1 induces TGF-β activation in vascular smooth muscle cells: implication for age-associated arterial remodeling

Remodeling of the arteries contributes to increased susceptibility to the diseases of aging, such as atherosclerosis. Fibrosis involves the accumulation of collagen, fibronectin, and other extracellular matrix components in the arterial wall and is a component of the vascular remodeling process.

Monocyte chemotactic protein 1 (MCP–1), metalloproteinase type II (MMP2), and transforming growth factor–β1 (TGF-β1) are all increased in expression in the aging arterial wall and are deemed to be molecular players in the fibrotic process. Previous work has shown that MCP-1 activates MMP2, and MMP2 can activate TGF-β1, in the rat aorta.

Spinetti and co-workers hypothesized that the increased levels of MCP-1 may be linked to the increase in TGF-β1 levels in vitro and in vivo.

In testing this hypothesis, they first showed that immunofluorescent detection of MCP-1 and TGF-β1 in young (8-month-old) and old (30-month-old) rat aortae led to a complete overlap in their signals, pointing to co-localization of these proteins in the vascular wall.

Using CD31 as a marker of endothelial cells and α-SMA as a marker of aortic vascular smooth muscle cells (VSMC), they further showed that the TGF-β1 signal was present within endothelial and VSMC regions of the arterial wall.

Real time PCR analysis using early passage VSMC showed that TGF-β1 transcript levels were increased in the old rat aortas and in young aortas exposed to MCP-1 for 24 hours, compared with the untreated young aortas. ELISA and western blot analysis showed that the TGF-β1 protein levels mirrored the age dependency and MCP-1 responsiveness of the TGF-β1 transcripts. Subcellular fractionation assays demonstrated the localization of TGF-β1 protein in these cells in the organelles, cytoplasm, and nuclei.

These data point to TGF-β1 production as a novel effect of MCP-1 signaling in VSMC and provide insight into the complex molecular regulation of arterial remodeling.

Spinetti and co-workers are currently analyzing the effect of MCP-1 siRNA transfection on TGF-β1 expression levels in VSMC to further define the relationship between these proteins.

Shedding Light on LAMPs

Aarthi Ashok

Katy Janvier, NICHD

Katy Janvier, Cell Biology and Metabolism Branch, NICHD; Principal Investigator: Juan Bonifacino
Role of the endocytic machinery in the sorting of lysosome-associated membrane proteins (LAMPs)

Lysosomal membranes are highly enriched in glycosylated transmembrane proteins that are appropriately termed lysosome-associated membrane proteins (LAMPs). Janvier and colleagues have set about to explore the cellular mechanisms behind the sorting of these proteins to the lysosomal membrane.

The most abundant members of the LAMP family are LAMP-1, LAMP-2, and CD63; they all carry tyrosine-based cytosolic sequences that are recognized by adaptor proteins (AP) involved in sorting proteins to endocytic and secretory compartments.

Previous work pointed to the existence of two possible pathways for the sorting of LAMPs to the lysosome: the direct and the indirect pathways. The former pathway involves the movement of LAMPs from the *trans*-Golgi network to endosomes and then to lysosomes, while the latter includes a movement of these proteins to the plasma membrane prior to their transport to endosomal compartments.

Janvier designed several experiments to dissect the contributions of these pathways to the trafficking of LAMPs in HeLa cells.

She first examined whether the expression of a dominant negative mutant form of dynamin 2, which blocks internalization from the plasma membrane, would affect the sorting of LAMPs.

FACS analysis revealed an increased cell surface expression of LAMPs in the presence of the dominant negative dynamin 2 compared with the levels present in cells expressing normal dynamin.

Next, using siRNA transfection, Janvier selectively depleted the μ subunit of each of the AP complexes (AP1, 2, 3, and 4) and found that depletion of the AP2 μ subunit (μ2) resulted in a significant increase in the cell surface levels of all three LAMPs.

Because AP2 is the adaptor protein responsible for internalization of cargo in clathrin-coated vesicles from the plasma membrane, Janvier compared the internalization rate of the LAMPs with that of a marker for the AP2 pathway, transferrin, in both the presence and absence of the μ2 siRNA.

The internalization rates of the LAMPs and transferrin were significantly diminished in the presence of siRNA, confirming the role of AP2 in the trafficking of LAMPs.

This finding was supported by experiments in which newly synthesized CD63, upon release from a brefeldin A block that held it in the ER, was sorted to the lysosomes in normal cells and was mostly present at the plasma membrane in cells transfected with the μ2 siRNA.

Finally, Percoll gradient fractionation of HeLa cells followed by immunoprecipitation of LAMPs showed that 40–60 percent of the LAMPs were prevented from trafficking to lysosomes upon AP2 depletion.

Janvier therefore concludes that about half of the LAMP proteins in the cell are sorted to the lysosomes via the indirect pathway, in which AP2 and clathrin play a key role. ■

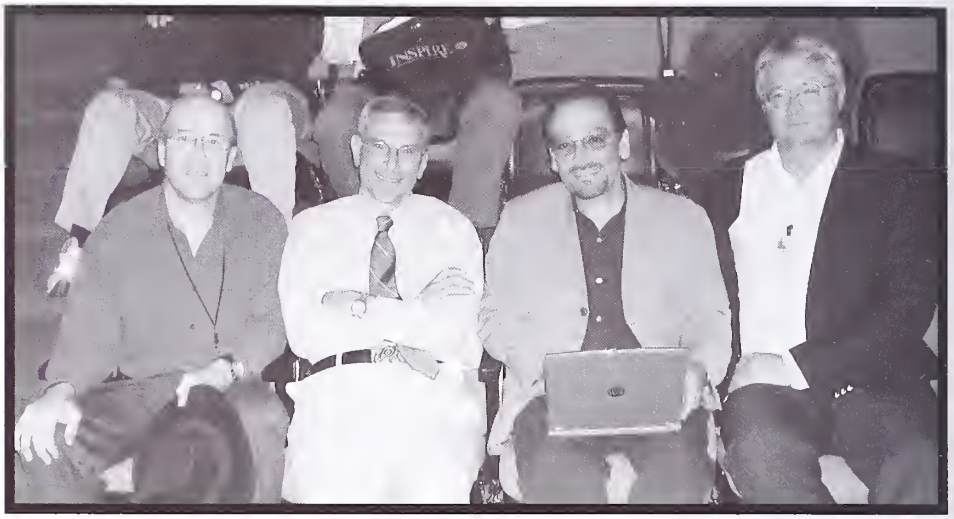
Complex Genetics and Common Brain Disorders

by Fran Pollner

The contribution of multiple genes to the expression of a given disorder may be harder to pin down than Mendelian genetics, but the more complex the underlying genetics, the more numerous the potential pathways to intervention.

Unlike "deterministic" single-gene causes of such conditions as cystic fibrosis or Huntington's disease, susceptibility genes merely predict an increased risk of associated disorders—an increased risk that once identified may be preempted, panelists said at a Research Festival symposium.

In the realm of common brain disorders, plowing through the genomic jungle to track alleles of vulnerability may help alter the course of some of the most pervasive, complicated, and recalcitrant conditions—drug abuse, alcoholism, and mental illness.



Fran Pollner

***Brain explorers**: (left to right) David Goldman, NIAAA; Robert Nussbaum, NHGRI; Daniel Weinberger, NIMH; and George Uhl, NIDA*

Addiction Vulnerability

Polydrug abusers seen at NIDA's Baltimore campus are the basis for "bedside-to-bench research" that is identifying the allelic variants that predispose to addiction vulnerability.

George Uhl, chief of the NIDA Molecular Neurobiology Branch, described studies surveying thousands of single nucleotide polymorphisms (SNPs) that track how "DNA markers and addiction move together through a population."

Several markers, Uhl said, have been found to be close to the functional variants; similar associations were found among unrelated polysubstance abusers, with minimal differences from Eu-

Pathways to Parkinson's Disease

Although parkinsonism is rarely inherited, understanding the nature of the genetic pathway to the disease sheds light on how to arrive there sporadically, observed Robert Nussbaum, chief of the Genetic Disease Research Branch, NHGRI.

The clear finding that specific toxins that interfere with mitochondrial function cause Parkinson's disease (PD) and the equally obvious fact that most PD patients have no family history of the disease help explain why the genetics of PD has been explored only in the last eight years, he said.

What has surfaced thus far—in twin studies—is that genetics comes into play in the context of early onset (before age 50) PD, with siblings the relatives at greatest risk.

Investigators at five other institutes—NINDS, NIMH, NIA, NHLBI, and NIAAA—are involved in research on PD genetics, Nussbaum said, noting that at least four PD loci have been identified, including α–synuclein (park 1, at 4q21) found in families in Greece, Italy, and Germany, and parkin, a ubiquitin E3 ligase (park 2, at 6q25–27).

"A key lesson," in the pursuit of PD heritability, Nussbaum observed, "is that hard as it is to find genetic causes, 30,000 genes [are] easy compared [with] the black box of environmental factors."

The underlying hypothesis of research undertaken by Nussbaum's team was that studying the rare Mendelian families—those with "deterministic" PD genetics—would elucidate the pathways to PD in the sporadic majority.

"We studied an early onset, autosomal dominant Italian family with linkage to 4q21 and found mutations." Another early-onset kindred, from Iowa, had no α-synuclein mutation, but, rather, three copies of a segment of chromosome 4—a triplication of the gene, he said.

The team has identified allelic variants with negative and positive associations; related animal work has shown that overexpression of α–synuclein in Drosophila and mice results in a neurodegenerative phenotype.

Nussbaum described collaborative studies with Eric Murphy of the University of North Dakota, Grand Forks, and Drake Mitchell's lab in NIAAA examining brain phospholipid measures in the α-synuclein knockout mouse.

They focused on cardiolipin, a lipid specific to mitochondrial membrane that is required for electron transport. Abnormalities in cardiolipin may produce reactive oxygen species, disrupting the mitochondria.

The knockout model, he noted, was not sufficient to eliminate cardiolipin altogether. However, cardiolipin sidechains can be manipulated by dietary fatty acid.

Dietary studies with variable polyunsaturated fat constituents will look at whether "loss of function and aggregation of α-synuclein, with damaged or lost mitochondria, contribute to PD," Nussbaum said.

Cardiolipin effects have been studied mostly in yeast, he added, "but it's an area ripe for study in mammals."

—Fran Pollner

ropean American and African American cohorts.

"Although environment also provides a large chunk" in the development of addiction, Uhl said, "the results of gene mapping suggest that we have markers with predictive power in European, African American, and Asian populations—and current data nominate 33 chromosomal sites that together may explain a significant amount of addiction vulnerability."

Among those genes implicated in addiction vulnerability are *NrCAM* (neuronal cell adhesion molecule), a morphine-regulated gene, and the cannabinoid receptor gene *CNR1*.

As with other addictions, heritability accounts for more than 50 percent of vulnerability to alcoholism, said David Goldman, acting chief of the Laboratory of Neurogenetics, NIAAA.

This substantial impact of genetics, Goldman said, influences susceptibility to nicotine, marijuana, and heroin addictions.

Genes implicated in susceptibility to alcoholism include the ethanol metabolism genes *ALDH2* (aldehyde dehydrogenase) and *ADH1B* (alcohol dehydrogenase) and *COMT* (catechol-O-methyltransferase).

Mental Illness

There is now clear proof, said Daniel Weinberger, chief of the Clinical Brain Disorders Branch, NIMH, that genes are strongly related to neural information processing systems, which in turn are related to behaviors and behavioral disorders. Thus, there is no longer any argument over the existence of a genetics of mental illness.

There are, however, questions regarding this genetics: "How many genes are involved, and how large is the effect of any one? What does it mean to be susceptible?" Weinberger asked. "We know about cancer genes and their effects on disruption of the cell cycle; biological susceptibility to mental illness and addiction is much more elusive."

The surprising finding, he said, is that linkage data have been at all successful in uncovering regions of the genome where susceptibility genes have been found. That success, he said, can be attributed at least partly to a "quirk of nature"—the fact that linkage regions tend to harbor multiple susceptibility genes. This neighborly arrangement has facilitated replication, for instance, of the identification of schizophrenia genes among populations around the world.

Strategies that have been used to identify candidate genes in mental illness include expression profiling, SNP associations, and chromosomal translocation, Weinberger said. At NIMH, SNP association has identified evidence of at least 10 schizophrenia genes. He pointed to the identification of *COMT* and, more recently, *GRM3* (glutamate receptor, metabotropic) as candidate genes in schizophrenia that have been studied extensively.

The *COMT* effect on dopamine—it inactivates dopamine in the prefrontal cortex—may explain the apparent association of *COMT* variations with an array of phenotypic expressions—psychosis, obsessive-compulsive disorder, anxiety, drug abuse, bipolar disorder, aggression, poor impulse control, and sensitivity to pain. "It may seem preposterous," Weinberger said, "but this could be a basic biological effect" that manifests itself in a variety of ways in different contexts.

Cognition studies using functional MRI in his lab have shown that *COMT* contributes to normal human variation in prefrontal memory processing, which varies with *COMT* genotype.

Genes involved in serotonin signaling and reuptake, such as the serotonin transporter protein gene and its promoter, also predict for depression in the context of environmental stress. Not surprisingly, effecting change in serotonin signaling is the basis for most of the antidepressant drugs on the market today, Weinberger observed. ■

Four More IOM Stars

The ranks of NIH scientists elected to the Instituite of Medicine expanded by four this year: **Zeke Emanuel**, director of the Department of Clinical Bioethics, CC; **Alan Guttmacher**, clinical advisor to the director, NHGRI; **Bob Nussbaum**, chief of the Genetic Disease Research Branch, NHGRI; and **Tom Quinn**, NIAID senior investigator. ■

Book Early and Enjoy the Club

If you like recondite books and have a somewhat eccentric mind, I've got a great book club for you.

The NIH Biomedical Computing Interest Group (BCIG) sponsors a highly successful (in terms of attendance, participant liveliness, and follow-up accolades) book club that was started over a year ago.

Good, friendly, informative dialogue occurs at every meeting. Participants feel free to speak or not to speak. Some read the books in detail and others don't.

We have already selected nine books for the 2005 program: three on computer science, three on biomedical sciences, and three on organizational behavior.

Here are the books and the dates they will be discussed:

- **1/27** *eXtremeProgramming eXplained*, Kent Beck
- **2/24** *The Triple Helix*, Richard Lewontin
- **3/24** *The 21 Irrefutable Laws of Leadership*, John C. Maxwell
- **4/28** *Leonardo's Laptop: Human Needs and the New Computing Technologies*, Ben Shneiderman
- **5/26** *Mapping Human History: Genes, Race, and Our Common Origins*, Steve Olson
- **6/23** *Micromotives and Macrobehavior*, Thomas C. Schelling
- **7/28** *Free Software for Busy People*, Mohammad Al-Ubaydli
- **9/22** *Life Evolving: Molecules, Mind, and Meaning*, Christian de Duve
- **10/27** *Peopleware: Productive Projects and Teams*, 2nd Ed., Tom DeMarco, Timothy Lister

You can get these books through most book suppliers, including the FAES Book Store and the NIH Library, or through interlibrary loan at your local library.

Authors Shneiderman, Olson, Al-Ubaydli, and perhaps others are likely to attend when their books are discussed

All meetings will be held in the NIH Clinical Center (Building 10) in the Medical Board Room (Room 2C116) on Thursdays from 5:30 to 7:30 p.m.

For more information, please contact Jim DeLeo at 301-496-3848 or

<jdeleo@nih.gov>

or refer to the BCIG website

<www.nih-bcig.org>.

—Jim DeLeo

Fare Thee Well: NIH Job Fair Aims to Open Doors beyond NIH

text and photos by Karen Ross

The NIH Job Fair, held on September 30 during the Research Festival, featured 43 exhibitors who filled five conference rooms in the Natcher Building. The fair was well attended. Many employers had a constant stream of visitors and after only a couple of hours, some had already run out of literature to distribute. The exhibitors ranged from multinational corporations to small local biotechnology companies and included a few representatives of alternative careers outside the traditional academic and industrial research spheres. Nearly all of the exhibitors had open positions and some conducted on-the-spot interviews.

Computercraft, a local company that develops and maintains NCBI's public genetics databases, including GenBank and RefSeq, is a four-year veteran of the NIH Job Fair that has hired one or two people from NIH each year. Gene Hill and other company reps were looking for candidates for five positions and kept busy collecting résumés and conducting interviews. Hill said they planned to review the résumés and schedule more interviews the following week. He also credited OE's Shirley Forehand with fine Job Fair organizing.

Three human resources specialists from the Montgomery County Public Schools (MCPS)—(l. to r.) Samuel Daniels, Elaine Tanenhaus, and Peggy Dolet (with Gloria Seelman, NIH Office of Science Education, standing)—were on hand to recruit fellows with an interest in public school teaching. Daniels explained that it's not easy to find certified science, math, and computer science teachers, so they look for people with science or math backgrounds and guide them through the teaching certification process, which involves taking some education courses and gaining teaching experience. Of course, Daniels added, one should also "be a good communicator, have a love for kids, and . . . have a warm personality."
Last year's Job Fair, Tanenhaus remarked, added one more NIH alum to the MCPS ranks.

Dave Henderson, an engineer for GE Global Research, came to the NIH Job Fair to promote and recruit for the company's new Biosciences Lab, which supports the newly created GE Healthcare Bio-Sciences business. The new lab has multiple openings in biology, chemistry, and biochemistry. Henderson was seeking candidates to fill bioinformatics positions and was impressed by the NIH turnout. "I didn't know quite what to expect," he said, "but I quickly got inundated with very well-qualified people." He viewed the Fair as "a nice opportunity . . . to get name recognition [and] to attract top talent to help build the organization."

Prospecting

Tina Tekirian, a fellow at NCI-Frederick who hopes to land an academic position, said she was disappointed that the Job Fair was focused on nonacademic posts. She did pick up some of the nonacademic exhibitors' brochures for her colleagues in Frederick, where the career center (part of the fellowship office) was closed several months ago. Another helpful resource, she suggested, would be a centralized source to which NIH PIs could send up-to-date university job bulletin board posts relayed by their colleagues.

Ed. Note: *The NIH Office of Intramural Training and Education has three job-hunting sites for NIH fellows. First, go to* **<http://www.training.nih.gov>***; then select (1) "***NIH Only***" for access to "***Current Outside Openings***" and (2) "***Careers***" for access to "***Virtual Job Fair***" and "***Virtual Career Center.***"*

NCBI fellow Damir Herman, who is seeking a position in bioinformatics or biostatistics, found a couple of promising companies at the Job Fair. "I don't expect NIH to look for my job," he said, "but they're doing a pretty good job of bringing people in . . . [and these people] are very eager to hire."

Prelims: How to Approach Job Fair and Other Job-Seeking Activities

by Karen Ross

Two weeks before Job Fair, NIH hosted two workshops on gearing up for job hunting. About 50 people attended a September 13 workshop led by Beth Fischer of the University of Pittsburgh, who offered NIH job seekers advice on how to prepare themselves and their résumés for the NIH Job Fair. Attendees indicated interests in both academic and industry research in an informal poll by Fischer.

The first part of the workshop was devoted to Job Fair preparation and etiquette. The goal of the job seeker at a fair, Fischer emphasized, is to land a full interview. The best way to accomplish this goal, she said, is to do extensive research beforehand. Job seekers should come to the employer's table with questions about specific products the company is developing or about hiring patterns or career paths at the company. "You want to give them everything you can to show that you are an interested professional," she said.

Fellows would be wise to visit the NIH Job Fair website, which lists all participating companies and, in many cases, descriptions of open positions and links to the companies' websites.

Dressing nicely is also important, Fischer said, adding that in previous years some employers at the NIH Job Fair complained that the fellows looked "a little shabby."

She also advised people to attend the Job Fair with their résumés in hand—and then she launched into a discussion of how those résumés ought to be crafted. She described the differences between a curriculum vitae (CV), the traditional format used to apply for academic positions, and the industry-oriented résumé. (The CV is an exhaustive chronological listing of career accomplishments, while a résumé is tailored to highlight the candidate's qualifications for a particular job.)

To illustrate some common problems, she distributed copies of a mock résumé that was full of typographical and formatting errors as well as irrelevant information that hid the applicant's real accomplishments.

The workshop appeared to be well-received. NIAID fellow Emiko Soeda and NINDS fellow Jean Tiong, both of whom intend to hit the job market in the near future, were enthusiastic about the program. Soeda remarked that job fairs are an unfamiliar concept to her because in her home country, Japan, young scientists most often get jobs through their advisors' personal connections. Tiong liked having the opportunity to critique a résumé and planned to use her new knowledge to modify her own.

The following week, on September 21, representatives from Wyeth Pharmaceuticals, including Matt Yudt, a Ph.D. scientist who did his postdoctoral work at NIH, offered advice on landing a job at a big pharmaceutical company. The program was sponsored by FELCOM, the Office of Intramural Training and Education, and the Office of Research on Women's Health.

They stressed that people seeking positions as scientists in industry, especially in these tough economic times, need to focus on jobs that require the specific skills and education they have—and that their résumé should be tailored to reflect that. Available positions, they noted, are usually described on the company's website.

Candidates who are selected for interviews are judged on both their science and their communication skills. They normally are required to give a research seminar, and the quality of their presentation and their ability to answer questions are closely scrutinized.

Yudt added that it is helpful if candidates can suggest commercial tie-ins to their research. And they should be enthusiastic and as knowledgeable as possible about the position for which they are interviewing.

Those who hope a job in industry will offer a respite from the long hours at the bench as a postdoc may be disappointed. In addition to their proprietary work, scientists at Wyeth are expected to publish two papers a year. Yudt said he frequently goes back to the lab to work in the evenings, and that promotions come faster to those who put in evening and weekend hours.

On the plus side, he added, promotions are plentiful, salaries are good, and the research atmosphere is collaborative. ■

Epigenetics

continued from page 1

Karen Ross

Epigenetics panel: *(left to right) Jay Chung, NHLBI; Shiv Grewal, NCI; Mirit Aladjem, NCI; Munira Basrai, NCI; David Schrump, NCI*

a variety of experimental organisms.

Some DNA regions destined to be silenced contain a short piece of repeated sequence. RNA made from the repeated sequence forms a double-stranded conformation, which is chopped up into small pieces by enzymes in the RNAi pathway.

The pieces, in turn, help recruit the enzymes and structural proteins needed to make heterochromatin to the homologous DNA sequence from which RNA was made.

Heterochromatin formation is epigenetic because it alters the DNA in a nonpermanent way that nevertheless is very stable and can be passed on to the next generation.

Replication Timing

Aladjem, of the Laboratory of Molecular Pharmacology, described new insights into how cells control when different parts of the genome are replicated.

In general, she said, regions with high levels of gene expression replicate early and silent regions replicate late.

To investigate why this is, Aladjem and her colleagues inserted the DNA sequences that code for the blood protein β-globin into a new home—a region of chromosome 15 that normally replicates late. In one orientation, the transplanted DNA was expressed and replicated early; in the other orientation, it was not expressed and was replicated late.

A particular chemical modification of the DNA known as methylation was associated with late replication. In fact, if the β-globin DNA was methylated before it was inserted, it replicated late in both orientations.

β-Globin DNA that was altered so that it could not be methylated, however, showed a normal pattern of replication timing, suggesting that methylation is not required for late replication. A portion of the β-globin sequence called the locus control region proved to be important for regulating replication timing.

Finally, Aladjem said, although late replication and gene silencing normally go hand in hand, the two processes are distinct, as newly inserted β-globin sequences replicate late even before they are fully silenced, a process that takes several weeks.

Epigenetics at the Bedside

Two drugs that induce epigenetic modifications of DNA are the subjects of clinical trials involving lung cancer patients, reported Schrump, of the Thoracic Oncology Section of the Surgery Branch.

Tumor cells undergo a complex pattern of epigenetic changes in their DNA that affect gene expression, Schrump said.

Early in tumor formation there is widespread demethylation of DNA, which leads to a general increase in gene expression; however, a few critical tumor suppressor genes undergo the opposite modification—they are hypermethylated and silenced.

Schrump is investigating whether two drugs—5-aza-2'-deoxycytidine (DAC) and depsipeptide (DP)—can awaken these antitumor genes and halt the progression of lung cancer. DAC inhibits DNA methylation; DP is one of a class of drugs called histone deacetylase inhibitors that block the removal of acetyl groups from histones. (Histones are DNA-binding proteins that organize and compact the DNA. Acetylation of histones is associated with increased gene expression.)

In a phase I clinical trial with DAC, Schrump reported, patients' tumors stabilized, although they did not shrink, and the expression of some tumor suppressor genes did increase. In addition, some tumors exhibited increased expression of tumor antigens that are known to be regulated by epigenetic mechanisms. A phase II trial with DP and a trial in which DAC and DP were given sequentially yielded similar results.

Schrump and his colleagues are now testing sequential doses of DP and flavopiridol (FLA), a drug that influences gene expression by an entirely different mechanism. Early evidence suggests that FLA may increase the effectiveness of DP and make cells more susceptible to programmed cell death.

The Multifaceted Per2

Per2, a protein that affects gene expression and cell cycle, turns out to have a surprising new function in metabolism. Jay Chung, Laboratory of Biochemical Genetics, NHLBI, discussed this protein of interest in another context: its role in regulating food intake and glucose levels in mice.

Per2 mutant mice develop tumors in their salivary glands, and their cells have an abnormal response to DNA damage. The mutants also cannot maintain a steady sleep-wake cycle if they are kept in constant darkness, which indicates that they have defects in their circadian clock.

Chung's group discovered that Per2 mutant mice, particularly females, gain weight unusually quickly when fed a high-fat diet. Like people with type 2 diabetes, the mice are insulin resistant,

More Epigenetics

On Deck: Zebularine

Epigenetics also took center stage at Hispanic Scientist Day on October 13. Keynoter Victor Marquez, chief of the Laboratory of Medicinal Chemistry, NCI-Frederick, discussed a promising anticancer drug called zebularine, which reduces DNA methylation much like DAC, the drug studied by Schrump's group.

Chemically speaking, zebularine closely resembles cytidine, one of the normal DNA bases. Incorporated into DNA at a low rate, it binds tightly to the enzyme responsible for DNA methylation, trapping it and blocking its further activity. The overall reduction in DNA methylation stimulates increased expression of important antitumor genes such as p16 and p53.

Karen Ross

Victor Marquez

This mechanism of action is very similar to that of DAC. Although DAC is the more potent of the two drugs, zebularine has a couple of important advantages. First, it is far less toxic than DAC because its activity is restricted mainly to tumor cells—the enzymes necessary to process zebularine so that it can get into DNA are expressed at much higher levels in tumor cells than in normal cells. Second, it can be administered orally—tumor growth was slowed in mice that drank water containing zebularine.

Marquez, in collaboration with the NCI Cancer Therapy Evaluation Program, is currently preparing for a clinical trial of zebularine. So far, the NCI Developmental Therapeutics Program has produced large quantities of the drug and is in the process of completing toxicity studies in animals needed for inclusion in an IND.

—Karen Ross

unable to control their blood sugar despite producing adequate levels of insulin.

Per2, Chung noted, appears to be part of the preopimelanocortin/α-melanocyte stimulating hormone pathway, which is known to regulate appetite. ■

NIH/Hughes Scholar Mootha Wins MacArthur Award

NIH undoubtedly trains many beautiful minds. In October, the MacArthur Foundation confirmed the intellectual beauty of one former trainee by awarding Vamsi Mootha one of its "genius awards"—a five-year, $500,000 no-strings-attached fellowship.

Mootha, 33, is currently an assistant professor of systems biology at his alma mater, Harvard Medical School in Boston (and assistant professor of medicine at Massachusetts General Hospital in Boston). He was one of 23 recipients of a 2004 Fellowship from the John D. and Catherine T. MacArthur Foundation.

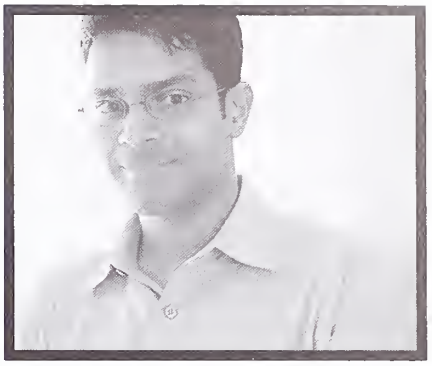
Mootha's research focuses on mitochondria. He used innovative "neighborhood analysis" data-mining methods to combine functional, expression, and gene position data to identify the flaw underlying the rare, fatal Leigh syndrome, French-Canadian Variant. LSFC claims one in 2,000 children born in the Saguenay/Lac-Saint-Jean region of Quebec. Mutations in the *LRPPRC* gene lead to cytochrome c oxidase deficiency, with resulting developmental delays and fatal build-up of lactic acid in the blood, typically after infection or other stress.

While the LSFC discovery was impressive, it is likely that what caught the eye of the MacArthur selection committee was Mootha's sleight-of-hand in pulling biological and clinical discoveries, like rabbits, out of unpromising and vast genomic and proteomic datasets.

Mootha and collaborators have now moved their mathematical sorcery to type 2 diabetes. After categorizing functional categories of genes from expression data, they were able to detect a difference in mitochondrial gene regulation between people with and without diabetes.

"Vamsi is not attempting to reduce the problem to its simplest elements, but to accept the complexity of biology and develop the tools we will use over the next several decades to unravel the interactions that naturally occur," observes NHLBI scientific director, Bob Balaban. Mootha was an NIH/Howard Hughes medical student in Balaban's lab from 1995 to 1997 before returning to Harvard to complete his M.D. Balaban calls Mootha's LSFC, diabetes, and overall mitochondrial proteomics "landmark studies in mitochondria research."

Balaban says Mootha revealed his genius potential within the first two weeks of setting foot in his lab. "Vamsi was simply a remarkable student," Balaban recalls. "His first paper was generated by making a novel technical observation, working out the details, and writing up the paper over a period of about a week."



The look of genius: *Vamsi Mootha*

The paper looked nearly flawless to Balaban. "I did not have to modify anything other than to add some references. This was also the first scientific paper he ever wrote!"

The journal reviewers agreed with Balaban's assessment and published the paper without any revision. Balaban calls Mootha "one of the brightest, most energetic fellows I have ever had in the lab"—and "one of the most enjoyable people to interact with . . . . The [MacArthur] committee did a spectacular job in identifying Vamsi as a genius. . . . It is going to be great to watch him soar."

And for his part, Mootha told *The NIH Catalyst*, "I was very fortunate to land in Bob Balaban's laboratory. [He] had set up a wonderful environment in which physicians, physicists, and biochemists could work together to use quantitative approaches to explore problems related to energy metabolism and human disease.

"The year at the NIH was a very special one. . . . It was during this time," Mootha recalled, "that I fell in love with mitochondrial metabolism."

Asked how he plans to use the "genius grant," Mootha has told the press he is uncertain, but his thinking is heading in directions that seem very much in the intramural NIH tradition of adventurous research [see editorial, p.2]. A Harvard press release says Mootha's initial thoughts are to investigate rare mitochondrial disorders. "I want to do something deliberate with the money, maybe research some riskier areas," Mootha said. "Some of my crazier ideas will be funded with this money."

—Celia Hooper

Recently Tenured

Patrice J. Morin *earned his Ph.D. degree at Boston University in 1995. He then did his postdoctoral research training at the Johns Hopkins Oncology Center in Baltimore. He joined the NIH as a tenure-track investigator in 1998. He is now a senior investigator at NIA in the Laboratory of Cellular and Molecular Biology and is head of the Cancer Genomics and Signaling Section.*

Patrice Morin

Our research focuses on the molecular mechanisms of ovarian tumorigenesis. In particular, we are interested in identifying genes and pathways that may become novel targets for detection and therapy.

The American Cancer Society estimates that in the United States this year more than 23,000 women will be diagnosed with ovarian cancer, and approximately 14,000 will die of the disease. Yet very little is known about the biology of ovarian cancer.

Ovarian cancer affects older women disproportionately, with more than half the cases diagnosed in women older than 60. In spite of the recent introduction of aggressive treatments, five-year survival rates for patients with advanced ovarian cancer are low, ranging between 5 and 30 percent.

Five-year survival can reach 95 percent if the diagnosis is made at an early stage, but only about one-quarter of patients are diagnosed early, when there are no symptoms. These facts make ovarian cancer a disease for which early detection represents an intervention of choice in reducing morbidity.

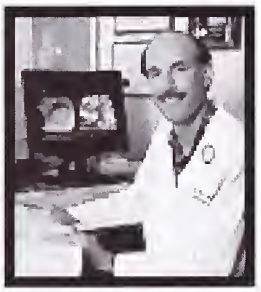
It is likely that the discovery of highly sensitive and specific tumor markers will greatly affect ovarian cancer management and lead to a significant increase in overall survival.

In the past few years, we have used serial analysis of gene expression (SAGE) and microarrays to examine gene expression in ovarian cancer and normal ovarian tissues.

We have identified several thousand genes expressed in each tissue and found numerous genes differentially expressed between normal and malignant ovarian cells, including novel transcripts that we have named HOSTs (human ovarian cancer–specific transcripts). Genes whose expression is elevated in ovarian cancer, especially those that encode secreted and/or surface proteins, may become targets for early diagnosis and various therapeutic strategies, such as immunotherapy. We are evaluating promising candidates and generating antibodies to investigate their clinical potential.

The large number of genes abnormally expressed in ovarian cancer may also provide clues to which molecular pathways may be relevant to ovarian tumorigenesis. We are using a variety of molecular biological tools to validate our SAGE results and dissect the molecular pathways responsible for the aberrant gene expression.

Of particular interest is the pathway involving the claudin tight junction proteins. We have found that these proteins are consistently elevated in ovarian tumors. Since our initial findings, other research groups have found that claudins are dysregulated in many other cancers.



Ronald Summers

We are currently examining signal transduction upstream and downstream of the claudin proteins in order to clarify their functions in cancer. Our current data suggest that claudins may be important for cell motility and invasion. Overall, the identification and characterization of pathways crucial for ovarian tumorigenesis will provide a better understanding of this disease at the molecular level and may suggest novels targets for therapy.

Aside from the difficulties of ovarian cancer detection, ovarian cancer treatment is also plagued by drug resistance. Approximately half of ovarian tumors are intrinsically resistant to chemotherapy, and a significant fraction of women with tumors that initially respond to chemotherapy eventually relapse with drug-resistant disease.

We have created an in vitro model of drug resistance consisting of isogenic cell lines differing in their sensitivity to cisplatin. Using SAGE, we have identified genes whose expression is altered in cisplatin-resistant cells. These genes encode proteins of the extracellular matrix and cell adhesion, such as collagen VI, collagen X1, and decorin.

We are currently investigating the mechanisms of cell adhesion-mediated drug resistance in ovarian cancer. We are also studying the roles of the phosphatidylinositol 3 kinase/Akt pathway, as well as the X-linked inhibitor of apoptosis pathway in ovarian cancer drug resistance using, among other approaches, siRNAs and somatic gene-targeting strategies.

Ronald Summers *received his M.D. and Ph.D. degrees from the University of Pennsylvania School of Medicine in Philadelphia in 1988. After a medical internship, he completed a radiology residency at the University of Michigan Hospitals in Ann Arbor and a body Magnetic Resonance Imaging fellowship at Duke University in Durham, N.C. He joined NIH in 1994 as a staff radiologist in the Clinical Center and is currently chief of the Virtual Endoscopy and Computer-Aided Diagnosis Laboratory in the Diagnostic Radiology Department of the CC Imaging Sciences Program.*

While at Duke, I attended a lecture by David Vining, a radiologist who was touting a new way of detecting colorectal cancer using computed tomography (CT) scans.

He called the test "virtual colonoscopy" and highlighted his lecture with "Fantastic Voyage"–like movies of the inside of the large intestine.

Here was the potential to make new types of radiologic diagnoses noninvasively. Vining's presentation sparked my imagination as I realized by performing research in virtual endoscopy I could combine my interests in medical imaging and computing to solve important clinical problems.

Upon arrival at NIH, I first explored virtual endoscopy's potential for detecting disease of the human airways.

In collaboration with James Shelhamer of the Critical Care Medicine Department and Michael Sneller and Steven Holland of NIAID, I embarked on a protocol to use virtual bronchoscopy to study patients with cavitary lung disease and airway stenosis.

Later, with David Schrump and Steven Finkelstein of the NCI Surgical Oncology Branch, I used virtual bronchoscopy to study patients with lung cancer.

We wrote a series of articles presenting our methodology for producing the virtual bronchoscopy images. We also conducted clinical validation studies that showed that virtual bronchoscopy could reveal morphologic abnormalities such as airway occlusions and endobronchial masses.

Based on these results, we moved virtual bronchoscopy from the bench to the bedside—from an experimental project to a routine clinical service offered to patients at the CC.

About 1998, I became interested in computer-aided detection (CAD). Medical images were becoming more complex, and radiologic interpretation of these images became more labor-intensive. I saw potential clinical value in automating the process of lesion detection.

Our approach was to determine those structural features, such as shape, that the radiologist and endoscopist have traditionally identified. Then we identified methods such as differential geometry and other mathematical and image processing techniques to isolate and quantify these features and, ultimately, improve upon them.

The outcome of this work was the first computer-aided detection system for virtual bronchoscopy. This system enabled us to locate endobronchial polypoid lesions with automated software that had high sensitivity and a low false-positive rate.

Simultaneously with this work, interest in virtual endoscopy had accelerated in the medical community. CT scanners were acquiring images faster, and image quality was improving. These advances allowed more accurate three-dimensional reconstructions and better virtual depictions of internal anatomy.

For example, several clinical trials showed that virtual colonoscopy had potentially high sensitivity and specificity for detecting colorectal polyps, precancerous growths that are the precursor lesion to colorectal cancer.

While polypoid endobronchial lesions are rare, colonic polyps are not. In addition, polyp detection is important, and detection and removal of them is the centerpiece of colorectal cancer prevention and treatment. It soon became clear to me that we could apply similar CAD technologies to find polyps on virtual colonoscopy and that there was clinical value in doing so.

In 2000, in collaboration with colleagues at Stanford University (Stanford, Calif.), my lab published a feasibility study that showed CAD could locate simulated polyps in human virtual colonoscopy scans.

One year later, in collaboration with colleagues at the Mayo Clinic (Rochester, Minn.), we published results of a clinical trial that showed CAD could find real colonic polyps in patients. These papers, published in the widely read journal *Radiology*, initiated a groundswell of interest in computer-aided colonic polyp detection.

Since then, researchers from institutions around the world have published on virtual colonoscopy CAD. Commercialization of computer-aided polyp detection is likely in the near future.

Currently my lab is working on improving the sensitivity and decreasing the false-positive rate of computer-aided polyp detection.

We are studying ways to help the colonoscopist precisely locate abnormal tissue found at virtual colonoscopy so that these abnormalities can be removed. We are verifying the performance of CAD in a screening population of patients and refining CAD to detect different histopathologic polyp types.

Other research areas we are working on include advanced image segmentation techniques to distinguish organs and lesions from normal background tissue and the application of CAD to detect other abnormalities on CT scans such as subcutaneous melanoma and bone metastases.

Our work would not be possible without a multidisciplinary approach that involves collaboration of computer scientists, engineers, statisticians, and clinicians.

Together we can bring the power of noninvasive imaging and computational methods to bear on health problems that affect many Americans. The NIH CC is an ideal place to do this kind of multidisciplinary work. ■

In Memoriam: John La Montagne

John La Montagne, NIAID deputy director since 1998 and NIH luminary since his arrival here in 1976, collapsed and died November 2 while standing in line at an airport in Mexico City. He was 61.

A chronology of his nearly 30 years at NIH includes his leadership positions in the NIAID Influenza Program, the Viral Vaccines Program, the Influenza and Viral Respiratory Diseases Program, the AIDS Program, and the Microbiology and Infectious Diseases Program (and Division) before he became NIAID deputy director.

Throughout his career, he was an internationalist, dedicated to the eradication of worldwide health scourges; in that endeavor, he served as

- A major organizer of the Multilateral Initiative on Malaria, an international effort spanning agencies from the United States, Europe, and Africa
- A member of the World Health Organization (WHO) expert advisory groups on vaccines and biologicals, as well as vaccines and immunization
- Chairman of the WHO Task Force on Strategic Planning for the Children's Vaccine Initiative
- An advisor to Pan American Health Organization programs in vaccine research implementation
- A member of the board of the Global Alliance for Tuberculosis Drug Development

He was also involved in biodefense strategies and NIH security and ethics initiatives.

In the words of NIAID Director Tony Fauci: "All of us are profoundly saddened by the loss of John La Montagne. Personally, he was a dear friend and one of the finest people I have ever known. Professionally, in an NIH career spanning nearly 30 years, his leadership and commitment to improving global health were remarkable. His generosity, wit, even-handedness and kindness made him a friend to all who knew him. He will be sorely missed."

NIH Internships for Students with Disabilities

On Wednesday, April 28, Ganesh Kumar worked until it was April 29, missing the last Metro out of the Bethesda Medical Center station. He stayed the night, working on his 3-D reconstructions of pancreatic tissue images and sleeping a few moments here and there on the couch in Sriram Subramaniam's Building 50 lab.

The next morning, his mentor pulled up a chair to the computer and together they peered over the series of pancreatic slices.

"How did you segment this position? Is that the nucleus?" Subramaniam asked, as they clicked through the images on the screen. Kumar was quick in his responses, alert, and looked well rested and fresh.

A sophomore at Carnegie-Mellon University in Pittsburgh, Kumar had taken a semester off to work with Subramaniam, chief of the biophysics section at NCI's Laboratory of Cell Biology. The following day, the 30th, would end his four-month stint at NIH, and he needed to tie up loose ends.

Kumar had arrived in January at the same time the lab was entering into a CRADA to evaluate and establish standards for an automated "slice and view" scanning capacitance microscope that, says Subramaniam, "yields 10 times better resolution than confocal microscopy." As a member of the CRADA team, Kumar used the microscope and produced weekly reports on the machine's output.

"He was in the right place at the right time," Subramaniam observes.

Kumar is working toward a bachelor of science degree in computer science; the previous summer, he'd done an internship at a major business corporation, working on databases. This time around, he wanted exposure to the biotech applications of his chosen field. "I was lucky," he says of his chance to work with Subramaniam on such an exciting project.

He anticipates graduate school, possibly medical school as well, and pursuing the biomedical and bioengineering aspects of computer science.

Enter Entry Point!

Kumar found his way to Subramaniam's lab through his own initiative and through contact with individuals involved in establishing a collaboration between NIH and the American Association for the Advancement of Science in an AAAS program called Entry Point!

Entry Point! was set up in 1996 to facilitate the entry of undergraduate and graduate students with disabilities into internships in private industry and government in science, engineering, math, computer science, and certain business fields.

Fran Pollner

All in a night's work: *Sriram Subramaniam (foreground) reviews the last batch of images generated by departing intern Ganesh Kumar*

NIH's Entry Point! is also looking for students majoring in biology, bioengineering, and biochemistry, as well as science students with writing and web design skills.

For more information, contact Delores Parron at 301-451-9677 or by e-mail: **<parrond@mail.nih.gov>** or visit the AAAS website: **<http://ehrweb.aaas.org/entrypoint/index.html>**.

—Fran Pollner

Pharmacology Training Programs

The NIGMS Pharmacology Research Associate (PRAT) program is now accepting applications for positions to begin October 2005. Applications must be received by **January 14, 2005.**

This is a 3-year competitive research fellowship program that supports training at NIH or FDA laboratories for postdoctoral candidates in the pharmacological sciences and related research areas.

Applicable areas of research may include, but are not limited to, molecular pharmacology, signal-transduction mechanisms, drug metabolism, immunopharmacology, chemistry and drug design, structural biology, endocrinology, bioinformatics, and neuroscience.

PRAT fellows receive competitive salaries as well as supply and travel funds. 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, contact the PRAT program assistant at 301-594-3583 or by e-mail **<prat@nigms.nih.gov>**, or visit the PRAT web site at **<http://www.nigms.nih.gov/about_nigms/prat.html>**.

ClinPRAT

The Clinical Pharmacology Research Associate (ClinPRAT) program is intended for physicians who wish to acquire specialized clinical and laboratory training in the pharmacological sciences.

For more information or application materials, contact Donna L. Shields at 301-435-6618 or by e-mail **<DShields@mail.cc.nih.gov>**, or visit the ClinPRAT Web site: **<http://www.cc.nih.gov/researchers/training/clinprat.shtml>.**

NIH-Duke Program Training In Clinical Research

Applications are being accepted for the 2005–2006 NIH-Duke Training Program in Clinical Research. The deadline for applying is March 1, 2005.

The program is designed primarily for physicians and dentists who want formal training in the quantitative and methodological principles of clinical research and is intended to be a part-time complement to ongoing clinical training.

Courses are offered at the NIH Clinical Center via videoconference. Academic credit for the course may be applied toward satisfying the degree requirement (24 credits of graded course work plus a 12-credit research project) for a Master of Health Sciences in Clinical Research from Duke University School of Medicine.

Applications are available in the NIH Clinical Center, Office of Clinical Research Training and Medical Education, Building 10, Room B1L403.

Additional information regarding coursework and tuition costs is available at the program website at **<http://tpcr.mc.duke.edu>**. E-mail queries can be sent to the same address.

Enrollment is limited. Interested individuals should check with their NIH institute or center regarding funding for participation. Successful applicants will be notified by July 1, 2005. ■

Demystifying Medicine

The popular Demystifying Medicine course will be offered again in 2005. The course aims to bridge the gap between Ph.D.s trained in basic science and the medical problems to which their skills and insights could be applied. Presentations of patients and pathology are accompanied by state-of-the-art analyses of related basic and clinical science.

Starting **January 4** and ending May 17, the course will be held every Tuesday from 4:00 to 6:00 p.m. in the Building 50 ground-floor auditorium (Rooms 1227 & 1233). All presentations will be videocast.

The course is geared to graduate and medical students, clinical and Ph.D. fellows, and staff. Background information and handouts will be available.

Those seeking academic credit for the course can register with FAES at **<http://www.faes.org>**; otherwise, registration is at the Listserv: **<http://list.nih.gov/archives/demystifyingmed/html>**.

Participants who attend at least 75 percent of the sessions and complete a web-based final examination will receive a certificate. The course schedule follows and can also be found at **<http://www1.od.nih.gov/oir/DemystifyingMed/index.html>**.

TCB at NIH: Entering A New Business System

NIH has begun replacing its Administrative Database (ADB) with the fully integrated NIH Business System (NBS) that will automate and link all of NIH's administrative processes, resources, and financial information.

One of the first two modules in place for the start of fiscal 2004—the NBS Travel System—was used to process 70,719 travel authorizations, 56,988 travel vouchers, and 6,543 local travel vouchers during the fiscal year ending September 30, 2004. (Because travel documents are now electronically routed, CANs have been replaced by "project" numbers.)

To help NIH users navigate the new system, an NBS Management Center was established in September 2003; 15,000 help calls were logged in fiscal 2004, and 99 percent of them have been resolved. In addition, each institute and center has appointed a liaison to the NMC.

The NBS team is now readying modules to be used in FY2006 (starting October 1, 2006)—property, acquisitions, station support and research and development contracts, supply/inventory, and several finance modules.

More information about the NBS project can be found at **<http://nbs.nih.gov>**.

2005 Demystifying Medicine for Ph.D.s

Date	Speakers	Subject
	January	
4	Henry Masur (CC) John Coffin (NCI)	HIV
11	David Henderson (CC) Kanta Subbarao (NIAID)	SARS
18	Jay Hoofnagle (NIDDK), Snorri Thorgeirsson (NCI), Win Arias (NICHD)	HCV and Liver Cancer
25	Peter Jahrling (USAMRIID) John Robbins (NICHD)	Diseases of Potential Terrorism: Ebola and Anthrax
	February	
1	Louis Miller (NIAID) Tom Wellems (NIAID)	Malaria
8	Don Kastner (NIAMS) Rafaella Goldbach-Mansky (NIAMS)	Fevers, Genes and History: Adventures in the Genomcs of Inflammation
15	Jennifer Puck (NHGRI) and TBN	Stem Cells
22	Chris Austin (NHGRI) Stephen O'Brien (NCI)	Genomics in Disease and Species
	March	
1	Husseini Manji (NIMH) Carlos Zarate (NIMH)	Bipolar Disease
8	Michael Rogawski (NINDS) William Theodore (NINDS)	Epilepsy
15	Ken Fischbeck (NINDS) and TBN	Amyotrophic Lateral Sclerosis
22	Nora Volkow (NIDA) Frank Vocci (NIDA)	Drug addiction
29	Thomas Starzl (Pitt) Crystal Mackall (NCI)	Transplantation: Tolerance *vs* Rejection
	April	
5	Bob Balaban (NHLBI) Steven Warach (NINDS)	Stroke and Imaging
12	Richard Cannon (NHLBI) Bryan Brewer (NHLBI)	Coronary Heart Disease
19	Phil Gorden (NIDDK) Marvin Gershengorn (NIDDK)	Diabetes
26	Michael Gottesman (NCI) Win Arias (NICHD)	Diseases of ABC Transporters
	May	
3	Warren Strober (NIDDK) Peter Mannon (NIDDK)	Inflammatory Bowel Disease
10	Lee Helman (NCI) Karen Antman (NCI)	Sarcoma
17	Finale: Symposium on Career Opportunities for PhD Postdocs	

CATALYTIC REACTIONS?

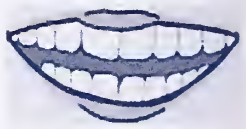
If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not **send it to us via e-mail: catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room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

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

In Future Issues...

- On the Roadmap: Nanotechnology
- IRP Roundup
- Women's Task Force Update

Kids' Catalyst: Teeth, Tongues, and Toes: It's All in the Genes



When someone tells you that you look just like your mom or dad or sister, they're not just being mean (just kidding!). People to whom you are the most closely linked genetically are your immediate family, but we all share genetic links even if we can't quickly trace back to a common ancestor.

Genetics is, to me, one of the most fascinating and important branches of science because it's seen everywhere, all of the time, and the discoveries made now may change our quality of life forever. It can explain why a flower is purple, why your hair isn't (one day), and maybe—again, one day—how to change from brown to purple. Of course, curing genetic diseases is right up there with the color of your hair . . . . it's all linked, and so are we.

There are a few genetic differences that are easy to see and track within your families and classes. The websites given below are springboards for additional research, but for these experiments all you really need is a piece of paper and willing participants.

Keep in mind that entire sections of libraries are devoted to genetics, and you could study it for the rest of your life—starting right here with your toes.

Second-Toe Woe: <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=189200>

Have all your subjects take off their socks and shoes (you can do this outside if it's not too cold) and tell you whether their second toe is longer than their big toe. The longer toe is genetic and is called a Roman Toe, not after the Romans, but after a scientist who studied it.

Two-Tooth Twang: <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=150400>

My all-time favorite, since I know someone very well who is missing her lateral incisors. Only 1.5 percent of us are missing those particular teeth, but an even higher percentage are missing other teeth (because they were born that way, and not because of an older brother). If you don't have all of your adult teeth yet, you may not know, but keep this one in mind. If you do run into a "two-tooth" (slang for having two front teeth instead of the usual four, since the two incisor sidekicks are missing), ask them whether their siblings or parents have the same thing. I have only ever met five two-tooths, and I've been asking for a long time.

Twirling Tongues: <http://www3.ncbi.nlm.nih.gov:80/entrez/dispomim.cgi?id=189300>

Can you roll your tongue so it looks like an O when you're looking in the mirror? Yep, this is genetic, too. Find out how many people in your class can, and how many can't. Figure out what percent of people can, and see how that number changes based on how many people you ask. (Hint: This will be a lesson in the importance of adequate sampling—and while you're at it, you might also do an ear count of attached vs. unattached ear lobes.)

—Jennifer White

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2E26, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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