

*by Karen Ross*

The answer is the Lindau Meeting, a unique gathering that allows young scientists to get an up close and personal look at scientists who are lead-



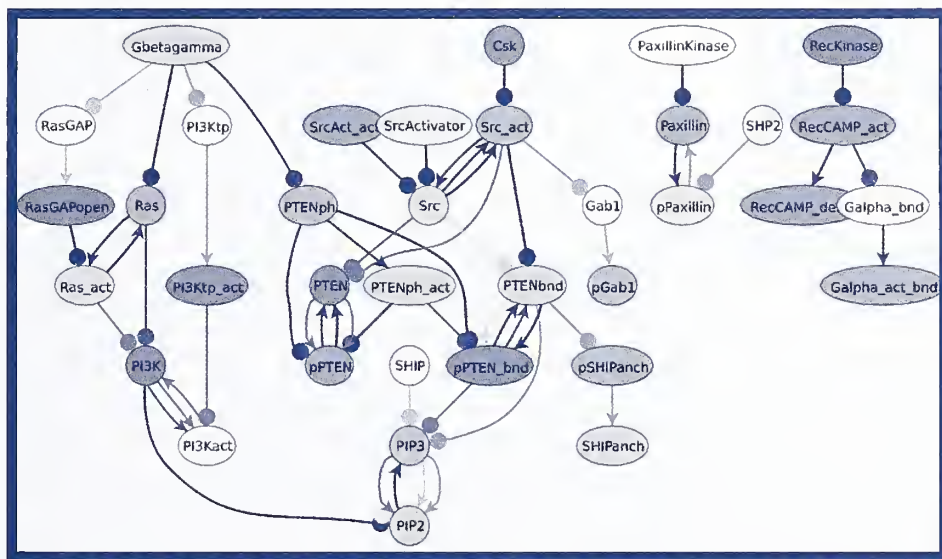
***Wish you were here:*** (front row, left to right) NCRR Program Director Sidney McNairy with GPP students Jean Lee, Steve Huffaker, and Andrew Patterson (and behind them another lucky student) on site at Lindau

The Lindau Meetings were founded by two physicians from Lindau—Gustav Parade and Franz Karl Hein—who wanted to establish a forum for Nobel laureates to meet with other scientists. With the help of Count Lennart Bernadotte of Wisborg, they held the first meeting for medical specialists in 1951.

Since then the topic of the meet-

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*by Jason Bardi*



**Signaling network** [for chemosensing] generated by mathematical modeling software that carries out spatially resolved simulations of the behavior of a given network when it is stimulated or perturbed. [Additional graphics accompany this article in the online Catalyst; see <<http://www.nib.gov/catalyst/2006/06.09.01/page1.html>>]

Advocating such an approach was perhaps unusual for a classically trained immunologist like Germain, who is deputy chief of the NIAID Laboratory of Immunology and chief of the Lymphocyte Biology Section.

But perhaps it was his *not* being a physical scientist that allowed Germain to appreciate what mathematics might bring to his field—especially then, he recalls. In 2001, the draft of the complete human genome had just been published, and biology was awash with ge-

nomic and related data. The field of immunology was going through a golden era of discovery, and many of the molecular and cellular players of the immune system were known. But the connections between the parts that had been catalogued—and deep insights into how this machinery produced immune phe-

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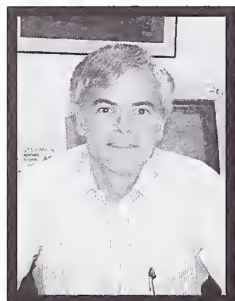
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## TRANS-NIH INTRAMURAL SCIENTIFIC INITIATIVES



Juan Rivera



Michael Gottesman

**H**igh-risk, high-impact science is key to the success of the intramural research program (IRP), and, indeed, the IRP embodies the means to undertake that kind of science. Although some of the most far-reaching, cutting-edge science initiatives are beyond the scope of an individual investigator or a single institute or center (IC), the sheer size of the IRP, in both scientific talent and resources, provides the landscape for conducting cutting-edge research not likely to be accommodated elsewhere.

In the past four months, many NIH investigators representing most ICs have participated in a process to identify interdisciplinary science initiatives that promise clear benefits to the scientific community (both intramural and extramural) and, ultimately, to the public health—and that need the leadership of an entity of the magnitude of the NIH IRP to come to life. Some of the general objectives of this effort are to:

- Identify unexploited scientific opportunities
- Harness the unique features of the IRP
- Encourage trans-NIH and intramural-extramural interactions
- Tap the creativity and talent of IRP investigators
- Give IRP scientists a stake in new scientific initiatives

Here we report on the progress of what we call the Trans-NIH Intramural Research Initiatives and discuss what is needed to implement the ideas chosen for further development.

### Start-Up

First, ICs nominated “out-of-the-box” thinkers from their ranks to participate in this process. In May of this year, an organizational meeting was held that resulted in the formation of six nonspecialized interdisciplinary think-tank work groups. These groups were to discuss the challenges and rewards of proposed innovative projects that might best be done as a collective IRP effort. After vetting the ideas put forward, each group nominated those thought to be of highest caliber for presentation and general discussion at a retreat to be held in Landsdowne, Va., on July 31, 2006. An additional bonus of the retreat was the opportunity for IRP scientists to interact and discuss with NIH Director Elias Zerhouni some of the issues facing the IRP and science in general. We heard a strong consensus for a continuation of these types of meetings in the future.

The retreat discussions identified four scientific areas of broad consensus for IRP involvement:

- Translational initiatives that take advantage of the Clinical Center and the strong laboratory-based immunology at NIH
- Imaging initiatives that focus on high-resolution technologies
- Systems-biology initiatives that allow collection and analysis of large data sets to understand molecular networks in health and disease
- Drug-discovery initiatives that allow the development of drugs for orphan diseases as well as the use of novel drugs in clinical trials

Recommendations to stimulate trans-NIH initiatives included:

- Large branch-lab-center structures working on single projects

- Stimulation of collaborations across NIH
- Increased availability of core resources, especially for smaller ICs
- Geographic co-localization to stimulate creative science
- Mechanisms for transfer of funds across ICs
- Additional competitive funding (similar to the Bench-to-Bedside or IATAP programs)
- Improved communication (at all levels)
- Development of training programs in the quantitative and clinical sciences

Some of these needs are already being addressed. For example, educational training initiatives to attract physical scientists and engineers as well as training programs in translational and clinical investigations are part of the efforts underway in the Office of Intramural Training and Education. Others of these are likely to be addressed in the planning and implementation of the particular science initiatives, and still others will be discussed with the IC scientific directors in an effort to stimulate trans-IC cooperation.

### Homing in

At a subsequent meeting August 4, the working group co-chairs selected three of the proposed initiatives with the intent of using them as models on which to build future initiatives:

- A translational initiative on immunity, autoimmunity, and inflammation that would also inform the development of initiatives in other areas such as neuroscience and stem cell research

- An imaging initiative on the development of high-resolution technologies to visualize molecules to cells that would focus on protein structure and high-definition resolution of single molecule movement in a cell

- A systems-biology initiative on molecular networks in cell activation and differentiation that would yield a framework for collecting and processing large data sets in multiple areas of interest (see also cover story on the initiation of a NIAID systems-biology program).

It was recommended that topic-specific implementation committees be formed to begin the detailed planning phase, and these committees are now meeting. It is important to note that implementation of these particular initiatives is expected to involve the creation of the infrastructure to facilitate other trans-NIH initiatives.

We emphasize that this effort is open to the IRP scientific community at large, and we encourage your participation in this process. The future of these efforts depends highly on how we as a community seize this opportunity. There has been a remarkable spirit of volunteerism that is greatly appreciated; it has been a hallmark in these efforts.

Not everyone can be a committee member, but this fact should not discourage you from forwarding your ideas to the committee chairs or members. The current committee membership will be posted on the Office of Intramural Research website.

Discussions between the members of the IRP scientific community and the committees are likely to result in more flexible and accessible structures that are critical to the long-term goals of NIH.

—Juan Rivera, Director, Trans-NIH Research Initiatives

—Michael Gottesman, DDIR



## TRANS-NIH HAPPENINGS: LECTURES, MEETINGS, COURSES, FESTIVALS

### *Principles and Practice Of Clinical Research*

Registration for the 2006–2007 “Introduction to the Principles and Practice of Clinical Research” is underway; the deadline for registering is **October 6**. The course runs from October 16, 2006, through February 28, 2007. Classes will be held on the NIH campus Monday and Tuesday evenings from 5:00 p.m. to approximately 6:30 p.m.

There is no charge for the course; however, the textbook *Principles and Practice of Clinical Research* is suggested as supplemental information for the course. A certificate will be awarded upon successful completion of the course, including a final exam.

Close to 800 students registered for the 2005–2006 program, which was also broadcast to several domestic and international locations.

For additional information or to register, visit the website at

<<http://www.cc.nih.gov/researchers/training/ippcr.shtml>>

or call the NIH Clinical Center, Office of Clinical Research Training and Medical Education, at 301-496-9425. An e-mail confirmation will be sent to those accepted into the program.

For reasonable accommodations, call 301-496-9425 between 8:30 a.m. and 5:00 p.m. at least seven business days before the event.

The course is designed for physicians and others training for a career in clinical research.

Interested persons are strongly encouraged to take a course in biostatistics such as STAT 200 or STAT 500, currently offered by the NIH/Foundation for Advanced Education in the Sciences, which is accredited by the Accreditation Council for Continuing Medical Education to provide CME for physicians. ■

### *Japanese and U.S. Scientists Address 21st-Century Frontiers*

Fifteen speakers—five from Japan, five from NIH, and five from U.S. institutions outside NIH—will be featured at a symposium on “Frontiers in 21st Century Biomedical Science: Highlights from Japan and the United States.”

Sponsored by NIH and the Japanese Society for the Promotion of Science (JSPS), the symposium will be held in Masur Auditorium, Building 10, **November 6–7, 2006** (day 1, 8:30 a.m.–6:00 p.m.; day 2, 8:30 a.m.–12:00 p.m.). JSPS fellows training at NIH will present posters.

NIH presenters are Susan Gottesman (NCI, small interfering RNA in bacteria), Amar Klar (NCI at Frederick, chromosome segregation), Ron McKay (NINDS, stem cells for the central nervous system), Keiko Ozata (NICHD, chromatin-binding proteins in mitosis), Thomas Waldmann (NCI, cytokine IL-15 and translational research in immunology), and Brandt Weinstein (NICHD, development of vascular system in zebrafish). ■

### *NIH Research Festival To Span Bench to Bedside*

The dates of this year’s Research Festival are **October 17 through October 20**, with poster sessions scheduled for October 17 and October 18.

The opening plenary session on Tuesday, October 17, at 9 a.m. will feature two examples of this year’s “Bench to Bedside” theme. Bill Gahl (NHGRI) and Juan Bonifacino (NICHD) will discuss disorders of lysosome-related organelles and Alan Heldman (JHMI) and Steven Sollott (NIA) will describe development of the taxol-coated stent for treatment of coronary artery disease.

Other events during this four-day annual showcase of the NIH Intramural Program will include boundary-stretching symposia; special exhibits on resources for intramural research; the Job Fair for NIH postdoctoral, research, and clinical fellows, with an opening address by NIH Director Elias Zerhouni; the festival food tent and music fair; and the Technical Sales Association scientific equipment tent show.

For a preliminary schedule of events, meeting venues, and online poster registration, go to the Research Festival web site at

<<http://researchfestival.nih.gov>>.

### *Demystifying Medicine*

Demystifying Medicine—a course to bridge the gap between PhDs trained in basic science and the medical problems to which their skills and insights could be applied—will be offered again in 2007.

Starting January 9 and ending May 8, the course will be held each Tuesday from 4:00 to 6:00 p.m. in the ground-floor auditorium of Building 50 (rooms 1227 and 1233). All presentations will be videocast and archived. There were more than 900 registrants last year, and *Science* and *Nature* carried articles about the course.

The course is geared toward graduate and medical students, clinical and PhD fellows, and staff. Those seeking academic credit can register with FAES: <<http://www.faes.org>>.

Others may register at the Listserv:

<<http://list.nih.gov/archives/demystifyingmed.html>>.

The course schedule will appear in the November–December issue of *The NIH Catalyst*. ■

### *NCCAM Lecture: Natural Products*

The next lecture in the NCCAM Distinguished Lectures series is set for **October 25, 2006**, 11:00 a.m.–noon in Masur Auditorium, Building 10. Ram Sasisekharan, professor of biological engineering and health sciences and technology, Harvard-MIT Division of Health Sciences & Technology, will speak on “Natural Products: Challenges and Opportunities.”

The lecture will be videocast at

<<http://videocast.nih.gov>>

and sign language interpretation will be provided.

For more information or for reasonable accommodations, call 301-594-5595 or the Federal Relay at 1-800-877-8339. Additional information about the series can be found at

<<http://nccam.nih.gov/news/lectures>>.



## GPP STUDENTS ON AN ISLAND WITH NOBELISTS

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ing has rotated annually among the three natural science disciplines recognized by the Nobel Prize—physics, chemistry, and physiology or medicine.

In recent years, the Lindau Council has also sponsored meetings for Nobelists and students in economics. Countess Sonja Bernadotte, Count Bernadotte's widow, is now the president of the council that oversees the meetings. She conducts the closing ceremonies, and a visit to her castle on Mainau Island, also in Lake Constance, is one of the highlights of the week-long conference.

At first, only German students participated, but today students from more than 20 countries attend, including a contingent of about 50 from the United States.

Students from the GPP participated in the Lindau Meeting for the first time this year, thanks to the impetus of Marshall Nirenberg, chief of the Laboratory of Biochemical Genetics in NHLBI and recipient of the 1968 Nobel Prize in physiology or medicine for his work on interpreting the genetic code.

According to Richard McGee, the GPP's Director of Graduate Student Affairs, Nirenberg approached GPP Director Mary Delong and asked, "Why aren't GPP students going to this great event?" Delong took over from there, requesting nominations from the supervisors of GPP students and overseeing the selection process.

According to the Lindau Meeting website, students are invited to attend "as a reward for the quality of their performance and research work"—for which Huffaker, Lee, and Patterson were judged very well qualified.

This year's Lindau Meeting was held June 26–30. In the mornings, students attended lectures presented by the Nobel laureates. Afternoons were devoted to discussion groups, in which students could meet 25–30 at a time with the laureates who had presented that morning.

Students and laureates ate meals together at nearby restaurants, and there were several social events that encouraged everyone to mingle.

Huffaker, Lee, and Patterson were impressed by the personal stories that many of the laureates shared at the meeting. Some of the scientists had fled Europe during World War II and viewed their invitation to Lindau as a homecoming, said Lee. Several others spoke about their regret that their scientific careers had deprived them of time with their families, said Patterson. Huffaker was heartened to meet so many scientists "who were at the top of the game and are kindhearted."

"To see that it is possible to make it through and still remain a good person, that is an incredible experience," he said.

Peter Agre, who received the 2003 chemistry prize for his discovery of water channels known as aquaporins was a favorite of both Lee and Patterson. They were able to have a lengthy con-



**Table Talk.** 1981 Nobelist Roald Hoffmann (left), whose lecture was "almost poetry," chats with NCRR Program Director Sidney McNairy and GPP student Jean Lee

about climate change that was narrated by John Cleese, of Monty Python fame, said Lee.

All three agreed that Roald Hoffmann, an expert on the mechanisms of chemical reactions and winner of the 1981 chemistry prize, gave one of the best talks. "His lecture was almost poetry," said Patterson. Hoffmann used his time at the Lindau Meeting to address the moral and ethical obligations of scientists.

Huffaker said of Hoffmann's talk, "It was back to this Einstein model where a Nobel laureate is not just somebody who makes extremely large breakthroughs and contributions in science, but also ends up being a social role model."

The U.S. students had many opportunities to talk to their counterparts from other countries. For Lee and Patterson, these conversations were a reminder of how lucky they have been to study at NIH, where resources are plentiful and responsibilities outside of research are minimal. "We're spoiled,"

said Patterson.

"But we appreciate it," added Lee.

Asked if they would recommend the Lindau Meeting to other students, Huffaker, Lee, and Patterson were unreserved in their enthusiasm. Patterson said, "Absolutely. It was a completely unique experience."

Lee said, "It's the only meeting I know that is specially geared to interactions between students and Nobel laureates."

Huffaker said, "[The originators] were spot on."

McGee would like other GPP students to experience the Lindau Meeting for themselves. "By all means we hope this becomes an annual event," he said. ■



Jean Lee

**Dockside.** The Nobelist contingent waves adieu to Lindau and the students they inspired as the meeting draws to a close

versation with him after many of the other students had gone home. He was "very personable," says Patterson, and deeply interested in why so few young people in the United States seem to be interested in studying science. Lee found Agre to be "down to earth" and eager to talk about topics other than his research.

Lee and Patterson also enjoyed hearing from Walter Kohn. Kohn, the winner of the 1998 chemistry prize, did groundbreaking work on computer programs that simulate interactions among atoms in materials. However, the topic of his Lindau lecture was global warming. He showed a movie he produced



## THE RESEARCH PURSUITS OF THE GPP TRAVELERS

**Stephen Huffaker**, who took part in one of the GPP's International Partnerships, did research on schizophrenia under the supervision of Sabine Bahn at Cambridge University in England and Daniel Weinberger, chief of the Clinical Brain Disorders Branch, NIMH. By comparing gene-expression patterns in brain tissue from people with and without schizophrenia, he identified variant forms of two neighboring genes that may contribute to the disease.

The products of these genes, Huffaker said, may be involved in "signal vs. noise processing" in the brain. This capability, which is thought to be defective in those with schizophrenia, allows the brain to pass useful information through complex neuronal circuits while minimizing the transmission of unnecessary chatter. Huffaker successfully defended his dissertation in July and will be attending Harvard Medical School in Boston this fall.

**Jean Lee**, who is in the process of writing her dissertation, studies the immune response to HIV with Andrew McMichael at Oxford University and Daniel Douek of the Human Immunology Laboratory in the Vaccine Research Center. Using simian immunodeficiency virus infection of monkeys as a model system, she has investigated how the immune system handles a highly variable and constantly mutating virus. She is also using X-ray crystallography to discern the atomic structure of complexes between viral proteins and receptors on immune cells. Lee is part of an MD/PhD program sponsored by NIGMS and the NIH-Oxford program. Upon completing her dissertation, she will resume her medical studies at Albert Einstein Medical School in New York.

**Andrew Patterson** completed his Ph.D. work on factors that regulate the synthesis of hemoglobin in February. He was part of the graduate program at George Washington University in Washington but did all of his research at NCI in the lab of Albert Fornace, who has since moved to Harvard University. Afterwards, Patterson moved one floor down in Building 37 to do postdoctoral work with Frank Gonzales in the Laboratory of Metabolism, NCI, on "metabolomics," tracking metabolic changes that occur in response to the stresses of diabetes or radiation exposure. His postdoctoral training is being funded by a competitively awarded Pharmacology Research Associate (PRAT) Fellowship.

—Karen Ross



Fran Pollner



Karen Ross



Karen Ross

## HIGH SCHOOLERS SHOWN GOOD SIGNS FOR THEIR FUTURE IN SCIENCE RESEARCH

**P**eter Blumberg knows English, German, and French, but the language that best complements his native English is sign language.

For the past six or so years, Blumberg, chief of the Section on Molecular Mechanisms of Tumor Promotion, NCI, has routinely recruited postbac students from Gallaudet, a local college with a national reputation that draws deaf and hard-of-hearing students from throughout the country. His lab typically is home to one or two postbacs from Gallaudet, most of whom go on to careers in biomedical research. A current Gallaudet graduate in the Blumberg lab, Vladimir Pavlyukovets, is completing a joint NCI-Johns Hopkins master's



Fran Pollner

Larry Pearce Peter Blumberg



program in biotechnology with a concentration in molecular targets and drug discovery.

Six years ago, Larry Pearce, a Gallaudet biology major, started as a postbac in the Blumberg lab and stayed on, becoming a biologist in 2003 and, according to Blumberg, he is "the technician handling the lab's capsaicin work and has co-authored more than 20 publications."

On an afternoon in July, Pearce conveyed the saga of capsaicin in PowerPoint and sign to 22 high school juniors and seniors from around the country who were enrolled in the Gallaudet Science Star program. A four-week summer residential program for deaf and hard-of-hearing students who intend to go to college and are interested in a career in the sciences, the program is foundation funded and designed to improve the students' academic and laboratory skills and expose them to research facilities and scientists working in the federal and private sectors in the Washington area.

Pearce's lively presentation traced the 10,000-year known history of capsaicin and its uses throughout the ages by Mayans, Chinese emperors, Native Americans, and Europeans—to its current standing as a heavily researched potential therapeutic in an array of medical conditions. The talk generated spirited questions from the students—some about the science presented ("How does capsaicin work?" "What part of the structure of capsaicin is responsible for the 'burn'?"?) and some about the life of the presenter ("How do you communicate with colleagues, especially those from countries where English is not the first language?")

Some of the students, Pearce said, were "most impressed by my responsibilities in the lab." The session, Blumberg said, was "super." He welcomes repeat performances each summer from now on.

—Fran Pollner

For information about Gallaudet's Science Star Program, also called the Summer Biology Enrichment Program, contact Ann Powell, director, or Zakiya Thorpe, coordinator, at 202-651-5385, or e-mail <Science.Star@gallaudet.edu>.



## SYSTEMS BIOLOGY AND THE NEW MATH

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nomena—remained elusive. Germain observes today, “We are still far from really understanding the operation of the immune system, by which I mean being able to predict and finely manipulate its behavior.”

A broader understanding of immune physiology, he says, might come from embracing a more comprehensive and quantitative approach—an approach broadly encompassed by the otherwise overused term “systems biology.” This is a way of studying biology that involves obtaining detailed information on enough components of a system (or even the entire system for simple organisms) to allow quantitative modeling of complex in vivo molecular and cellular events, such as pathogen-induced disease or immune system responses in mice or humans.

To that end, Germain will be leading a new intramural program that will combine systems level analysis with mathematical modeling to better understand host defenses and immune pathology—the Program in Systems Immunology and Infectious Disease Modeling (PSIIM).

**Systems Biology Basics**

Systems biology is a way of asking how large systems of molecules, cells, and tissues interact with each other. In the past few years, numerous studies have revealed the presence, actions, and interactions of many of the genes, proteins, lipids, carbohydrates, and other molecules in healthy and diseased tissues.

But knowing the molecular players may not be enough to translate these research results into health benefits. How the pieces fit together to generate what we observe as cellular or, on a higher scale, organismal behavior may depend on many variables, such as their concentration and location in the cell and the signals the cell receives from its environment, Germain notes.

Furthermore, even if all these variables are known, predicting what will happen to the system over time is complicated by the fact that the interactions are numerous and non-intuitive, and they often result in nonlinear behavior. The number of relevant components and interactions, he observes, surely exceed the oft-quoted limit of seven items that the average human can hold in short-term memory at one time.

The only tools equal to the task are mathematical and machine based—allowing us to translate hypotheses about the systems of interacting molecules and cells into formal descriptions and then equations that can be evaluated quantitatively with the help of computers.

But the requisite level of expertise in applied mathematics and computer science is beyond the scope of most biology laboratories.

“Biologists often think about being more quantitative and trying to model their sys-

tem of interest explicitly, but they would like to do this without having to become expert in the mathematics and computer scripting needed to do such modeling at a sophisticated level,” Germain says. “Having access to a resource such as a strong, well-staffed systems-biology program can help make that happen.”

**Biologist Meets Theorist**

When he published his *Science* article in 2001, Germain was well aware that his own expertise was not in mathematics and computer science. But when a colleague introduced him to Martin Meier-Schellersheim, a physicist who had spent his time as a Ph.D. student in Germany working on ways to create computational programs to model biological systems, Germain saw the perfect opportunity to move his ideas forward.

“It was very clear that Martin’s goals were absolutely congruent with what I wanted to do,” recalls Germain. “And what he wanted was to be in a place that had the biology to interact with the software tools that he would create.”

The two began working together when Meier-Schellersheim came to NIH as a postdoctoral fellow in the Laboratory of Immunology in 2001. Over the next several years, as Meier-Schellersheim continued improving his modeling and simulation software, Germain worked with the leadership of NIAID to develop plans for a formal program in systems immunology built around the advances in computational biology that were being developed in the lab. NIAID Director Anthony Fauci and then-acting NIAID Scientific Director Kathryn Zoon expressed substantial interest in such a program—which was reinforced in 2005, when NIH Director Elias Zerhouni and Deputy Director for Intramural Research Michael Gottesman sat down with Germain and Meier-Schellersheim to discuss systems biology and the work of the laboratory.

Zerhouni asked probing questions on topics such as whether the new software Meier-Schellersheim had developed dealt adequately with stochastic behavior. After getting what were clearly satisfying answers, Zerhouni expressed great interest in the research program being built around the new software approach, given its congruence with extramural Roadmap Initiatives to which he had made a strong commitment.

The end result of all these discussions and interactions was the recent decision by Zoon, now newly appointed director of NIAID’s Division of Intramural Research, to identify the resources needed to establish the PSIIM.

The immediate goal of the PSIIM will be to use a systems approach to better understand the complex biochemical networks that regulate the interactions between infectious organisms and the human or animal cells they infect.

The program will use state-of-the-art experimental approaches to determine how closely simulations of biological models can explain and predict real behavior and improve the models when they fail to match reality. As the models improve, scientists will eventually gain the ability to predict how drugs and other interventions will affect a cell or organism and whether the host will tolerate them.

Although most of the studies will be conducted with ordinary infectious pathogens, special facilities in the new C.W. Bill Young Center for Biodefense and Emerging Infectious Diseases will enable

PSIIM scientists to examine such questions with microbes that cause diseases such as anthrax, virulent forms of influenza, tularemia, and plague.

The PSIIM approach will allow scientists to seek more complete answers to key questions that could not be addressed at this scale even a few years ago—such as how infectious organisms invade human cells, how the toxins they produce cause cell and tissue destruction, and how these pathogens evade or manipulate the immune response.

“Once we understand these interactions in a more systematic way, we can make strategic decisions about how to interfere with infectious disease pathology or how to direct immune responses to better fight infections,” says Zoon, adding that these new insights can serve as the starting point for the design of new drugs to treat diseases or the development of new vaccines.

**When the Immune System Goes Awry**

Likewise, PSIIM will allow scientists to ask how perturbations in some of the same networks that defend against infectious agents lead to autoimmune diseases, which arise when the immune system goes awry.

One example Germain discussed in his 2001 *Science* article is multiple sclerosis (MS), a disease that usually first appears in adults between the ages of 20 and 40 and manifests in intermittent episodes of an array of impairments, such as loss of balance and muscle control, numbness and pain, and compromised vision and hearing.

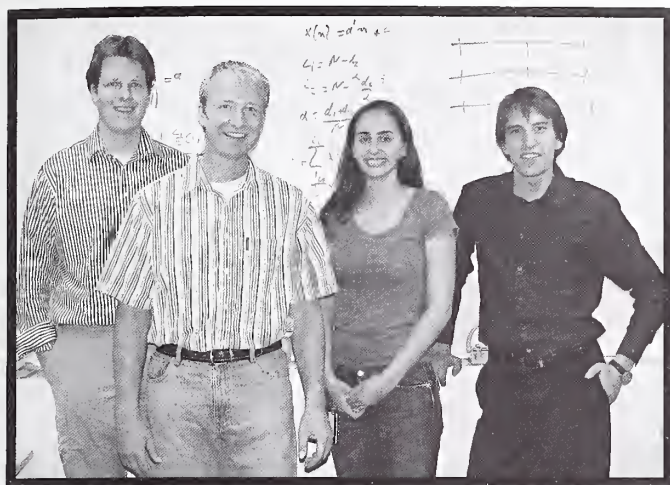
MS is characterized by the presence of autoreactive T cells that recognize, attack, and destroy myelin sheaths within the cen-



Jason Bardi

**PSIIM Director Ron Germain** hoping to bring quantitative analysis and computer modeling to mainstream immunology





Ronald Germain

**Current PSIIM Crew:** (left to right) Frederick Klauschen, postdoctoral fellow; Martin Meier-Schellersheim, staff scientist and creator of Simmune; Alison Wise, postbac student; and Bastian Angermann, physics Ph.D. student in a joint program with the University of Hamburg, Germany, and the PSIIM

tral nervous system. The resulting disruption of the neuronal transmission of electrical impulses gives rise to the symptoms.

Much is known about MS etiology, "and we have a good idea of the nature of pathogenic cells that are present in people who have the disease," says Germain, but many unanswered questions remain. For example, how does the disease start? Autoreactive T cells undergo clonal expansion during an immune response, rapidly multiplying until their numbers are thousands of times greater in diseased than in normal individuals. But how many cells does it take to start the process ultimately leading to tissue damage?

"The answer could be as few as one," given the explosive growth potential of T lymphocytes and the feed-forward effects that accompany the initial expansion and production of immune effector cells that damage tissue, Germain notes. "But what are the conditions that allow that first cell to respond and to initiate a process that eventually breaks through the many checkpoints that have evolved to prevent such autoimmunity?" By creating computer models able to simulate the biology of cells, tissues, and, eventually, organisms, Germain and his colleagues hope to answer questions like these.

### Enter Simmune

One of the main tools for addressing these issues is a software package called Simmune, through which researchers may easily make, modify, and run simulations of detailed quantitative models of the biological systems they have studied in their labs for years.

This software package, created by Meier-Schellersheim and his associates, allows a scientist to use a simple graphical interface to define the interactions between pairs of molecules. These are the building blocks for signaling networks that when activated can produce hundreds or thousands of multimolecular complexes. The software automatically creates mathematical representations of these resulting networks from this simple mo-

lecular binding information. Once the scientist adds quantitative information on association/dissociation rates, enzymatic transformation rate, and the like that come from laboratory measurements, Simmune allows the researchers to investigate complex signaling activities within simulated cells without ever having to work with the underlying equations.

Before Simmune, making such mathematical models by hand could take months and required extensive expertise in applied mathematics. Even making changes to an existing model was very time-consuming, limiting the extent of what could be modeled.

"One of the great advantages of Simmune is that it gives biologists a way to do the difficult mathematics needed for such modeling without having to actually be involved with the mathematics," says Germain. "The hope is that these models will provide a deeper understanding of how complex behaviors arise, leading to new insights into disease."

### Test Cases

In the past year, a beta version of the new software has been developed and tested; Germain and Meier-Schellersheim expect to release this version for academic purposes this fall.

In a well-air-conditioned basement computer laboratory on the NIH campus this summer, Meier-Schellersheim demonstrated the new software to a visitor. He clicked a few buttons and built a "molecule," which resembled a simple version of the old ball-and-stick models from introductory chemistry classes. One end of the molecule was designated the binding spot for another molecule that was also encoded using this simple interface.

"This particular end of the molecule can also be defined in the software as binding to additional molecules, providing an easy way to specify the complex set of interactions a single protein can engage in," said Meier-Schellersheim. He explained that once the numerous interacting components are entered, along with relevant data such as their concentrations and distribution, the software then automatically builds the equations that allow a simulation of biological activity to take place.

Meier-Schellersheim, Germain, and their colleagues described the first stringent test of Simmune this summer in the journal *PLoS Computational Biology*.<sup>2</sup> Showing that the

new software can accurately predict cell function in both time and space, they used Simmune to model a complicated cell-biological behavior known as chemosensing—a fundamental biological process whereby cells sense and respond to external signals, such as inflammatory chemicals involved in an immune response.

They modeled what happens in a stimulated cell to the distribution of a membrane-associated phospholipid. The concentration of the phospholipid changes during chemosensing mainly due to the action of two enzymes that synthesize or break down this molecule.

Contrary to previous thinking that one unknown cell-wide mechanism exerts different effects at different cell sites, the Simmune model predicted that the enhanced concentration of phospholipid at the "front" end of the cell (facing the source of chemical signals) resulted from a combination of two known mechanisms—a very rapid local inhibitory activity and the slower movement of another molecule to a distant part of the cell.

In collaboration with Tian Jin and Xuehua Xu of the Laboratory of Immunogenetics, NIAID, the team tested its Simmune-generated predictions in the laboratory and found a very close match with the experimental data.

The real power of the software, Meier-Schellersheim adds, is that it can be applied to nearly any cell-based biological system. "This is a tool that can simulate signaling and cellular processes in general," he says, "whatever system you are interested in."

And the real strength of the PSIIM program, Germain observes, comes from the connections it will help establish among scientists throughout and beyond NIH.

At the moment, though, the core PSIIM team is still being assembled. Germain is working on recruiting team leaders to head up groups in areas such as bioinformatics and proteomics, which will eventually be core parts of the PSIIM.

"We are very hopeful that what we have started in our institute will build out as a trans-NIH initiative, with strong links to the extramural community as well," says Germain. "The ultimate goal is not only to solve important problems in immunology and infectious disease within our group, but also to establish a large network of teams engaged in creating the quantitative tools and computational methods for all biomedical investigators to use in the coming years." ■

1. R. Germain, "The art of the probable: System control in the adaptive immune system," *Science* **293**, 240 (2001).

2. M. Meier-Schellersheim, X. Xu, B. Angermann, E.J. Kunkel, T. Jin, and R.N. Germain, "Key role of local regulation in chemosensing revealed by a new molecular interaction-based modeling method," *PLoS Comput. Biol.* **2**(7), e82 (2006).



## SUMMER POSTER DAY: SO MANY QUESTIONS EN ROUTE TO ANSWERS

by Dustin Hays  
and Fran Pollner

A record 670 students in NIH summer research programs presented 651 posters on Poster Day August 3. Here are write-ups of 11—all of which are works in progress. They ask these questions:

- Will a multivalent Ebola virus vaccine achieve protective immunity against both the Sudan and the Zaire virus strains?
- What are the pathways by which alcohol affects long-term potentiation and related memory and learning?
- Will opioid medication to alleviate osteoarthritis-induced musculoskeletal pain adversely affect sex and stress hormone levels in men?
- What environmental factors play a role in the development of autoimmune diseases in discordant twins or siblings?
- Do complications during pregnancy increase the risk of schizophrenia in the offspring?
- Can dental-pulp stem cells serve as a source of differentiated neuronal cells?
- Can patients with multiple sclerosis benefit from an agent approved for use in preventing transplant rejection and treating uveitis?
- Do the same criteria for metabolic syndrome hold for both African-American and Caucasian adolescents?
- What is the relationship of chronic stress to telomerase activity?
- Do certain cytokine promoter polymorphisms predict risk for polyp relapse and colon cancer?
- What demographic factors contribute most to self-reported health status?

### EBOLA VACCINE PACKING A ONE-TWO PUNCH

**Lidenys Varela, Johns Hopkins University, Baltimore, Md.**

**"Measuring Ebola Glycoprotein Antibody Response in Immunized Nonhuman Primates Using Enzyme-Linked Immunosorbent Assay (ELISA)"**

**Co-authors: Michael Bailey and preceptor Nancy Sullivan, Biodefense Research Section, NIAID-VRC**

Mortality after Ebola virus outbreaks are as high as 90 percent. Two Ebola virus subtypes, the Zaire strain (Z) and the Sudan strain (S), account for 99 percent of all human Ebola-related deaths. There is currently no licensed vaccine for Ebola, but an effort is underway at NIH to develop a multivalent vaccine that protects against both virus strains.

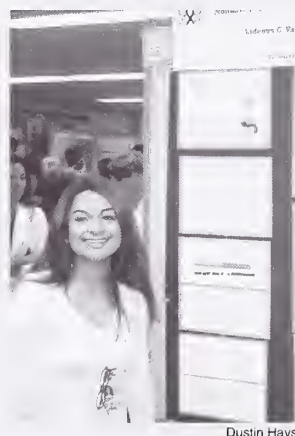
Lidenys Varela, who is starting her sophomore year at Hopkins, tested the immunogenicity of a combination genetic Z/S Ebola vaccine in cynomolgus macaques. Essentially two vaccines de-

livered simultaneously, each consisted of an adenoviral vector encoding slightly different Ebola virus surface glycoproteins—GP(Z) and GP(S).

In a previous study, the GP(Z) vaccine generated a robust immune response, as measured by antibody production, and protected macaques against challenge with live Zaire virus.

Three weeks after immunization with the combination vaccine, sera from eight macaques were assayed via enzyme-linked immunosorbent assay (ELISA) to determine specific GP(Z) and GP(S) antibody responses.

In all cases, Zaire strain-specific antibody production was similar to that in the



Lidenys Varela

previous study in which all macaques survived subsequent challenge with live Zaire virus. In all but one subject, GP(S) generated antigen-specific antibody titers that rivaled those for GP(Z), suggesting that multiple antigens can be included in the vaccine and simultaneously elicit robust immune responses.

Why one macaque did not demonstrate a GP(S) response is not known, Varela said, but she noted that the ELISA data indicate that all the other macaques developed protective immunity against the Sudan as well as the Zaire strain.

—Dustin Hays

### AUTOIMMUNE DISEASE AND THE ENVIRONMENT OF DISCORDANT SIBS

**Mary Conlon, Georgetown University, Washington, D.C.**

**"Assessing Environmental Factors Implicated in the Pathogenesis of Systemic Autoimmune Diseases in Twins or Siblings Discordant for Disease"**

**Co-authors: Laura James-Newton, Lisa Rider, and preceptors Mark Gourley and Frederick Miller, Office of Clinical Research, Environmental Autoimmunity Group, NIEHS**

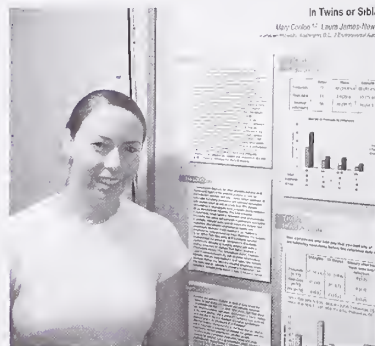
Little is known about the causes of autoimmune disorders, but as Mary Conlon pointed out in her poster presentation, a less than 50 percent autoimmune disease concordance in monozygotic twins presents "strong evidence for an environmental influence."

Conlon, who is entering her senior year at Georgetown, examined data gathered through the NIEHS Twin-Sibs study, conducted at the NIH Clinical Center, to

identify environmental risk factors associated with four specific autoimmune disorders—rheumatoid arthritis, scleroderma, systemic lupus erythematosus, and myositis.

Patients with one of these four conditions and an unaffected twin or same-sex sibling separated in age by no more than 47 months made up the study group; healthy volunteers who did not have an affected sibling made up the control group.

Subjects underwent a physical examination and completed an extensive questionnaire about their health history and ex-



Mary Conlon

posure to suspected environmental risk factors. Conlon analyzed data related to vaccination history, past infections, ultraviolet light sensitivity, and past surgical procedures.

Initial results of this ongoing study (more families are being recruited) show a significant association between prior *Herpes zoster* infection and the subsequent development of autoimmune disease. Other environmental exposures continue to be evaluated as possible risk factors.

—Dustin Hays



## ALCOHOL AND NEURONAL SYNAPSES

**Brian S. Park, University of Maryland, College Park**

**"Ethanol Effects on Corticostriatal Synaptic Plasticity"**

**Co-authors: David Lovinger and preceptor Henry Yin, Laboratory for Integrative Neuroscience NIAAA**

Generally defined as the long-lasting strengthening of a neuronal synapse, long-term potentiation (LTP) in the central nervous system is believed to play an important role in learning and memory.

Brian Park, a college sophomore, examined ethanol's (EtOH) effects on LTP using an in vitro rat model consisting of a fresh coronal brain slice comprising the dorsomedial striatum—a region known to contribute to memory. Brain slices were bathed in an artificial cerebral spinal fluid to which ethanol was added to concentrations 2 mM, 10 mM, and 50 mM.

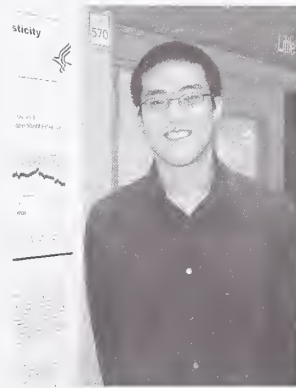
Using this model, Park took field potential readings to measure LTP. The readings were made by stimulating the

striatum via small electric pulses emitted through a tiny electrode inserted into the brain slice.

Transmissions were then received through a second recording electrode inserted nearby—along a neuronal pathway leading through the striatum.

Once a baseline measurement was established, a series of high-frequency stimulations (HFS) was delivered to the striatum, and then recording was resumed using the baseline stimulation parameters. The administration of HFS was used to induce LTP through the activation of calcium-dependent second-messenger systems in the postsynaptic cell.

Normally, the signal received becomes greater, indicating that LTP has occurred and that synapses along the stimulated neuronal pathway have become stronger.



Dustin Hays

Brian Park

Compared with controls, LTP of ethanol-exposed samples decreased in a dose-dependent manner and were significantly lower at the 50-mM EtOH concentration.

Park also took LTP field potential readings of samples exposed to the NMDA receptor antagonist APV because ethanol is known to inhibit NMDA receptors, a type of glutamate receptor believed to induce LTP through signal trans-

duction.

LTP was significantly reduced in the presence of APV, but was reduced even further in the presence of APV plus 50 mM EtOH. This phenomenon, Park said, suggests that LTP may involve multiple pathways.

—Dustin Hays

## OPIOID PAIN RELIEF AND SEX AND STRESS HORMONES

**Justin Meunier, Louisiana State University School of Medicine, New Orleans**

**"Effects of Opioid versus Placebo Administration on Sex and Stress Hormones in Men with Chronic Musculoskeletal Pain"**

**Co-authors: Suzan Khoromi, Ranganath Muniyappa, Nora Gray, Mitchell Max, and preceptor Mark Blackman, Laboratory of Clinical Investigation, NCCAM**

Chronic musculoskeletal pain in the general population is underreported and undertreated. Opioid medications can help manage pain but may also affect sex and stress hormones in men—an associated drop in testosterone levels has been documented among male chronic heroin users, for instance.

The clinical consequences of a decrease in testosterone, such as that naturally associated with aging or that induced by chronic opioid use, include loss of skeletal muscle mass and bone mass and an increased risk of heart disease.

The sex hormones under investigation in the current study are leutinizing hormone (LH) and testosterone, and the stress hormones are adrenocorticotrophic hormone (ACTH) and cortisol.

Justin Meunier, now a second-year medical student, presented data from an ongoing two-part investigation of the effects of low-dose opioid administration on sex and stress hormones in men with chronic musculoskeletal pain due

to osteoarthritis (OA).

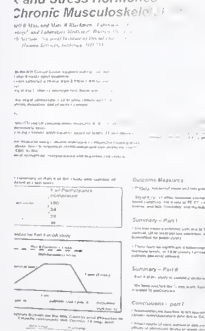
Part 1 of the study asked the question: "Does chronic pain alone have effects on male sex and stress hormones?"—an important question, Meunier observed, because it has been demonstrated that acute pain causes increased catecholaminergic axis activity and decreased gonadal steroid function.

Based on findings in the 16 men with chronic OA pain and 12 healthy volunteers involved in the study, however, the answer, Meunier reported, is "No."

The study was designed with stringent recruitment criteria, excluding individuals with confounding illnesses that might have affected findings, such as endocrine dysfunction, inflammatory arthritis, too high or too low body mass index, and depression. Men with a history of prior opioid use were also excluded.

Thus, neuroendocrine function appears not to be significantly altered in healthy men with chronic musculoskeletal pain, suggesting that prior reports to the contrary resulted from the confounding effects of coexistent illness or medication use.

oid vs. Placebo Administration  
and Stress Hormones  
Chronic Musculoskeletal



Dustin Hays

Justin Meunier

leased morphine sulfate, an opioid; a placebo group; and a standardized treatment (nonopioid analgesic) group, which serves as a control for the placebo group so that placebo effects on the hormones in question may also be studied.

The study involves two visits to the NIH Clinical Center for overnight blood sampling—one at the outset and one after the drug-escalation period. Blood is collected every 20 minutes for a 12-hour period and then analyzed for levels of ACTH, cortisol, LH, and testosterone. Also during both visits a 24-hour urine sample is collected to measure epinephrine, norepinephrine, dopamine, and cortisol.

—Dustin Hays



## SUMMER POSTER DAY: QUESTIONS EN ROUTE TO ANSWERS

continued from page 9

**EXTRACT OF WISDOM TEETH: A SOURCE OF STEM CELLS?****Maiko Sakai, Harvard School of Dental Medicine, Boston****"Investigation of Neuronal Differentiation Potential of Dental Pulp Stem Cells"****Co-authors: Junji Mineshiba and preceptor Pamela Robey, Craniofacial and Skeletal Diseases Branch, NIDCR**

"There's a lot being done to determine the potential of bone-marrow stem cells as a source of neural cells, but no one knows the potential of dental-pulp stem cells. This has been a really exciting project," said Maiko Sakai, describing her quest to establish neuronal cell differentiation in mouse and rat brain slices from stem cells originating in human dental pulp.

The suggestion that dental pulp stem cells could be a source of neural cells emerged in a previous study demonstrating expression of neural markers in cell culture; the challenge now is to achieve similar results in organ culture and in

vivo, Sakai said.

During the course of her summer project, Sakai obtained pulp cells from adult third molars that had been extracted in the context of needed dental care; identified the mesenchymal stem cell marker CD146 by immunocytochemistry; carried out magnetic- and fluorescent-activated cell-sorting techniques, and fluorescently labeled the cells for tracing their activity in rat and mouse brain tissue.

But she was doubtful that she would still be at NIH to observe firsthand the outcome of her work here. Her first attempt at preparing the tissue samples for her experiment fell short of perfect and, consequently, "my initial results are not that reliable," she said. Her technique improved the second time around—she col-



Maiko Sakai

lected more slices and from more propitious brain areas in the hippocampus that are known to house neural cells—but, she noted, there would probably be more time required for the differentiation process than she would have before returning to Boston for her second year at the Harvard School of Dental Medicine.

The results of her first round of experiments suggest that dental-pulp cells survive in brain tissue, with some developing axon-like structures. Thus far, Sakai said, dental-pulp stem cells seem to have the potential for differentiating into neurons, "but we still don't know."

—Fran Pollner

**OBSTETRIC FACTORS IN THE BIRTH OF SCHIZOPHRENIA****Allie Gold, Maret School, Washington, D.C.****"Obstetric Complications as a Risk Factor for Schizophrenia: Data from the Sibling Data Base"****Co-authors: Daniel Weinberger and preceptor Stefano Marenco, Clinical Brain Disorders Branch, NIMH**

"No one really knows that much about the causes of schizophrenia, and the results so far from our study are 'iffy,'" Allie Gold observed, but the study is providing a foundation for the development of a new, more detailed questionnaire to probe the potential relationship of specific obstetric complications (OCs) and the development of schizophrenia in the affected offspring.

The study compared information gathered from the NIMH Sibling Study with reports in the literature linking various OCs to later schizophrenia. These previous reports are not entirely consistent with one another regarding specific OC occurrence, severity, or patterns, and the current exploration yielded findings consistent with some reported associations and not others.

Forceps delivery, Rh incompatibility, and the use of drugs—legal or illegal—during pregnancy emerged as significant factors in the later development of

schizophrenia in offspring—the first two consistent with some previously reported findings and the third heretofore absent from discussion in the literature.

Overall, however, the number and severity of OCs reflecting prematurity, fetal malnutrition, and fetal distress—including preeclampsia, a strongly associated finding in some previous studies—were similar in patients and control subjects in the current study.

The influence of OCs on intelligence, as measured by the Wide Range Achievement Test (WRAT), was also examined. Patients had significantly lower WRAT scores than healthy volunteers, and patients with an OC history had lower WRAT scores than patients without an OC history. But there were also some unexpected WRAT findings, such as higher scores among healthy volunteers with an OC history and higher scores among both patients and healthy volunteers with a history of Rh incompatibility.

The NIMH team gathered its informa-



Fran Pollner

Allie Gold

tion from responses to a questionnaire given to the mothers of 373 patients with schizophrenia and 380 control subjects whose offspring did not have schizophrenia. The response rate in the former group was 50 percent and that in the latter, 70 percent.

This disparity in response rate was considered a potential source of bias, as was the mothers' perhaps faulty memory regarding long-past obstetric events, Gold noted.

The new questionnaire should help clarify some of these issues, she said.

Gold's NIH summer experience came between her junior and senior years in high school and a year after an accident in which she sustained a severe brain injury. She attributes her survival and complete recovery to an "incredible shock-trauma team and medical staff." Her intention, she said, is to become a doctor, "like everyone in my family," and focus on the brain and cognition.

—Fran Pollner



## TELOMERASE ACTIVITY, IMMUNE RESPONSE, AND CHRONIC STRESS

**Yixiao Zou, Georgia Institute of Technology, Atlanta**  
**"Telomere Length and Telomerase Activation in Peripheral Blood Lymphocytes of Chronically Stressed Individuals"**

**Co-authors: preceptors Nan-ping Weng and Amanda Damjanovic, Laboratory of Immunology, NIA**

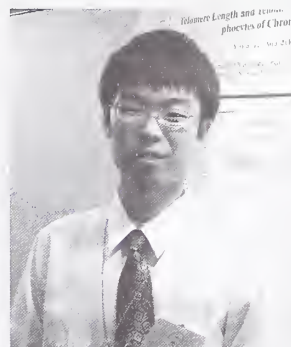
Recognizing the critical role of telomeres in the aging process and immune response, and prompted by the observation that chronically stressed individuals tend to have weakened immune responses, Yixiao Zou and his mentors investigated the effect of chronic stress—in the form of long-term caregiving to Alzheimer's disease patients—on telomere length and telomerase activity in such primary caregivers.

Data from 29 healthy caregivers

(mostly spouses) 57 to 75 years old and their age- and sex-matched control subjects have been analyzed so far. "Telomere length, activation-induced T cell telomerase activity, as well as T cell proliferation rate, were comparable between two groups," Yixiao Zou acknowledged, "but further analysis is needed to characterize the duration and intensity of stress experienced by the caregivers."

The one significant difference that emerged between the cohorts was a decreased percentage of natural killer cells in the caregivers, "which concurs with the weaker immune system hypothesis," Zou observed.

The study cohorts were recruited by in-



Fran Pollner

Yixiao Zou

vestigators at Ohio State University in Columbus, who collected and sent samples of peripheral blood mononuclear cells to the NIH researchers.

The NIA researchers anticipate continuing this work—increasing the number of subjects and conducting a longitudinal study to determine the rate of telomere shortening and loss of telomerase activity, Zou said.

A biomedical engineering student at Georgia Tech, Zou characterized the summer program as a "great hands-on experience" that will serve him well in his chosen field.

—Fran Pollner

## POLYMORPHISMS AND POLYPS RECURRENCE

**Grace Lee, Richard Montgomery High School, Rockville, Maryland**  
**"Interleukin-10 Promoter Gene Polymorphisms and Their Influence on Interleukin-10 Protein Levels among Participants in the Polyp Prevention Trial"**

**Co-authors: Leah Sansbury and preceptor Elaine Lanza, Laboratory of Cancer Prevention, NCI-CCR**

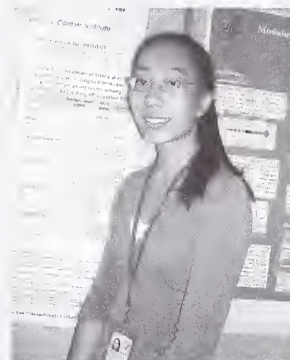
In the summer after her graduation from Richard Montgomery High School in Rockville, Md., and preceding her freshman year at the Massachusetts Institute of Technology in Cambridge, Grace Lee explored the relationship of interleukin-10 (IL-10, an anti-inflammatory cytokine) promoter polymorphisms, IL-10 serum levels, and the risk of recurrence of adenomatous polyps in the colon—a precursor to colorectal cancer.

She and her co-workers analyzed data collected from 558 people enrolled in the Polyp Prevention Trial. They focused

on three polymorphisms of interest, with special attention to the G/G genotype of the -1082 polymorphism, an allele variously reported to be associated with increased and decreased levels of IL-10 in other studies, Lee said.

In the current study, the other two polymorphisms (-819 and -592) had no apparent influence on IL-10 serum levels, but serum levels were significantly lower in individuals with the -1082 G/G genotype ( $P = 0.01$ ).

However, neither that genotype nor the lower serum levels of this anti-inflammatory cytokine appeared to correlate with an increased risk of adenoma recurrence over the four years covered by the data, a finding at theoretical odds with a previously reported association of the genotype with increased cancer risk.



Fran Pollner

Grace Lee

During the period covered by the study, 212 individuals experienced adenoma recurrence and 346 did not. The study cohort had a personal history of adenoma but not of colorectal cancer, their average age was 62, and the majority was white and male.

More sophisticated statistical models that would adjust for individual and adenoma characteristics are on the team's agenda, Lee said, as are studies on the influence of serum levels of other inflammation-related cytokines on adenoma recurrence. Her own plans, Lee added, include becoming a premed and majoring in biology.

—Fran Pollner

## EXPLORING DACLUZIMAB IN MS TREATMENT

**Caitlin Griffith, Grove City College, Grove City, Pennsylvania**

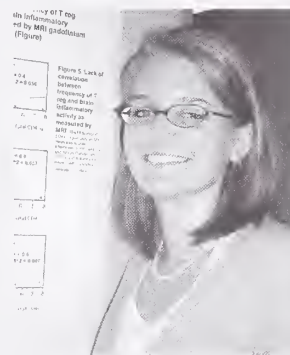
**"Effect of Anti-CD25 Monoclonal Antibody Therapy on Regulatory T Cells in Patients with Multiple Sclerosis"**

**Co-authors: preceptor Unsung Oh, Gregg Blevins, Nancy Richert, Henry McFarland, and preceptor Steve Jacobson, Neural Immunology Branch, NINDS**

Ongoing studies of anti-CD25 monoclonal antibody (dacluzimab)—an agent developed at NIH and already FDA-approved to treat uveitis and to prevent post-transplantation organ rejection—point to its potential therapeutic usefulness in ameliorating autoimmune disorders such as multiple sclerosis (MS).

The current study sought to measure the ability of dacluzimab to block activation of regulatory T cells (T reg)—and also of activated effector CD4+ T cells—in patients with relapsing-remitting MS.

A group of 10 patients with MS received dacluzimab infusions monthly for one year. Peripheral blood analysis showed a significant decline in T reg, as reflected in levels of T reg-specific markers such as Foxp3, and a somewhat smaller decline in effector T cells as well.



Fran Pollner

Caitlin Griffith

will include functional assays.

Brain inflammatory activity, however, as revealed by MRI, did not correlate with T reg decline.

Caitlin Griffith, a biochemistry major beginning her second college year, called the lack of correlation a "phenomenon." She noted that the MRI picture also "does not reflect the clinical findings" that have been reported to accompany dacluzimab administration. Continuing dacluzimab studies, she said,

—Fran Pollner



continued from page 11

## SELF-REPORTED HEALTH: THE INFLUENCE OF DEMOGRAPHICS

**Denisha Little, Winston-Salem State University, N.C., "The Link Between Self-reported Health and Demographics in the HANDLS Study"**

**Co-authors: Michele Evans, Melissa Kitner-Triolo, and preceptor Alan Zonderman, Research Resources Branch, Clinical Research Branch, and Laboratory of Personality and Cognition, NIA**

If you know someone's age, race, socioeconomic status, and perceived degree of friendliness in the neighborhood, you'll have a pretty good idea of how that person views his or her health.

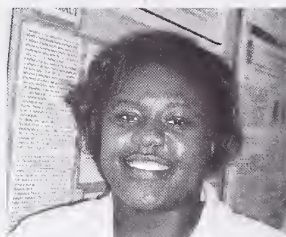
Analysis of responses to an in-home questionnaire taken by 657 Baltimore residents enrolled in the HANDLS study (Healthy Aging in Neighborhoods of Diversity across the Life Span) supported most of the hypotheses informing the design of the questionnaire.

As anticipated, older respondents, African-Americans, and people of lower socioeconomic status (SES) reported

being in poorer health than participants who were younger, white, and of higher SES.

Only one of several neighborhood characteristics expected to influence self-rated health status was borne out—agreeing that people not getting along well with one another was linked to poorer self-rated health. Contrary to expectations, women were no more likely than men to rate themselves healthy.

Interestingly, low SES (below 125 percent of the poverty level) erased the differences in self-reported health status between whites and African-Americans. Although higher-SES whites reported better health than higher-SES African-Americans, lower-SES whites were as likely to report poorer health status as lower-SES African-Americans.



Fran Pollner

Denisha Little

For Denisha Little, a gerontology major—biology minor at Winston-Salem State University, establishing reliable predictors of self-reported health status is just the beginning of her explorations in the field. She will be returning to NIH next spring to spend her last semester continuing this research.

On her research agenda are adding certain items to the questionnaire, correlating self-reported with actual health status of the participants, targeting particular areas in Baltimore to discern changes from one block to another, and parsing out "cultural" factors—such as diet, exercise, fear of the medical establishment—in self-reported and actual health status.

—Fran Pollner

## METABOLIC SYNDROME: THE INFLUENCE OF AGE AND RACE

**Benjamin Easter, Princeton University, Princeton, N.J.**

**"Metabolic Syndrome and Insulin Sensitivity in African-American and Caucasian Children and Adolescents"**

**Co-authors: Jennifer Gustafson, Margaret Rutledge, Joan Han, Sheila Brady, and preceptor Jack Yanovski, Unit on Growth and Obesity, Developmental Endocrinology Branch, NICHD**

The objective of the current study—involving 104 African-American and 161 Caucasian children ages 6 through 13—was to explore the relationship between metabolic syndrome and insulin sensitivity in the pediatric population and to examine the prevalence by race of the various components of metabolic syndrome.

"The particular criteria used to diagnose metabolic syndrome in the pediatric population are debated, and its prognosis is unclear," Benjamin Easter said. "We are trying to untangle all the components and see how race figures into establishing criteria for metabolic syndrome." The study, he added, is part of two larger long-term studies on growth and obesity.

Easter, now a senior at Princeton who will be applying to medical school,

noted that his being an economics major had given him an edge in using a novel statistical model called "ordered probit analysis" to determine the effect of insulin sensitivity on the likelihood of an individual's meeting from zero to five of the criteria for metabolic syndrome. The five components were age- and sex-specific cut-offs for waist circumference, blood pressure, HDL cholesterol, fasting glucose, and triglyceride level, with three or more of these deemed to constitute metabolic syndrome.

The prevalence of metabolic syndrome did not differ by race, but the prevalence of triglyceride levels high enough to meet metabolic syndrome criteria was significantly lower in African-Americans, supporting findings in previous studies and suggesting that race-specific criteria might be appropriate, Easter said. Other race-specific differences fell short of statistical significance.

Insulin sensitivity was ascertained both by the elaborate hyperglycemic clamp procedure and by fasting insulin and glucose



Fran Pollner

Benjamin Easter

levels (the QUICKI index). The two correlated well with one another, supporting the use of the more easily tolerated QUICKI method in clinical situations involving children, Easter noted.

When controlling for age, race, sex, and body-mass index, insulin sensitivity as measured by the QUICKI index, but not hyperglycemic clamp, was significantly associated with meeting more criteria for metabolic syndrome.

Of particular interest was the finding that three factors—body-mass index, waist circumference, and HDL cholesterol—were predictive of insulin sensitivity, but metabolic syndrome itself was not predictive when its individual components were included in the analysis.

"It may be that the diagnosis of metabolic syndrome isn't all that useful in children. Maybe just those three factors tell us what we need to know," Easter said.

—Fran Pollner



## MORE TRANS-NIH HAPPENINGS

continued from page 3

### Immune Deficiency And Malignancies

The Office of AIDS Malignancy Program in conjunction with the Office of International Affairs, NCI, is hosting the 10th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies, **October 16-17, 2006**.

Basic, epidemiologic, and clinical aspects of research on malignancies in HIV-infected and other immunosuppressed individuals will be covered.

The objective is to enable information exchange between laboratory- and clinically based investigators to decrease the interval between basic discovery and clinical application.

The meeting will be held at the Bethesda North Hotel & Conference Center (5701 Marinelli Road, North Bethesda, MD 20852).

Online information, including registration and preliminary agenda, are available at:

<[http://](http://www.palladianpartners.com/aidsmalignancy/index.htm)

[www.palladianpartners.com/aidsmalignancy/index.htm](http://www.palladianpartners.com/aidsmalignancy/index.htm)>

Registrations will be accepted until **October 9, 2006**, or until the meeting capacity has been reached. ■

### Surviving Stress

The "Fourth Symposium on the Functional Genomics of Critical Illness and Injury" will be held **November 13-14, 2006**, at the Natcher Conference Center.

The preliminary agenda for the NIGMS-Clinical Center-sponsored meeting on "Surviving Stress: Organ Systems to Molecules" can be seen at <[www.strategicresults.com/fg4](http://www.strategicresults.com/fg4)>.

Registration is online through **Thursday, October 19, 2006**. There will be no on-site registration. ■

### Chemistry History

Chemist Alfred Bader, founder of Sigma-Aldrich, the world's largest supplier of research chemicals, will speak on the history of that company, "with advice to young scientists," on **Thursday, October 5, 2006**, in the Lipsett Auditorium, Building 10. ■

### Antiviral Drugs And Resistance

The "7th Annual Symposium on Antiviral Drug Resistance: Targets and Mechanisms," sponsored by the University of Pittsburgh and co-sponsored by the HIV Drug Resistance Program, NCI, will be held **November 12-15, 2006**, at the Westfields Conference Center in Chantilly, Va.

For detailed information, to register, and to submit an abstract, go to the website:

<<http://web.ncifcrf.gov/campus/symposium>>

Registration will be accepted until **November 6**, or until the capacity of the venue is reached.

The deadline for submission of abstracts for oral presentation is **September 18**; abstracts submitted after this date will be considered for poster presentation until **October 13**, or until capacity is reached.

Questions may be addressed to Anne Arthur at

<[arthura@ncifcrf.gov](mailto:arthura@ncifcrf.gov)>.

### Hispanic Scientists Research Showcase

As part of the 2006 Hispanic Heritage Month celebrations, the NIH-Hispanic Employee Organization is sponsoring the Seventh NIH-Hispanic Scientist Day, **October 12, 2006**, in the Lipsett Auditorium, Building 10.

This event seeks to showcase the contributions of Hispanic and Hispanic-American postdocs, scientists, and clinical investigators at NIH, FDA-CBER, and USUHS.

The day's activities will start at 10:00 a.m. with a keynote address, "Judging Performance: The Hispanic Perspective," by Richard Tapia of Rice University, Houston, Texas.

A poster session and reception will follow from 12:00 to 2:00 pm. All members of the research staff are invited to present their unpublished or published data. Posters to be presented at the NIH Research Festival are welcome. Please send your abstract (not to exceed 1 page) by **September 22, 2006**, to Norma Street

<[streetn@cc.nih.gov](mailto:streetn@cc.nih.gov)>

or Migdalia Rivera-Goba

<[mrriverag@mail.cc.nih.gov](mailto:mrriverag@mail.cc.nih.gov)>.

### Clinical Bioethics Course

The NIH Department of Clinical Bioethics is again offering its course on "The Ethical and Regulatory Aspects of Clinical Research," from October 4, 2006, through November 15, 2006. The course will be held Wednesday mornings, from 8:30 to 11:30 a.m., in Building 10, Lipsett Amphitheatre.

For agenda details, faculty information, educational objectives, and target audience—and to register—go to the Clinical Bioethics website:

<<http://www.bioethics.nih.gov>>.

Sign language interpreters will be provided. Individuals with disabilities who need reasonable accommodation to participate should contact Mertis Stallings:

<[mstallings@cc.nih.gov](mailto:mstallings@cc.nih.gov)>.

This event will also be videocast live via the Internet. To participate off-site as a group, contact Becky Chen at

<[bchen@cc.nih.gov](mailto:bchen@cc.nih.gov)>

no later than one week before the start date to make arrangements. Federal TTY Relay number is 1-800-877-8339. Closed captioning will be available.

The required textbook, "The Ethical and Regulatory Aspects of Clinical Research: Readings and Commentaries" (JHU Press), is available at the FAES Bookstore, Building 10, B1 level, or check with a local retail bookstore in your area.

The National Institutes of Health/Foundation for Advanced Education in the Sciences is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. ■

This is a required course for the Clinical Center Core Curriculum Certificate. ■

### Ready To Report?

Anyone interested in covering selected symposia and posters at the NIH Research

Festival (October 17 and/or 18), for publication in *The NIH Catalyst*, please e-mail <[catalyst@nih.gov](mailto:catalyst@nih.gov)> or call 301-402-1449.



## RECENTLY TENURED

**Robert Brosh** received his Ph.D. in biology in 1996 from the University of North Carolina at Chapel Hill. He did postdoctoral work in the Laboratory of Molecular Gerontology (LMG), NIA, becoming a tenure-track investigator in that lab in 2000. He is currently a senior investigator in the LMG.

Our research has focused on the mechanisms of human helicases in pathways of nucleic acid metabolism that are important for the maintenance of genomic stability.

We have been particularly interested in the molecular and cellular functions of the WRN helicase, which is defective in the premature aging disorder Werner syndrome. It is our belief that understanding how the WRN helicase and related DNA helicases work to maintain chromosomal stability will lead to greater insights into the processes of cellular senescence, aging, and cancer.

A significant challenge to understanding the basis for the rapid onset of aging phenotypes in Werner syndrome has been defining the mysterious cellular role of the WRN helicase. To address this issue, we developed a model genetic system to explore WRN catalytic functions and protein interactions. This approach enabled us to provide the first in vivo evidence that a conserved noncatalytic domain of WRN helicase plays a critical role in facilitating the processing of DNA structural intermediates that arise during replication.

Our research findings suggest that WRN and related RecQ helicases coordinately act with structure-specific nucleases to maintain genomic stability during replicational stress.

Although considerable progress has been made in understanding the functions of certain DNA helicases, little was known about RECQ1, the first human RecQ helicase discovered. Our work demonstrated for the first time that in addition to its helicase activity, human RECQ1 efficiently catalyzes DNA-strand annealing.

We also identified and characterized the interaction of RECQ1 with human mismatch-repair factors that are important in the regulation of genetic recombination, elucidating the essential role of RECQ1 in the DNA damage response.

We are currently investigating the

unique role of RECQ1 in maintaining chromosomal stability in model human and mouse systems. We have shown that RECQ1-deficient cells display profound chromosomal instability, strongly suggesting that mutations in RECQ1 are likely to give rise to cancer or a human disease associated with genomic instability such as a premature aging or DNA repair disorder.

In the future, we will focus on the interactive roles of human helicases in network pathways that are important for chromosomal stability.

We are also characterizing the biochemical functions of other human helicases that are either genetically linked to human disease or believed to have important, though as

yet unclear, roles in genome homeostasis. Most recently, we have focused on the BRCA1-associated C-terminal helicase (BACH1), an enzyme genetically implicated in breast cancer and Fanconi anemia and whose molecular and cellular functions are not well understood. Our research aimed to determine the potentially unique role of BACH1 in DNA repair and to track how BACH1 deficiency can lead to cancer.

We have discovered that BACH1 preferentially unwinds specific early DNA recombination intermediates of double-strand break repair, providing new insights into the DNA substrate specificity of BACH1.

We are currently studying BACH1 polymorphic variant proteins that are associated with breast cancer and characterizing protein partners of BACH1 that are likely to be relevant to the function of the helicase in DNA interstrand cross-link repair.

We plan to use cell- and biochemical-based screening strategies to identify small-molecule inhibitors of the Fanconi anemia/BRCA pathway, proceeding from the hypothesis that such drugs could sensitize cells to DNA-damaging chemotherapy.

**James Doroshov** received his M.D. degree in 1973 from Harvard Medical School in Boston. He was chairman of the Department of Medical Oncology and Therapeutics Research and associate director for clinical research at the

City of Hope Comprehensive Cancer Center in Los Angeles for 23 years before joining NIH in 2004. He is currently director of the Division of Cancer Treatment and Diagnosis and a senior investigator in the Laboratory of Molecular Pharmacology, NCI.

My laboratory will focus on the role of oxidant-mediated signal transduction in cell proliferation and cell death. I will pursue three lines of research within the theme of oxidant stress-mediated effects on cell growth: NADPH oxidase 1, the glutathione peroxidase gene family, and the mechanism of action of anticancer quinones.

First, we will be studying NADPH oxidase 1, a member of a recently discovered epithelial NADPH oxidase gene family that shares substantial homology with the NADPH oxidase of polymorphonuclear leukocytes. NADPH oxidase 1 catalyzes the NADPH-dependent reduction of oxygen to superoxide after binding of ligands for receptor tyrosine kinases (including EGF, PDGF, and VEGF).

Using stable shRNA constructs, we have found that NADPH-dependent reactive oxygen species play a critical role in growth factor-mediated signal transduction in tissues, such as the colon, that abundantly express NADPH oxidase isoforms.

Recent studies have demonstrated that a series of flavin dehydrogenase-binding iodonium analogs block constitutive oxidant production and cell growth in human colon cancer cells in the nanomolar concentration range; at the same time, they induce apoptosis, p27 accumulation, and blockade of the G1-S transition.

These effects are ameliorated by exogenous hydrogen peroxide and are also associated with alterations in signaling by the Met pathway.

These agents also have a unique pattern of growth inhibition in the NCI 60-cell line-screening assay. In vivo, the iodonium analogs have substantive therapeutic activity in two different human colon cancer xenograft models.

Future studies will involve the synthesis of novel members of the iodonium drug class as potential therapeutic agents. We will also evaluate the effects of those drugs on the expression of genes regulated by oxidant stress



Robert Brosh



Fran Pollner

James Doroshov



in human colon cancer cells.

In a second project, we are examining the role of the glutathione peroxidase gene family in the prevention of oxidant-mediated gastrointestinal carcinogenesis. Glutathione peroxidases are the major intracellular proteins that catalyze the detoxification of hydrogen peroxide and lipid hydroperoxides.

In collaboration with my former colleagues at the City of Hope, I identified a novel cytosolic glutathione peroxidase—named GPX-GI—encoded by the *Gpx2* gene. *Gpx2* is expressed primarily in the distal small and large intestinal epithelium and is highly modulated by trans-retinoic acid,  $\gamma$ -irradiation, and selenium.

Approximately 80 percent of the peroxidatic activity of the distal intestine in the mouse is provided by GPX-GI and 20 percent by the constitutive GPX-1 enzyme.

When the *Gpx1* and *Gpx2* genes are knocked out, mice develop severe inflammation of the small and large intestine that is indistinguishable from Crohn's disease by light microscopy. In recent studies with this model, double-knockout mice at five months of age and older demonstrated a high (about 30–40 percent) incidence of adenocarcinomas in the distal intestine, at the site of the lowest glutathione peroxidase activity. Mice raised in a germ-free environment did not develop signs of inflammation after weaning and were cancer-free.

More than 90 percent of tumors in this model system demonstrate altered intracellular localization of  $\beta$ -catenin, suggesting that mutations in the *Apc* gene pathway may play a role in the intestinal carcinogenesis observed for *Gpx1/Gpx2* double-knockout mice.

This model system is one of the first to demonstrate by genetic means that chronic oxidant stress, produced by inhibiting the expression of antioxidant genes, is associated with the development of intestinal neoplasms indistinguishable from human adenocarcinomas.

Future studies with this model will focus on the molecular evolution of oxidant-induced tumors and the development of novel molecules that could interfere with the inflammatory and carcinogenic processes.

Finally, we are evaluating the role of reactive oxygen radical formation in the mechanism of cell death produced by

anticancer quinones, including the anthracycline antibiotics (such as doxorubicin) and other small molecules with clinically proven antineoplastic activity.

An evaluation of the spectrum and mechanism of DNA base damage produced by anticancer quinone-induced free radical formation is ongoing for both in vivo and in vitro systems.

We have also explored the role of reactive oxygen production by the anthracycline antibiotics, arsenic trioxide, and bisphosphonate anticancer agents in modifying EGF-mediated signal transduction.

As a result of pronounced (more than 80 percent) protein tyrosine phosphatase inhibition by arsenic trioxide-, anthracycline-, or bisphosphonate-induced oxidant stress, the phosphorylation of EGFR after exposure to EGF is dramatically prolonged, leading to a continuous, and potentially lethal, upregulation of EGF-mediated signal transduction.

These observations suggest an important role for drug-enhanced oxidant stress in modulating cell proliferation signals by a variety of small molecules, and a novel strategy for therapeutic combinations based on the drug-related modulation of oxidant-mediated signal transduction.

**Peter Kwong** received his Ph.D. from Columbia University in New York in 1995 and continued his postdoctoral training there under the mentorship of Wayne Hendrickson. In 2000, he joined the Vaccine Research Center, NIAID/NIH, where he is currently chief of the Structural Biology Section.

My group is attempting to apply structural biology to the development of an effective HIV-1 vaccine. Despite the enormous potential of atomic-level design—successfully used, for example, in the development of the HIV-1 protease inhibitors—current vaccine development makes little use of atomic-level information. We are trying to change this.

One area in which we and others have already made an impact is in understanding how HIV-1 is able to evade the humoral immune system.

Determination of the structure of the HIV-1 gp120 envelope glycoprotein, the primary target of neutralizing antibod-

ies against HIV-1, showed how N-linked carbohydrate can form both an immunologically silent face—with carbohydrate masquerading as “self”—and also can protect neighboring epitopes through an “evolving glycan shield.”

We also showed how conformational flexibility of gp120 can combine with quaternary restrictions within the viral spike to prevent antibody neutralization.

These studies served to define the underlying mechanisms that protect HIV-1 from the humoral immune response.

But can one use structural biology in actual vaccine design? Currently, my group is following two lines of investigation.

One line involves the precise delineation of functional constraints to identify potential footholds of conservation and exposure.

In a collaborative study, we investigated antibodies that bound to the co-receptor-binding site on gp120 and found them capable of neutralizing not only HIV-1, but also the even more evolutionary divergent HIV-2. We found such CD4i antibodies to develop to high titers in most HIV-1-infected individuals.

Unfortunately, our analysis also found that the virus hides the site of co-receptor binding, so that before engagement of the primary HIV-1 receptor, CD4, the co-receptor site is not formed.

These studies demonstrate the strength of functional constraints in restricting epitope variation. But they also identify an important weakness: Functional conservation does not necessarily engender epitope exposure, which is required for antibody neutralization.

We are currently exploring how function might constrain the site of CD4 binding, which—unlike the co-receptor-binding site—must be available as an initial site of attachment.

A second line of investigation involves structural analysis of the broadly neutralizing antibodies thus far identified that have the ability to neutralize diverse isolates of primary HIV-1.

Only four antibodies of such ability have thus far been identified—2F5, 2G12, 4E10, and b12.

We have determined the structures of both 2F5 and b12, each with their HIV-



Peter Kwong

Peter Kwong



## RECENTLY TENURED

1 envelope epitopes.

In a collaborative study, primarily with David Baker's group at the University of Washington, Seattle, Joe Sodroski's group at the Dana-Farber Cancer Institute in Boston, and also with Gary Nabel's and Rich Wyatt's groups at the Vaccine Research Center, we are currently generating epitope mimics unencumbered by known mechanisms of humoral evasion.

Tests of these epitope mimics in small animals should reveal their potential to elicit antibodies with abilities similar to the template broadly neutralizing ones.

Whether the confluence of structural information that we are generating is sufficient to elicit broadly neutralizing antibodies will depend in part on our ability to iteratively optimize immunogenicity and also on structural parameters of conformational mimicry, epitope accessibility, elicited potency, neutralization breadth, and target specificity.

Our investigations have already led to insight into the parameters governing antibody elicitation and neutralization. True success, however, will depend on whether or not we succeed in creating immunogens capable of substantially reducing the incidence of HIV-1 infection in humans.

**Carl Lupica** received his Ph.D. in psychobiology and neuroscience from Wayne State University, Detroit, Mich., in 1989. He did postdoctoral work at the University of Colorado Health Sciences Center in Denver and held faculty positions in the pharmacology department there and at the University of Arizona Medical School at Tucson before joining NIH in 2002 as an investigator in the Cellular Neurobiology Research Branch, NIDA. He is currently a senior investigator and chief of the Electrophysiology Research Unit, NIDA.

During my time at the University of Colorado, NIH funding launched my career as an independent researcher studying the physiological mechanisms through which opiate drugs alter synaptic transmission in brain areas involved in pain perception and cognition.

This work resulted in several novel discoveries, including the identification of a new signal-transduction mechanism

coupled to opiate receptors and the observation that  $\mu$  and  $\delta$  opiate receptors are segregated to distinct classes of inhibitory neurons in the hippocampus.

After that, while at the University of Arizona Medical School, I began NIH-funded studies to determine the physiological mechanisms through which the newly discovered endogenous cannabinoid molecules altered brain function.



Carl Lupica

These studies, now continued at the NIDA intramural research program, have identified the substrates upon which cannabinoid CB1 receptors and endogenous cannabinoids act to regulate the function of brain reward circuits and memory processes in the hippocampus.

Among the most significant findings attributed to my work are (1) the identification of voltage-dependent calcium channels as the mechanism through which CB1 receptors transduce their signal in inhibitory neurons in the hippocampus and (2) the discovery that dopamine neurons located in the central reward circuit of the ventral tegmental area (VTA) synthesize and release endogenous cannabinoid molecules.

These latter studies also determined that under conditions of increased excitability and during sustained bursting activity, the endogenous cannabinoid molecules released from VTA dopamine neurons regulate the strength of synaptic input to this nucleus.

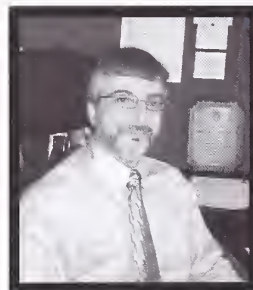
This action provides a likely explanation for the ability of cannabinoid CB1 receptor antagonists to diminish craving for several classes of abused drugs, such as opiates and nicotine, because all these drugs share the ability to increase VTA dopamine neuron activity and bursting.

Additional ongoing studies in my laboratory combine modern physiological techniques such as patch clamp electrophysiology and confocal microscopy to identify the molecular changes that occur in the brain as a result of the prolonged use of marijuana and exposure to its psychoactive ingredient,  $\Delta^9$ -tetrahydrocannabinol.

One of our goals is to identify the

mechanism through which prolonged marijuana use in humans can cause persistent cognitive deficits, and to gain a further understanding of the role of endogenous cannabinoids in regulating the activity of these cognitive neural circuits.

**Alan Michelson** received his M.D. and Ph.D. degrees from Harvard Medical School in Boston in 1986. His graduate thesis work was undertaken under the supervision of Stuart Orkin at Children's Hospital Boston. He subsequently completed an internship in internal medicine at Brigham and Women's Hospital in Boston, followed by a postdoctoral fellowship with Tom Maniatis at Harvard University. In 1992, he joined the faculty at Harvard Medical School and Brigham and Women's Hospital and was appointed an investigator of the Howard Hughes Medical Institute. Earlier this year, he moved to NHLBI as associate director for basic research; he is also a senior investigator in the Genetics and Developmental Biology Center, NHLBI.



Fran Pollner

Alan Michelson

My laboratory has had a longstanding interest in the mechanisms that govern the specification, differentiation, and assembly of diverse cell types into complex tissues and organs during embryogenesis. We have been addressing these issues using development of the heart and body wall muscles of the *Drosophila* embryo as a model system.

Our initial studies demonstrated that homeotic genes act autonomously in the early mesoderm to establish the unique identities of muscle founder cells, thereby contributing to the diversification of the mature muscle pattern.

Using unbiased genetic screens, we then uncovered separate roles for signaling by two receptor tyrosine kinases (RTKs)—epidermal and fibroblast growth factor receptors (EGFR and FGFR, respectively)—in mesoderm development: FGFR activity is required for the migration of mesodermal cells after gastrulation, whereas both EGFR and FGFR signaling contribute directly to the commitment of muscle and cardiac cell fates.

We further showed that the RTKs act together with three other signaling pathways—Wingless (Wg, a WNT family member), Decapentaplegic (Dpp, a



bone morphogenetic protein superfamily member), and Notch—to promote the progressive determination of uncommitted mesodermal cells. Wg, Dpp, EGFR, and FGFR exert positive, cooperative effects on cell fate specification, whereas Notch functions in an inhibitory manner.

These findings prompted us to investigate how individual cells interpret multiple convergent signals in a tissue-specific manner. Results revealed that a considerable degree of signal integration occurs in the nucleus. Using a particular muscle and cardiac identity gene as a model, we found that a single transcriptional enhancer is directly regulated by the transcription factors acting downstream of all three positive signals that specify the fate of the cell in which this enhancer functions.

Moreover, tissue specificity of the generic signaling pathways is conferred not only by their combinatorial effects, but also by two mesoderm-restricted transcription factors that cooperate with the three signal-activated regulators bound to the same enhancer.

A key principle emerging from these studies is that subtypes of related cells are specified by unique combinations of a limited number of signals and tissue-restricted selectors. A major focus of our current work is dedicated to testing and refining this hypothesis using a more comprehensive systems-level approach. To this end, we have undertaken genome-wide expression-profiling studies of purified subpopulations of both wild-type and informative mutant primary embryonic cells.

A meta-analysis of the combined microarray datasets derived from these experiments led to the assignment of several hundred genes to either of two myoblast subclasses, predictions that we independently validated by whole-embryo *in situ* hybridization. We are now determining whether these large sets of co-expressed genes are also co-regulated by similar mechanisms.

In an ongoing collaboration with Martha Bulyk and her research group at Brigham and Women's Hospital, we are applying computational algorithms that predict the locations of *cis*-regulatory modules on a genome-wide scale and that assess the fit of a particular transcriptional regulatory model to a set of co-expressed genes. These strategies have enabled us to identify a subset of transcription factors that comprise a core

code for the regulation of a subset of myoblast genes, a model that we validated using transgenic reporter assays to test the functions of candidate enhancers.

The next question that we are addressing is how cell-type specificity is superimposed on the core transcriptional code. Central to these investigations is our prior discovery of previously uncharacterized transcription factors that are candidate cell-specific selectors.

We are using protein-binding microarray technology to characterize the DNA binding specificities of these factors, with the resulting motifs incorporated into our computational framework to predict novel transcription factor combinations that are responsible for differential gene expression in muscle and cardiac cells.

Classical genetics and RNA interference directed against these factors are also being used to selectively perturb the associated transcriptional networks, thereby assessing the functional significance of newly identified regulators and their predicted combinatorial interactions.

Additional work is in progress in my laboratory to examine how co-expressed target genes function in the later differentiation and morphogenesis of the heart and body wall muscles.

**Forbes D. Porter** received his M.D. and Ph.D. from Washington University in St. Louis in 1989 and then trained in pediatrics and clinical genetics at St. Louis Children's Hospital. After a postdoctoral fellowship in the lab of Heiner Westphal (LMGD, NICHD), he became a tenure-track investigator in the Heritable Disorders Branch, NICHD, in 1996. He is currently a senior investigator in that branch.

Any given birth defect or genetic syndrome is relatively rare, but viewed in the aggregate, genetic defects are a significant component of child health care. My interest has been in understanding the biological processes that underlie birth defects and using these rare syndromes to understand more-common genetic problems.

My laboratory has been studying a group of human malformation and mental retardation syndromes caused by in-

born errors of cholesterol synthesis. The most common of these disorders is the Smith-Lemli-Opitz syndrome, or SLOS, an extremely variable disorder with a broad clinical spectrum. Severely affected infants often die before or soon after birth, whereas the findings in children with milder cases can be limited

to minor physical abnormalities associated with learning problems or autistic-like behavior.

Children with SLOS have low cholesterol levels and elevated levels of a cholesterol precursor molecule known as 7-dehydrocholesterol. Because sufficient cholesterol does not cross the placenta, normal development is impaired. My group

studies SLOS both in clinical protocols and in the laboratory.

One of our first accomplishments was to clone the gene responsible for SLOS. To date more than 100 different mutations of this gene have been identified in SLOS patients. After cloning the human gene, we identified the mouse gene and produced mouse models of SLOS to study the biological changes associated with the syndrome and to test various therapeutic interventions.

In collaboration with Phil Beach's laboratory at Johns Hopkins in Baltimore, we have shown that the hedgehog signaling pathway is impaired in SLOS cells. Proper hedgehog signaling is important for multiple developmental processes, and disruption of this signaling pathway can cause birth defects.

We have also developed mouse models of desmosterolosis and lathosterolosis—two rare SLOS-like human malformation syndromes—which have helped us separate the effects of low cholesterol from those due to precursor accumulation.

In addition to our basic science work, I currently follow more than 50 patients with SLOS in whom we are studying the beneficial effects of increasing dietary cholesterol intake. Cholesterol therapy enhances the overall health of SLOS patients, many of whom in the past died in the first few years of life. Growth and nutritional status are improved, and the children also appear to be less irritable. However, dietary cholesterol therapy does not improve learning because it does not get into the brain.

We are currently studying the safety



Forbes Porter

Forbes Porter



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and efficacy of simvastatin to alter brain cholesterol levels in these children. In blocking cholesterol synthesis, simva-statin also decreases the synthesis of abnormal sterol 7-dehydrocholesterol—and may also paradoxically increase cholesterol levels. We would like to determine if alleviating the biochemical disturbance in the brain exerts a positive effect on either learning or behavior.

**Peter Schmidt** received his M.D. degree in 1982 from the Royal College of Surgeons and the National University of Ireland in Dublin. He completed a residency in psychiatry at the University of Toronto and joined the Biological Psychiatry Branch at NIMH in 1987. He is currently a senior investigator in the Section of Behavioral Endocrinology, NIMH.

The goals of my program are threefold:

- To identify the sources of vulnerability for the development of mood disorders during periods of altered reproductive function

- To evaluate the potential role of hormonal therapies in reproductive endocrine-related mood disorders

- To determine the neural mechanisms underlying the mood-regulating effects of gonadal steroids

My early work, much of it in collaboration with David Rubinow at NIMH and Lynnette Nieman at NICHD, focused on women with severe premenstrual dysphoria (PMD).

We used the progesterone receptor antagonist RU486 and GnRH agonists to demonstrate that the symptoms of PMD could occur in the absence of normal luteal-phase progesterone levels.

Nonetheless, symptoms depended on exposure to physiologic levels of ovarian steroids, with behavioral sensitivity manifested in those women with PMD but not those without PMD.

These observations of differential behavioral sensitivity informed my subsequent studies of the relationship between changes in reproductive aging and affective adaptation.

My group has used several strategies to test the hypothesis that declining reproductive function plays no role in the onset of mood disorders that occur in women at midlife.

We initiated what is still an ongoing history study in which we prospectively evaluate asymptomatic premenopausal

women to determine whether an onset of depression is coincident with a specific phase of the menopause transition.

We have also examined the effects on mood of reversing selected aspects of age-related hypogonadism by administering reproductive hormones, the secretion of which decline by or during midlife. Specifically, we demonstrated the short-term antidepressant effects of estradiol therapy in women who developed depression during the menopause transition.

In an ongoing study, we are examining the effects of the selective estrogen-receptor modulator raloxifene and the phytoestrogen rimostil in a separate group of depressed perimenopausal women.



Peter Schmidt

Additionally, we have documented the antidepressant efficacy of the adrenal androgen DHEA in men and women with midlife-onset depression.

In future studies of the potential relationship between reproductive senescence and mood disorders, we will study selective estrogen-receptor antagonists as they become avail-

able for human use. We will examine the specific roles of estrogen receptors alpha and beta in the psychotropic actions of estradiol and in the effects of estrogen withdrawal on the onset of perimenopause-related depression.

Finally, my group is conducting studies of experimentally induced hypogonadism. In one study, we examined the effects on mood of estradiol withdrawal in asymptomatic women with a past history of perimenopausal depression.

In another study, we administered a GnRH agonist—a depot brand of leuprolide acetate—in normal volunteers to investigate the symptomatic and physiologic consequences of hypogonadism.

In this latter study, performed in collaboration with Karen Berman at NIMH, we demonstrated that hypogonadism eliminates—and physiologic ovarian steroid replacement restores—the cognition-activated regional cerebral blood flow in the dorsolateral prefrontal cortex, inferior parietal lobule, and posterior inferior temporal cortices of the human brain—regions implicated in the regulation of cognitive function and emotional state.

Considerable effort is now underway

to reconcile these and related findings on the neuroregulatory effects of ovarian steroids with findings from the Women's Health Initiative of an increased risk of dementia in women taking combined estrogen-progestin therapy

Reproductive endocrine-related mood disorders have a well-defined biological stimulus that we can demonstrate is critical in the precipitation of affective disturbances.

Thus, these conditions afford a unique opportunity to identify neural substrates involved in the regulation of affective state.

The availability for study of known triggers (such as gonadal steroids) and associated signaling pathways dramatically increases the likelihood of identifying mechanisms of both affective-state regulation and illness susceptibility.

The impact of these studies, therefore, extends beyond reproductive endocrine-related mood disorders to mood disorders in general, as well as to our understanding of the relevance of brain development and plasticity in affective disturbance.

**Jeffery Taubenberger** received an M.D. in 1986 and a Ph.D. in 1987 from the Medical College of Virginia in Richmond. He completed a residency in anatomic pathology at NCI and served as chairman of the Department of Molecular Pathology at the Armed Forces Institute of Pathology before joining NIAID in 2006. He is currently a senior investigator in the Respiratory Viruses Section, Laboratory of Infectious Diseases, NIAID.

My group is interested in studying the pathogenesis and evolution of influenza A viruses, with special emphasis on pandemic influenza. Influenza A viruses are found in a wide variety of hosts, including wild birds, domestic poultry, horse, pigs, humans, and other mammals.

Influenza causes yearly outbreaks and, occasionally, novel pandemic influenza strains emerge in humans ultimately derived from bird influenza viruses. The most devastating pandemic on record was the 1918 "Spanish" influenza, which may have killed as many as 50 million people globally in 1918–1919.

There is concern that a new influenza pandemic might emerge if the current H5N1 avian influenza virus ultimately adapts fully to humans.

Before coming to NIAID, my laboratory group was able to determine the



complete genetic sequence of the 1918 virus using tiny fragments of viral RNA recovered from the lungs of victims of the 1918 pandemic. With colleagues in several institutions, we re-constructed the 1918 virus using reverse genetics, and the first experiments with the virus were conducted in high-containment labs at the CDC.

As do some of the virulent H5N1 viruses in animal models, the 1918 virus induces a strong acute inflammatory response, suggesting that the immune response itself may be a component of the pathogenesis of these viral infections.

At NIH, my laboratory is based in the new C.W. Bill Young Center for Biodefense and Emerging Infectious Diseases (Building 33). We will focus on different experimental models to map the genetic basis of the virulence of the 1918 influenza virus and compare it with recent highly pathogenic avian influenza viruses that have caused fatal infections in humans. We also hope to identify genetic changes that are associated with host switching in influenza viruses.

To do this, we will also need to expand the number of influenza genome sequences available, both from human and animal strains, and my laboratory will continue to collaborate with the NIAID Influenza Genome Sequencing Project.

Analyses of hundreds of human influenza virus genomes are demonstrating that the evolution of human influenza strains is more complex than previously thought. Influenza viruses in humans evolve rapidly, and frequent antigenic changes in the surface proteins require routine reformulation of the vaccine.

With our collaborators around the country we are also engaged in prospective avian influenza surveillance in wild birds. We are working to develop rapid molecular genetic diagnostic assays to improve influenza surveillance in humans and in animal populations.

We are also developing models to examine the significance of other mutations identified by genomic analyses of contemporary human influenza viruses to understand selection in the context of viral fitness.

We are continuing to derive sequence information from archival influenza cases, some as early as 1907. By plac-

ing the emergence of the 1918 pandemic virus in the context in which it emerged, we may be able to more fully understand how pandemic strains emerge in a form that allows them to spread efficiently to humans.

We have identified several influenza-positive pre-1918 cases and will be screening influenza cases from the 1920s as well to help identify unique genetic signatures of virulence of the pandemic virus. The goal of all of these projects is to better understand how pandemic strains emerge in humans, as

well as the genetic basis of how influenza viruses cause disease in humans. These findings may ultimately lead to new avenues for treatment and may help mitigate the impact of a future pandemic.



Jeffery Taubenberger

**Yingzi Yang** received a Ph.D. in molecular biology from the Weill Medical College of Cornell University in New York in 1996. After completing a postdoctoral fellowship in the laboratory of Andy McMahon at Harvard University in Cambridge, she joined the Genetic Disease Research Branch, NHGRI, as a tenure-track investigator in 2000. She is currently head of the Developmental Genetics Section and a senior investigator in the Genetic Disease Research Branch, NHGRI.

My laboratory studies vertebrate limb development and skeletal morphogenesis. Our goals are to understand the mechanisms by which molecular signals are transduced and integrated in a regulatory network to control cell proliferation, differentiation, and organization and to gain insight into key regulatory events during limb and skeletal morphogenesis.

To that end, we focus on the signaling mechanisms of Wnts and Hhs (hedgehogs) in the limb and skeletal system and how abnormalities in these two signaling pathways lead to birth defects, skeletal diseases, and tumor formation. Our multidisciplinary approach combines the strength of mouse molecular genetics with embryology, functional genomics, and the cell and organ culture systems in the developing limb.

My previous work elucidated the regulation of early limb-patterning events that provide temporal and spatial information for the initial formation of the skeletal elements. My current research addresses how signaling molecules regulate skeletal development in the limb, a later morphogenetic process.

I seek to understand several fundamental events in this process: the regulation of mesenchymal condensation, the differentiation of chondrocytes vs. osteoblasts from mesenchymal progenitor cells, the coordination of chondrocyte proliferation with maturation, and the induction and maintenance of synovial joint.

I have made several major discoveries in this current research effort:

- Different Wnts play distinct roles in regulating chondrocyte differentiation.

- The canonical Wnt pathway is both necessary and sufficient for synovial joint induction and determines whether mesenchymal progenitors differentiate into chondrocytes or osteoblasts.

- The noncanonical Wnt5a signaling promotes chondrocyte differentiation by inhibiting the canonical Wnt signaling activity.

- The canonical Wnt pathway interacts with the Indian hedgehog (Ihh) signaling pathway in distinct ways during different processes of skeletal morphogenesis, and Wnt5a acts in parallel pathways with Ihh to coordinate chondrocyte maturation.



Fran Pollner

Yingzi Yang

My lab is continuing to study how Wnt and Hh signaling pathways interact with other pathways in skeletal development, and we are now exploring the role of Wnt and Ihh signaling in bone diseases, such as osteoarthritis and bone tumors. My lab is also actively investigating the molecular mechanism underlying the control of cell and tissue or-

ganization by the planar cell polarity pathway in both embryonic development and adult tissue homeostasis.

My hope is that our research in basic skeletal developmental biology will lead to clinical studies that advance disease prevention, diagnosis, and treatment. ■

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## CATALYTIC REACTIONS?

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

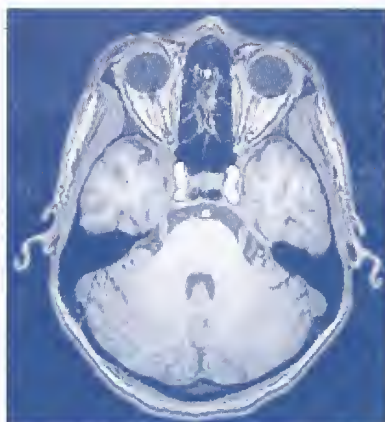
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## Kids' Catalyst: Reading Minds

Years ago, there was only one way to really see the structures of the living brain, and it involved high-risk procedures and was therefore a last resort.

Now, with little more discomfort than lying in the same place for a while, we can capture fantastic images like the ones to the right and below. We can zoom in



*Can you see the eye sockets?*

not only on the structure of the brain, but also on which particular part of it is working when one is thinking. Talk about reading minds!

But fMRIs (functional magnetic resonance imaging scans), CTs (computerized tomography scans), and X-rays are just some of the acronym soup helping doctors diagnose and study the body in ways never before possible without actual exploratory surgery.

With medical imaging and significant advances in technology, we can see minds working—and hearts and other organs—and get those pictures that are worth a thousand words.

—Jennifer White



*fMRI of the brain of an anonymous NIH'er*

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