FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

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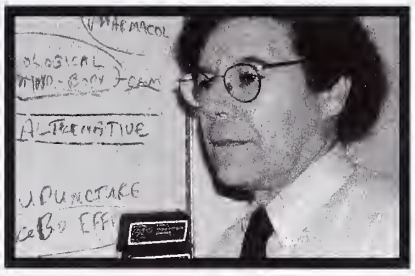
Interview with Marc Blackman

NCCAM Launches Intramural Protocols

by Fatima Husain

As Harvard's Charles Rosenberg said in July in the debut of the NCCAM series of *Distinguished Lectures in the Science of Complementary and Alternative Medicine*, up until the late 19th century, all medicine was holistic and multidisciplinary, and what is considered complementary and alternative medicine (CAM) today was considered mainstream medicine then.

Today, however, although it commands an enthusiastic following



Fatima Husain

Marc Blackman

among the lay public, much of the medical mainstream views CAM somewhat skeptically.

CAM was accorded a niche at NIH when Congress established the Office of Alternative Medicine in 1992. Its goal was to replace both skepticism and enthusiasm with science. In 1998 the office achieved Center status, and in the spring of 2001, Marc R. Blackman became the first clinical director of the newly established NCCAM Division of Intramural Research. Since that time, Blackman has initiated an ambitious intramural clinical research program.

Blackman's office is in one of the houses across from the Children's Inn on the NIH Bethesda campus. The number of scientists and staff con-

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NIH Team Harnesses Bioinformatics, Genetics to the Task

World Trade Center Victim Identification Pushes Frontiers of Forensic Science

by Celia Hooper

On September 13, 2001, with the world stunned by the devastation of the World Trade Center, the Office of the Chief Medical Examiner for the City of New York stood amidst another desperate landscape—perhaps the biggest challenge that has ever faced the U.S. forensics community.

The office had no guide for collecting the data that would be needed in the grim task of identifying unknown thousands of victims, most of whom would not be identified by traditional methods but, rather, by genetic markers amplified from bits of otherwise indistinguishable tissue.

Two-Way Calls: For Help and To Help

Along with frantic inquiries from the victims' families and politicians calling on their behalf, there were numerous offers of help—DNA sequencing, genetics expertise, metadata analysis, bargain rates for mitochondrial DNA analysis. Even sorting out the offers of help seemed overwhelming amidst the clamor and chaos.

The New York medical examiner's office (OCME) turned to DNA forensics experts at the National Institute of Justice (NIJ), part of the Department of Justice. The daunting task of assembling a brain trust to advise the OCME fell to NIJ's Lisa Forman, a Bethesda resident and one-time NIH guest researcher.

In late September, while describing to a friend the vast, complex, and sometimes marginal genetic data that somehow had to be pieced together, there came a spark of recognition: similarities with the Human Genome Project.

At her friend's suggestion, Forman put in calls to the National Human Genome Research Institute (NHGRI) and the National Center for Biotechnology Information (NCBI), asking their respective directors, Francis Collins and David Lipman, for help.

As it turned out, HHS and NHGRI had already been among those exploring channels for offering expertise, sequencing—whatever was needed. The same was true for the International Genetic Epidemiology Society and the American Society of Human Genetics.

Thus it was that a small group of NIH scientists eventually found their way to Forman's brain trust—the Kinship and

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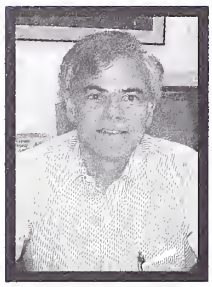
What Is Special about the NIH Intramural Research Program?



Michael Gottesman

It is useful from time to time to re-evaluate the structure and function of the NIH intramural research program—and the arrival of a new NIH director who asks for an overview of IRP contributions gives us the opportunity to do just that.

In a recent visit with the Scientific Directors, Dr. Zerhouni asked for examples of the IRP's past and continuing contributions to the overall NIH research effort. He was particularly interested in those that would be difficult or impossible to pursue using other funding mechanisms.

The resulting list was impressive and underscores the uniqueness of the research environment provided by NIH, the special features of the IRP that enable our intramural scientists to avoid noninnovative science and pursue riskier paths that may open onto major advances in our basic knowledge and clinical abilities.

Salient IRP characteristics include relatively long-term stable funding, which allows scientists to undertake research with a potentially high payoff but a long germination period; a critical mass of researchers who can interact collaboratively to assemble teams to attack complex problems; the ability to purchase major capital equipment and create facilities; short start-up time to address urgent problems in public health and to develop newly emerging scientific fields; and the premier clinical research facility in the country for conducting innovative research that takes basic science from bench to bedside.

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Here are some examples of the research fostered by these unique features.

- **Long-term investment:** Nobel prize–winning contributions in establishing the genetic code, determining how neurons communicate, and discovering the basis for transfer of information into cells by the action of hormones, among others.
- **Teamwork:** the development of vaccines against hepatitis, childhood bacterial infections, and papillomaviruses associated with cervical cancer, as well as other cancer vaccines; current work at the Vaccine Research Center and NIAID to develop a vaccine against HIV-AIDS and Ebola; and assembly of a critical mass of bioinformatics expertise at the National Center for Biotechnology Information, NLM, to archive and analyze DNA sequence information.
- **Resources:** Powerful instruments including multi-Tesla magnets and high-resolution microscopes to probe subcellular structures; MRI equipment to visualize the functioning of the brain and heart; and an animal imaging facility that is second-to-none in developing new technologies to yield high-resolution images of normal and pathological tissue in animal model systems.
- **Short start-up:** Response to HIV-AIDS epidemic and biodefense needs; one of the first centers to adapt microarray technology for diagnosis of cancer, to use positional cloning technology to isolate novel disease genes, and to develop vectors that have facilitated the recombinant DNA revolution.
- **Clinical research:** Lithium to treat manic-depressive illness; fluoride to prevent tooth decay; first artificial heart valve; multiple chemotherapeutic agents to cure cancer; detection of hepatitis viruses to make the blood supply safe; the first effective treatment of HIV-AIDS; development of new approaches to organ and tissue transplantation, including transplantation of pancreatic islet cells; the study of families with rare genetic diseases to facilitate cloning of many different genes associated with human inherited diseases such as Parkinson's disease and hereditary deafness syndromes; and other population-based studies to determine the role of environmental and genetic causes of human disease and to document biological changes associated with normal development, aging, and drug and alcohol abuse.

To capitalize on the special features of the intramural program, especially the ability to bring state-of-the-art resources and teams of scientists to bear on difficult scientific problems over a long period of time, we have begun to design centers that allow even closer interaction of scientists with similar interests. The neuroscience center, emerging now in the southwest corner of the Bethesda campus, epitomizes this approach.

NIH intramural scientists have used the extraordinary opportunities inherent in the NIH way of doing research to great advantage. I encourage young scientists in training here to shy away from "me, too" science and avail themselves of the unique climate here for more creative work.

I am certain the readers of this essay can think of other unique features of the intramural program that have led to research with a major impact on modern biomedical research. As always, I welcome your thoughts and examples.

—Michael Gottesman
Deputy Director for Intramural Research

Catalytic Reactions

In response to the Call for Catalytic Reactions, I would like to register the following:

On Research Challenges

One of the key challenges in responding to many of the scientific issues we need to address is the paucity of clinical research staff both on campus, as well as extramurally on the domestic and global scenes (particularly in countries where some of the most urgent disease problems exist). In order to move the burgeoning basic research findings through translational and then clinical and population-based studies, the research personnel issues must be addressed. Doubling the NIH research budget without doubling and tripling the budget for research training and career development may be the most important challenge facing us.

On Special Interest Group (SIG) Effectiveness

Perhaps the SIGs have reports and recommendations that might be disseminated broadly, not only to IC Scientific Directors but to IC Directors and their planning offices as well as to program directors administering both intramural and extramural portfolios.

On *Catalyst* Coverage

It might be edifying to learn about international collaborations that evolve from initial collaborative research projects between and among intramural scientists and Visiting Scientists. Once foreign scientists return to their home countries, are there continuing collaborations and are there new collaborations that evolve with our extramural scientist communities? These case studies might be useful not only in justifying the various programs but in stimulating additional needed international collaborative research.

—Lois K. Cohen, Director, NIDCR Office of International Health

—Regarding extramural funding for clinical research training, NIH launched three award programs in fiscal 1999:

- *The Clinical Research Curriculum Award (K30) enables institutions to provide didactic training on the fundamentals of conducting clinical research. Courses may include, but are not limited to, study design, biostatistics, bioethics, and regulatory issues.*
- *The Mentored Patient-Oriented Career Development Award (K23) enables individuals to obtain mentored research experience.*
- *The Mid-Career Investigator in Patient-Oriented Research Award (K24) is a complement to K23, providing support to the mentors and allowing them protected time to devote to patient-oriented research.*

Since their inception, NIH has funded a cumulative total of 496 K23 awards and 215 K24 awards; 57 K30 awards were made in FY 2001.

An additional NCRR-funded clinical career development award to help institutions develop degree-granting programs in clinical research was launched in FY 2002. It is anticipated that 10 programs will be funded during the pilot phase.

—Belinda Seto, OER

—Regarding the next chapter in the research lives of visiting scientists once they go back home, see "GRIP Strength: Building Bridges to Developing Countries One Scientist at a Time," page 4, on a related NIH program—Ed.

On Important Questions In Biomedical Research Today

What is the earth's sustainable population and how can we humanely reduce our population to that level?

—Carl Henn, OD

Behavioral and Social Sciences Resources at the NIH Library

The NIH Library offers access to key resources relevant to the behavioral and social sciences—many available via a desktop computer from the Library's web page at <**http://nihlibrary.nih.gov**>).

Below is a guide to some of the more important resources. (The Library also conducts training classes, personal tutorials, and online animated tutorials in effective search techniques; click on "Training" at the Library's website.)

- For **books,** search the NIH Library catalog at <**http://nih-library.nih.gov**> or Books-In-Print at <**http://www.booksinprint.com/bip/**>. Items in Books-In-Print can be ordered.
- **Journals** can also be found in the catalog, and a list of **online journals** can be accessed from the Library's web page under "Electronic Resources, Online Journals." Additional online journals are available from ScienceDirect and JSTOR, a digital archive of back issues of more than 100 journals in the arts and sciences, including many sociological and anthropological titles.
- The Library provides desktop access to **databases** covering the behavioral and social sciences literature. These resources, featured below, can be accessed from the Library's web page under "Electronic Resources, Databases." (Librarians can also search these and other databases, such as Sociological Abstracts. To arrange this, call 496-1080 (Monday–Friday, 8:30 a.m–5:00 p.m.).

—HAPI (Health and Psychosocial Instruments)
<**http://gateway.ovid.com/autologin.html**>
provides information on measurement instruments in the health fields, psychosocial sciences, and organizational behavior and identifies measures needed for research studies, grant proposals, client/patient assessment, and program evaluation.

—PsycINFO
<**http://gateway.ovid.com/autologin.html**>
covers the professional and academic literature in psychology and related disciplines, indexing more than 1,300 journals from 1887 on. The alert service provides e-mail updates.

—WEB OF SCIENCE
<**http://publishorperish.nih.gov/**>
allows searching the Social Sciences Citation Index, which contains bibliographic information and cited references from more than 1,700 social sciences journals from 1980 on. The Porpoise alert service provides weekly e-mail updates.

—MATHSCINET
<**http://www.ams.org/mathscinet/**>
provides access to Mathematical Reviews and Current Mathematical Publications from 1940 on. Bibliographic data and review texts are available from 1975 on.

The Library also provides **Customized Library Services** for a fee to groups needing assistance with large projects. Librarians can develop search strategies, conduct online database searches, and develop databases using bibliographic software such as EndNote or Reference Manager. For more info on custom services, call Susan Whitmore at 301-496-1157. ■

GRIP Strength

Building Bridges to Developing Countries One Scientist at a Time

by Sharon Hrynkow, Ph.D., Deputy Director FIC, and Philip Chen, Ph.D., Senior Advisor to the Deputy Director for Intramural Research, OIR

Mock Peer Review Panel *(left to right): Georgia Atella from Brazil, Vincente Baca-Ruiz from Mexico, Alassane Dicko from Mali, Kamala Tirumalai from India, and Philip Chen*

photos by Ernie Branson

Sharon Hrynkow (left) and Georgia Atella

It began with the misperception that women from developing countries are not as well represented in the NIH Visiting Program as their male counterparts.

After digging into the data, however, we learned that it is geography, not gender, that underlies underrepresentation in the program.

At the time we checked into it (March 2001), the striking finding was this: Of the 2,500 foreign trainees in the Visiting Program, only 20 were from sub-Saharan Africa. Moreover, other regions of the world in which the burden of disease is exceptionally high were also poorly represented: Zimbabwe, Uganda, Indonesia, Bolivia, and Kazakhstan, for example, each had only one individual on campus at that time. (As for a suspected gender imbalance, with just a few exceptions, the ratio of male to female participants from countries with per capita income less than $3,125 actually approached 1:1.)

As with many experiments, this unexpected realization led us down another road. When we considered the global burden of disease and the disproportionate share of that burden borne by the lower income countries of the world, we began to ask ourselves if we could do more to recruit postdoctoral trainees to the Visiting Program from these disease-burdened nations and help them to return home afterwards.

Based on our experience with programs sponsored by the Fogarty International Center (FIC) and the NIH extramural research program, we know that enhancing scientific infrastructure in resource-poor settings depends on people returning home after a successful training experience. So, we decided to take a look at what was happening with the Visiting Fellows on campus.

This decision led to a series of consultations with junior scientists from countries in the developing world and countries in economic transition. The results of these consultations have provided much food for thought, as well as action.

Think Globally, Act Locally

FIC works with almost every NIH Institute and Center through an array of extramural research and research training programs to reduce disparities in global health; it is well positioned to work with scientists on campus who are from the developing world.

Supporting "Science for Global Health," FIC has decades of experience working with developing-country partners on research and training projects, building research capacity one scientist at a time in the fields of AIDS, maternal and child health, environmental health, and other global health challenges.

It was easy to project the value of helping to advance the careers of young scientists from developing countries after they finished their training at NIH and returned home. The objective is to potentiate their effectiveness in their home countries' scientific communities and as part of the next generation of global health leaders.

Working closely with OIR and ORWH, FIC hosted a meeting on campus last March to hear from these future leaders how they planned to transition back to their home countries and how prepared they felt to apply for NIH extramural awards. We learned that the experiences of fellows from the developing world in many ways mirror those from the United States and other developed countries: The apprehension associated with writing a grant is universal—as is the need for mentoring and role models.

But there were also some specific differences. Many of the fellows were unaware of opportunities through FIC and other NIH mechanisms to receive grant support on return to their home country. Fellows also stressed the need for support that would enable them to network with others and among themselves on return home—the establishment of an "alumni" group, for example.

In settings in which the scientific infrastructure is weaker than in the United States, reliance on colleagues with like experience and some means of communicating from country to country emerged as key.

As a way of jumpstarting a communication network, participants suggested the establishment of an NIH ListServe of the 600-plus scientists from the developing world in the intramural program so that an easy exchange of information and experience could take place. They also emphasized the need for hands-on experience in writing grants to be able to launch their independent careers on return home.

Get a GRIP

Over the next several months, we consulted broadly across NIH, with the FIC Advisory Board, and then again with the fellows about a program that we ultimately rolled out as the Global Health Research Initiative Program (GRIP) for New Foreign Investigators.

To help launch independent research careers, the GRIP provides up to $50,000 for salary and research costs for up to five years to visiting fellows on their return home. As an RO1 mechanism, it is highly competitive and peer-reviewed through the NIH process.

The response to the GRIP Request for Applications (RFA) was enthusiastic, and the first round of awards will be made in September 2002. FIC partners in this first GRIP round were OAR, ODS, ORWH, NINDS, NIA, OBSSR, NIMH, NEI, NHLBI, NIGMS, and NIEHS.

To provide practical experience in the grant-writing process, NIGMS joined with the Office of Education to host a one-day session on how to write an NIH grant. This was open to the entire community and was well attended by fellows from the developing world.

FIC followed a few weeks later with a mock peer review session in which PIs from the University of Maryland and Johns Hopkins University in Baltimore

dissected two of their own grants—one unsuccessful, and then the successful revision—using a group of 20 of the fellows as the review panel. This practical session was well received, and FIC plans to hold another such event shortly.

The second GRIP RFA will be issued in September 2002. With more NIH ICs already signing on, we expect an even greater response for the next round, as well as even more participants in the next mock peer review session.

Where Do We Go from Here?

FIC acted on the suggestion to establish and maintain a ListServe for fellows from developing countries and countries in economic transition. Another ListServe, supported by OIR, will soon be in place to connect all of the international fellows on campus.

Currently in discussion is an initiative to link visiting fellows with extramural mentors, beginning with the networks already supported through FIC and its partner ICs. OIR has actively encouraged multiple mentors, since an extramural mentor would provide an excellent complement to advice received from intramural mentors. Coming full circle, the fellows will work with FIC and OIR to boost the ranks on campus of fellows from low-income countries.

Kamala Tirumalai, a visiting fellow from India working in the Laboratory of Cellular and Molecular Immunology, NIAID, is now leading a subgroup of the fellows to explore a range of ideas and potential activities to bring to the larger group for consideration and implementation. The intramural-extramural mentoring program is one project. Another is developing ways to use home country newspapers and media outlets to disseminate information about the fellows' research successes as a means of helping them transition homeward.

Tirumalai is optimistic that what for many are "currently rather bleak" career prospects in their countries of origin will be substantially boosted by the ongoing consultations between FIC, OIR, and visiting fellows and the fellows' brainstorming sessions—not to mention the extramural awards. ■

For more information on the GRIP, contact Aron Primack, FIC, at 301-496-1653. To join the Developing Country ListServe or for information on past or upcoming meetings of the fellows, contact Chris Keenan, FIC, by e-mail or on 301-496-1415. For information about the NIH Fellows Committee (FelCom), contact Deborah Cohen at 301-402-1907.

Brody's Site No Fly-by-Night

by Rashmi Nemade

What began as the curiosity-driven project of a research scientist moving from one field to another has grown into one of the most functional and acclaimed websites in cyberspace today. "The Interactive Fly," Thomas Brody's invention to comprehend Drosophila biology, has been honored with a 2002 Sci/Tech Web Award from ScientificAmerican.com, which hails the site as a "monumental magnum opus that has become a standard in the field of developmental biology."

The Interactive Fly website **<http://sdb.bio.purdue.edu/fly/aimain/1aahome.htm>** features information on tissue and organ development, gene hierarchies and their functions, biochemical and developmental pathways, images—and more.

Judy Brody

Thomas Brody

Brody, a senior NINDS fellow and member of the Neurogenetics Unit, in Ward Odenwald's laboratory, actually created this website as a means of facilitating his career transition from immunology and genetics to developmental biology, using Drosophila as a model organism. "I found it difficult to assimilate all the fragmentary information in the literature and realized that if I wanted to display the hierarchy of gene activation, repression, interactions, and protein interactions—to move up and down the developmental hierarchy—the only way to do this would be in cyberspace." Brody persevered more than two years—cataloging, indexing, cross-linking—and the Interactive Fly was born in the summer of 1996.

Six years later, the site now contains information that would fill more than 10 volumes of the Encyclopaedia Britannica, receives more than 3 million hits a year, and is used by everyone from high school students to senior researchers and grant reviewers. It's now hosted by The Society for Developmental Biology and FlyBase, the database of the Drosophila genome.

FlyBase itself, a consortium of groups in the United Kingdom, Harvard University (in Cambridge, Mass.) and the University of Indiana at Bloomington, is "perfectly adequate," Brody says, but does not so easily allow users "to move from gene to gene seamlessly and understand interactions and hierarchies." With the Interactive Fly website, on the other hand, novice or expert can maneuver through and grasp the Drosophila genome with just a few clicks.

Another way the Interactive Fly is "different from anything else on the web," Brody says, is that it is "text-based" not "database-based" —all the information on the site has been published elsewhere, is cross-linked accordingly, and is presented in context. Given that more and more Drosophila genes are being discovered, along with their vertebrate homologs, the format is especially useful for all biologists.

For each gene, the site provides information on vertebrate evolutionary homologs, gene regulation and targets of activity, protein expression and effects of mutation, and—most important, says Brody—a biological overview that explains in understandable fashion aspects of a gene's discovery and biological function. The user-friendly text is largely the work of Judy Brody, the site's meticulous editor and Thomas Brody's wife.

Asked about similar websites for other models, Brody says "we are continually talking about how to parse the information of the Interactive Fly into a database format highlighting information on other organisms—but we have not made any commitments yet." ■

NCCAM's Blackman
continued from page 1

nected to the NCCAM intramural program has increased substantially, and the cohorts have established quarters at various locations on the Bethesda campus.

Blackman is not a newcomer to NIH—he was a clinical postdoc at NIDDK from 1975 to 1977 and an NIA guest researcher from 1980 to 2001. Before his arrival at NCCAM, he was chief of endocrinology and metabolism and the program director of the General Clinical Research Center at the Johns Hopkins Bayview Medical Center in Baltimore, as well as a professor of medicine at Hopkins.

The *Catalyst* interviewed Blackman in July, a month after the launch of NCCAM's first intramural clinical trial—of electroacupuncture to reduce delayed nausea in cancer chemotherapy patients.

Q: First, what was your personal experience with alternative medicine and what attracted you to the position at NCCAM? What was your sense upon arrival here 15 months ago—and what is it now—of NIH's proper role in exploring and defining alternative therapeutic approaches?

BLACKMAN: Regarding the first question, I've had 20 to 25 years of clinical, research, and teaching experience related to endocrinology and aging. The hormones I've been interested in—growth hormone, sex hormones, and DHEA (dehydroepiandrosterone)—are also of interest to many in CAM fields. As for other components of CAM, of which there are many, I'd had no experience before coming to NCCAM.

In terms of what attracted me to the position, I viewed it then—and now—as an exciting and challenging opportunity to contribute, with many others, to a huge area of public health interest and concern, namely, the escalating use of CAM modalities by the US public.

I envision collaborating extensively with colleagues inside and outside of NIH and working closely with diverse stakeholders in the field of CAM to create a more robust knowledge of the effectiveness and safety of select CAM modalities . . . and contributing to training and patient care.

At NCCAM, we have established a scientific program centered on the theme of chronic stress. In particular, we have chosen to focus our clinical and translational research efforts on depression, cognitive decline, musculoskeletal frailty, chronic pain and related syndromes, and sleep disorders, particularly in the elderly. Each of these conditions is associated with substantial use of one or another CAM modality.

Fatima Husain

Marc Blackman

We have also created an administrative, clinical, and laboratory infrastructure and have begun research programs in endocrinology, diabetes, and oncology.

With time, we intend to establish additional research programs in neurobiology, clinical immunology, cardiovascular medicine, and pharmacology.

During these first 12–15 months, we have initiated our first three clinical research protocols and several laboratory studies, and we have established a series of exciting collaborations with investigators in multiple other institutes.

In addition, we have worked with other NIH colleagues to develop a Clinical Center–based Integrative Medicine Task Force, which we are very excited about.

This task force has several charges. The first is to create an integrative medicine consult service for Clinical Center inpatients and outpatients. This would be novel at NIH and, in fact, at most US institutions. The task force will also oversee licensing, credentialing, and quality assurance of those who apply CAM practices within the NIH Clinical Center.

We also propose to evaluate the success of this entire consultative service, with all its regulatory and educational components, as a health-care research study and to report the results of that assessment in a peer-reviewed journal in the future.

Q: Do you have the sense that practicing physicians feel uncomfortable about CAM, or that, if presented with the kind of scientific evidence that NCCAM expects to produce, they will modify their practice accordingly?

BLACKMAN: Health-care providers are trained to evaluate information, and they expect and want to be informed properly of the effectiveness, safety, and potential utility of diverse mainstream and CAM interventions.

I think that there is a skepticism [among health care providers], which obviously varies from person to person, but in a general sense, it is healthy skepticism based upon the desire for more information.

It's understandable, given that the majority of CAM modalities have yet to be rigorously evaluated. I think that unhealthy skepticism about CAM practices, based in bias, is far less common.

At the NIH, I think there is a growing feeling that CAM represents an area of important research. In fact, during my brief time here, I have been cheered and stimulated by the positive feedback from numerous NIH scientists.

These are highly skeptical people who articulate that there is a compelling need for further investigation of those CAM modalities that show potential to benefit the public's health.

Q: So much of CAM seems to rest on patient belief structures (mystical belief systems, placebo effect, self-fulfilling prophecy, etc.)—for instance, if a patient believes acupuncture will work, it will. How can NCCAM effectively evaluate those belief systems that are difficult to measure or quantify?

BLACKMAN: You've touched upon one of the challenges in CAM-related clinical research. Clearly, the complex integrative systems intrinsic to many CAM practices demand that we develop new paradigms of conceptualization and implementation of clinical investigation.

One example is placebo-related research. About a year and a half or two ago, NCCAM partnered with other NIH institutes to host an extraordinarily successful workshop on the science of the placebo effect. As a consequence of that workshop, interest has grown in more rigorously evaluating the biology of the placebo effect.

Just this year, a Swedish group published some seminal observations in the area of pain interventions that are quite exciting and involve brain imaging [*Science* **295**:1737-1740, 2002].

Q: How do you decide which study to pursue?

BLACKMAN: We work hard to research the relevant literature and to focus on those issues in our areas of research interest that have high public health importance and sufficient evidence to justify further scientific inquiry.

Clearly, we must also ensure that any proposed study is feasible and that we can meet its resource needs. Moreover, we consult with other scientific colleagues and other CAM stakeholders at NIH and in the extramural community.

In our first intramural CAM protocol, we sought to investigate the potential role of electroacupuncture in treating a particularly vexing problem in cancer patients, namely, postchemotherapy nausea and vomiting.

We chose to study young adults in their twenties and thirties with pediatric-type sarcomas in whom chronic and anticipatory postchemotherapy nausea and vomiting are common and greatly reduce quality of life. These patients are treated with multiple successive rounds of highly emetogenic chemotherapy at three-week intervals. Glucocorticoids and other antiemetic drugs fail to curb the nausea and vomiting and are associated with major side effects.

Although electroacupuncture has proved beneficial in the management of nausea and vomiting occurring acutely (within 24 hours) postchemotherapy, it has not yet been investigated for such symptoms occurring chronically (2–5 days). Our study will address this issue in a controlled fashion.

Another of our intramural clinical studies will address endocrine-immune relationships in premenopausal women with recently detected rheumatoid arthritis. We hypothesize that the heightened inflammatory milieu of these patients, typified by augmented cytokine activity, is associated with suppressed growth hormone and DHEA production and that the effects of endocrine-immune disruption contribute to important extra-articular manifestations of arthritis—specifically, osteopenia, sarcopenia, increased body fat, and increased risk of diabetes and cardiovascular disease.

From a CAM perspective, we are interested in both the joint and extra-articular manifestations of rheumatoid arthritis.

In subsequent studies, we hope to evaluate the effects of modulating the growth hormone or DHEA axis, in conjunction with the best of the mainstream anti–rheumatoid arthritis medications.

Q: How do you and your various collaborators settle on experimental paradigms and protocol details?

BLACKMAN: As you know well, scientific collaboration requires coming to a consensus with one's colleagues and collaborators as to the specifics of the hypothesis, specific aim, experimental design and method, and analysis, interpretation, and reporting of data.

Clinical research in CAM poses additional challenges regarding novel approaches to design, especially with regard to experimental controls. Needless to say, we and our colleagues discuss these thoroughly in our planning sessions. Planning for our acupuncture study served as a good example of this process.

We also routinely send our nascent protocols for independent scientific evaluation by experts not involved in the study before submitting the final protocol to the Institutional Review Board.

Q: What lies ahead?

BLACKMAN: During the next several years, we plan to build our intramural program and to work closely with colleagues here at NIH to substantially expand our CAM-related research, clinical, and educational activities.

One of our goals, among many, is over time to incorporate chiropractic research into some aspects of our clinical investigations of musculoskeletal disorders.

Chiropractic is a good area to explore because it is a well-criticized field with well-documented types of training. Properly done, I think this would be a substantial contribution to research and to the care of patients with certain musculoskeletal disorders.

I've been quite cheered by the positive reception accorded our initial efforts by colleagues at NIH, and I believe that their scientific goals are consonant with the perspective of the general public, which desires that we bring the best of complementary and alternative medicine into the mainstream. ■

Hispanic Heritage Month Celebration: Two Parts

Language and Access to Care" is the theme of the 2002 NIH Hispanic Heritage Month Celebration, Part 1, taking place Thursday, **September 19, 9:00 a.m.–12:30 p.m.**, in Lipsett Auditorium, Building 10.

Remarks by Marta Leon-Monzon, president of the NIH Hispanic Employee Organization, NIH Director Elias Zerhouni, and US Surgeon General Richard Carmona will precede lectures by Thomas Münte on "How to Handle Two Languages with One Brain: A Neuroscience Perspective," Nilda Peragallo on "Language and Culture: Bridges or Barriers," and Carlos Zarate on "Pilot Hispanic Research Initiative in Mood Disorder Patients."

An exhibit and reception follow at the Building 10 Visitor Information Center, 12:30–2:00 p.m.

Part 2—NIH Hispanic Scientists Day—will be held at Lipsett Thursday, **October 10, 12 noon–3:00 p.m.** It kicks off with a talk by Antonio Fojo on "Multidrug Resistance in Cancer: Laboratory Studies and Clinical Correlates," followed by a talk on NIH grant opportunities and positions by Milton Hernandez. and concludes with posters and a reception at the Visitor Center. For more info, contact Leon-Monzon at 496-4564 or **<leon.@od.nih.gov>**.

Sign language interpretation will be provided. For reasonable accommodations to participate in this event please contact the NIH Office of Equal Opportunity and Diversity Management at 301-496-6301. Additional information is available at

<http://mrb.niddk.nih.gov/ray/file/HHM2002/>.

Victim Identification
continued from page 1

Data Analysis Panel (KADAP). They joined the panel with others from academia, private and public DNA testing labs, the National Institute of Standards and Technology, the Armed Forces Institute of Pathology, the NIJ, and OCME.

A Transforming Experience

NHGRI's Leslie Biesecker says "scientific advisory committee" doesn't seem adequate to describe the group. "The intellectual process has been so dynamic, so sober, so focused on this incredible task," Biesecker says. "This group of people has such a commitment and desire to do this as well as it can possibly be done—it goes beyond any group of scientists that I've ever been involved with. It's been an amazing process."

KADAP member Elizabeth Pugh, director of bioinformatics and statistical genetics at the Center for Inherited Disease Research (a center funded by NIH through a contract with the Johns Hopkins School of Medicine in Baltimore), says she has been similarly inspired by the staffs of the OCME and the New York State Police (NYSP), which have worked closely with the KADAP.

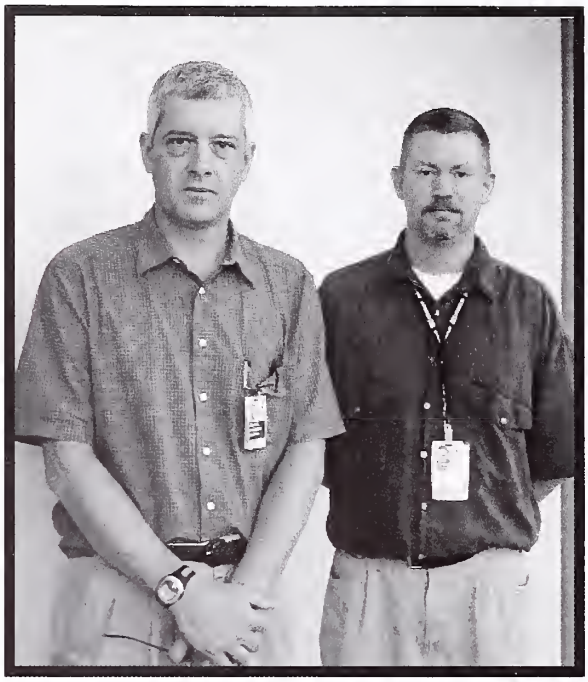
"I am continually awed at the knowledge, expertise, dedication, and commitment of the OCME and NYSP personnel who are on the front lines of this unprecedented identification process," Pugh remarks. "It has been a privilege to assist them in whatever small ways I could."

The KADAP has met bi-monthly since October 2001, and the two other NIH-affiliated staff on the panel—Joan Bailey-Wilson and Steve Sherry—have, like Biesecker and Pugh, been struck by the experience.

Bailey-Wilson, head of the statistical genetics section of NHGRI's Inherited Diseases Branch, notes that the KADAP was extra work for everyone. "We are incredibly busy, but this was something we felt like we had to do. There isn't much we could do, but this was something. We had the skills."

NCBI's Sherry has found working synergistically with his fellow KADAP members and the fruits of the group's efforts profoundly rewarding. "It's just been a real privilege to work with these people," he told *The NIH Catalyst*.

"Working with SNPS in medical genetics and therapeutics is something we do all the time at NCBI. It leads physicians to provide better health care for someone, sometime," says Sherry. "But we here [in NCBI] don't see that, except as a cluster of intense use of the databases—where a gene was found in months, not years, resulting in a fast track for treatment.



Celia Hooper

Leslie Biesecker (left) and Steve Sherry

"But the forensic experience is different. Every conclusion is a connection of a lost loved one to a family. I do it for them. It brings closure."

The Magnitude of the Problem

At the first meeting of the brain trust, the OCME conveyed the magnitude of the problems to the group. "The sheer scale of the project was comparable to 15 simultaneous airplane crashes, but [at the time] we didn't know how many people were missing," Sherry recalls.

The number of people killed at the Pentagon was known, thanks to sign-in procedures; passengers on the airliner that crashed in Pennsylvania, as in other airline disasters, were listed on a manifest. But at the World Trade Center, "It took months just to figure out who was missing," he says.

The KADAP also realized that in the confusion following the disaster, there were procedural difficulties that could impede victim identification. These included blocked communications between computer systems and a jumble of numbering systems for victim and family samples, storage files, artifacts, and analysis data. The form for identifying relationships between relatives and presumed victims had been ambiguous, the instructions to families unclear.

Making Connections

In its next meetings, the group quickly defined and assumed tasks: creating a booklet for family members of victims to help with a second round of reference sample collections; identification of tools that might be useful for massive genetic matching and sorting; programs to straighten out numbering systems and help computer systems talk to one another; and, perhaps most important, clear, logical organization of all the efforts. John Snyder of the OCME likened the work of the group to "building an airplane while trying to fly it."

Biesecker, working with Kathy Hudson, Jane Ades, and Derryl Leja from NHGRI and Robin Wilson-Jones from the NIJ, dove into the task of producing a booklet to help families understand molecular forensic identification—how it works, its limitations, and how they could contribute to the identification process—what Biesecker calls "making the connection between a high-tech process and the emotional needs of a family."

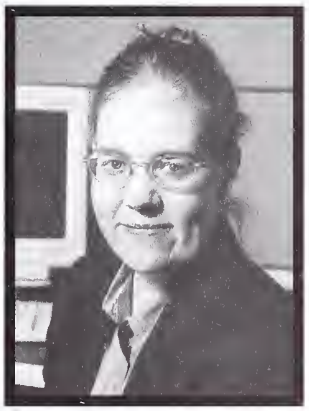
The booklet, written in Spanish and English, simply and with dignity, was produced in record time: 15,000 copies were delivered to New York around New Year's Day. The pamphlet is already being circulated, adapted, and copied by law enforcement agencies and other groups across the country.

Bailey-Wilson, Pugh, and Sherry joined others in reviewing software that could be adapted for matching and kinship analysis. NIJ's Forman says the group considered public-domain programs used in airline crashes, in identifying victims of war in Bosnia, and in paternity and criminal cases, as well as a program developed by the US armed forces. "It was pretty clear that none of the programs came close," Forman re-

calls. "We didn't have the right tools."

Pugh and Sherry went to work with NIJ's contractors Amanda Sozer and Steve Niezgoda and with the program developers to adapt the programs to the new demands of the World Trade Center identifications.

Sherry carefully thought through and mapped the information flow needed to coordinate the far-flung parts of the process, from data collection to analysis, reporting, and quality assurance.



Elizabeth Pugh

Since last autumn, data have been pouring through the complex pipeline, with its architecture heavily influenced by pipeline designs used in the Human Genome Project. Time pressures in getting the system operating were intense as families awaited confirmation that their loved ones had died so that they could hold funerals.

Increasing Complexity

Sherry says that the work plan prioritized the easiest identifications, then moved on to the most challenging. The easy matches were those in which there was a reliable reference sample of a victim's DNA from before the disaster and an uncompromised sample from the World Trade Center site. The hardest matches are still in the pipeline and heading for some of the most exhaustive and cutting-edge techniques ever applied to forensic DNA.

Joan Bailey-Wilson

Forman says scientists working with the identification project developed and built on established tools for high-throughput and nonstandard mitochondrial DNA analysis and more stringent extraction of nuclear DNA needed for severely degraded and co-mingled samples. "The tools were improved because they had to be," Bailey-Wilson says.

These more complex data and more distant kinship matching needs have, in turn, led to new computational challenges. "This analysis being done leads to an incredible informatics challenge," says Forman. "Steve Sherry has just been phenomenal . . . in stretching the power of the technologies."

But Forman says pushing the technology to tease out the most difficult identifications had not initially been envisioned. She had originally imagined the project would be completely finished with the application of standard techniques. Then, at a meeting in June, members of a family who'd lost their brother, James Cartier, in the disaster spoke briefly and poignantly to the group.

"They said that without some identification of their brother, they could not rest. In that 15 minutes, I completely changed my mind about how far we had to go to 'completely finish,'" Forman says. "There will be a point when science has no more answers, but everything has to be tried."

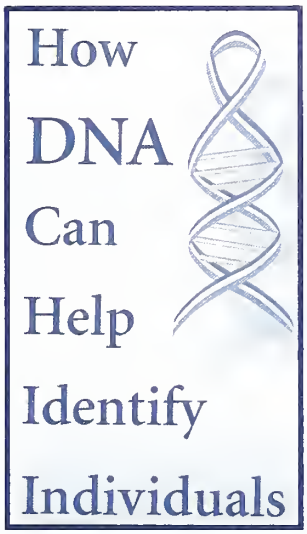
A New Discipline

Looking toward a September 9–10 meeting of the group in New York, Forman was amazed at the list of "deliverables" that had flowed from the group's work.

Beyond the incredibly daunting task of identifying hundreds of victims was the booklet for families and improved forensic tools—which will all be placed in the public domain.

In addition, the group has drafted specific and complete directions for handling comparable natural or manmade disasters in the future and begun to develop guidelines for improving training in forensic science.

In fact, Forman believes the work of the group and Sherry's insight may have inadvertently spawned a valuable new discipline—computational forensics. "At one point Steve naively said, 'put your computational forensics people on this problem.' We all just looked at each other. Until that moment, such a thing didn't exist."



Cover of the booklet for families produced by NHGRI and the National Institute of Justice for the New York City Office of the Chief Medical Examiner

Collection of victim samples ended on May 31, 2002. By August, the easiest identifications had been made, with a few thousand samples still flowing through the pipeline. Application of some of the new tools to the most challenging samples remained, as did NIH's participants in the identification project.

"I think all four of us from NIH have a commitment to stick with the process as long as our input is needed," Biesecker says. "We are in it for the long haul. We are pushing the boundaries of the science." ■

CSR Seeks Interns

The Center for Scientific Review (CSR) is seeking new recruits for its Review Internship Program, which offers scientists training and experience in scientific research administration. Interns will work with a diverse and dedicated group of scientists in their fields and help coordinate state-of-the-art scientific review meetings. This year, CSR is encouraging NIH intramural scientists as well as those in academia and industry to apply.

Applications submitted by November 1, 2002, will be considered for positions starting no sooner than February 2003. Applications submitted by February 1, 2003, will be considered for positions starting in August 2003.

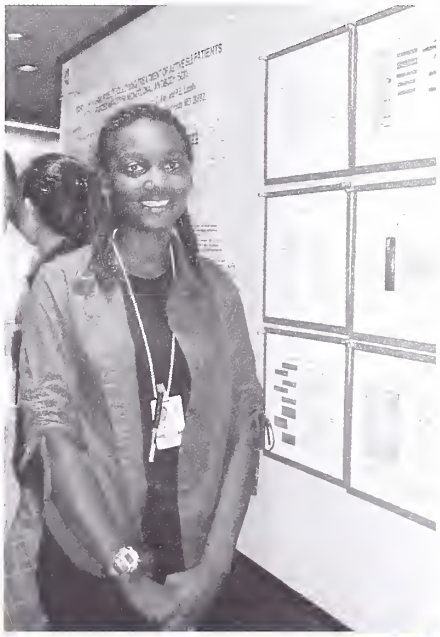
Additional information about the program, application forms, and other requirements can be found on the CSR website:

<http://www.csr.nih.gov/Internship.htm>.

General inquiries about this new program can be directed to Mary Elizabeth Mason at 301-435-1114. ■

'Tis the Season

Having devoted their summer months to research at NIH, this year more than 400 students displayed the fruits of their labor at Poster Day, held on August 8th. Not unlike every year, 2002 brought together a variety of research interests and students from all over the U.S. whose educational level ranged from high school student to university graduate. Also not unlike every year, the random selection of the few posters that appear on these pages reflects the uniformly fascinating quality of all the research projects.

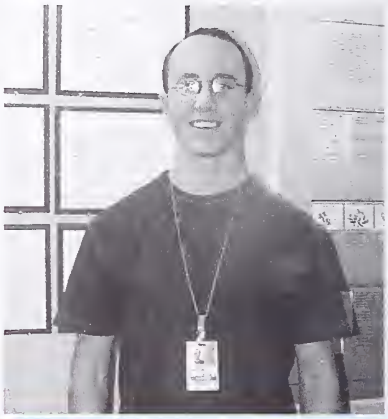


LaToya Stewart
"The Technology Behind DNA Forensics: Fingerprinting with Short Tandem Repeat (STR) Loci"
Preceptors: Craig Chang and Kuan Wang Laboratory of Muscle Biology, NIAMS

Stewart graduated from Henry E. Lackey High School in Indian Head, Md., and spent her summer up to the elbows in DNA before heading to Lebanon Valley College in Annville, Pa., in the fall. Ask her what she wants to be "when she grows up," and she replies with no hesitation: "A forensic specialist for the FBI." It is no surprise, therefore, that she designed her own summer project.

While trying to understand the technology behind DNA forensic fingerprinting with short tandem repeat loci, Stewart simulated a crime scene by mixing different samples of human DNA and exposing them to environmental insult—varying degrees of temperature, darkness and light, overdrying, and contamination with animal DNA, for example. She performed PCR with a multiplex primer mix and analyzed the samples by DNA electrophoresis.

She says she will major in chemistry and molecular biology—and she wants to come back to NIH next summer.



Eric Maklan
"Retroviral Mediated Delivery of Short Hairpin RNAs for RNA Interference in Mammalian Cells"
Preceptor: Vittorio Sartorelli, Laboratory of Muscle Biology, NIAMS

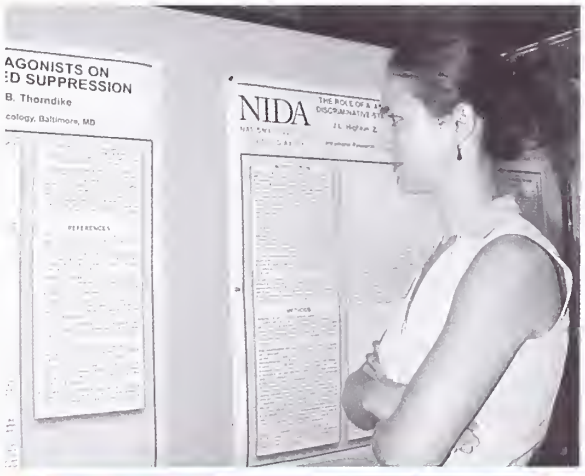
Working on a project that has become a hot commodity in the world of medical research, Maklan used a retroviral system to mediate delivery of short hairpin RNA for RNA interference in mammalian cells, thus disabling the cell from expressing the corresponding protein.

A biology major at Brandeis University in Boston, where he is entering his junior year, Maklan has set his sights on going to medical school.

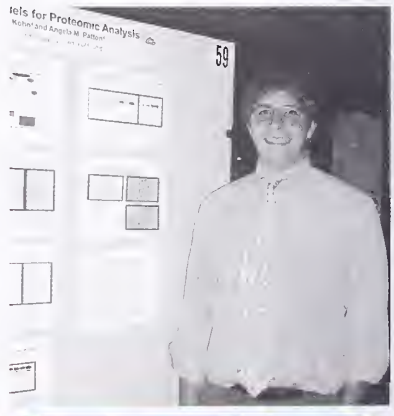
A graduate student in behavioral neuroscience at American University in Washington, D.C., Grakalic says her summer's work here has solidified a decision to pursue a career in research.

Grakalic's project used dopamine antagonists (D1) SCH 23390 and (D2) eticlopride to measure classically conditioned effects of cocaine on an operant baseline in food-deprived rats.

Her findings suggest that, at least in rats, the D2 antagonist may block the expression of cocaine-induced appetite suppression.



Ivana Grakalic
"Effects of Dopamine Antagonists on Cocaine-induced Conditioned Suppression"
Preceptor: Charles Schindler, Behavioral Neuroscience Research Branch, NIDA



James Saltsman
"Using Angiogenesis Models for Proteomic Analysis"
Preceptors: Angela Patton and Elise Kohn, Laboratory of Pathology, NCI

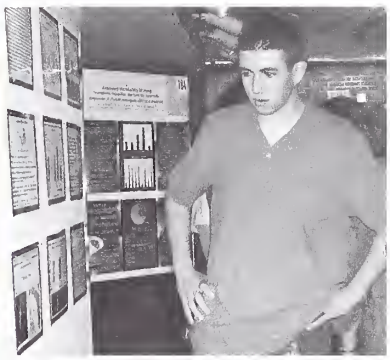
text by Nadia Khan
photos by Fran Pollner

Sylvia Major (center)
"Protein Microarrays for Cancer Drug Discovery"
Preceptor: John Weinstein, Laboratory of Molecular Pharmacology (LMP), NCI
Also pictured: (right) Satoshi Nishizuka, LMP research fellow and co-author, and (back to camera) interviewer Nadia Khan

After completing her undergraduate studies at Cornell University in Ithaca, N.Y., Major joined the LMP through the NIH Undergraduate Scholarship Program. She will complete a full year at NCI and is making plans to start graduate and medical school soon after.

For this project, Major and her colleagues in the LMP Genomics & Bioinformatics Group, the NCI Laboratory of Pathology, CIT, and the FDA Center for Biologics Evaluation and Research profiled the NCI-60 collection of cancer cell lines using reverse-phase protein lysate microarrays. Using P-scan and clustered-image map visualizations, they were able to analyze cancer-relevant proteins. Proteins highlighted included c-ErbB2 and E-cadherin.

Benjamin Kaplan-Singer
"The Role of Osteonectin in Breast Cancer Metastasis"
Preceptors: Jennifer Koblinski, Hynda Kleinman, Craniofacial Developmental Biology and Regeneration Branch, NIDCR



Unexpectedly, Kaplan-Singer's summer studies indicated that osteonectin does not affect cell proliferation, a result, he says, that suggests the need for a new approach to studying osteonectin's role. A graduate of Richard Montgomery High School in Bethesda, Md., Kaplan-Singer aspires to become a physician and researcher.

André Kydd (left)
"Improved Methods for Analyzing Simple Sequence Length Polymorphism Markers in Polysubstance Abuse-associated Regions of Chromosomes 4 (rSA3) and X (rSA16)"
Preceptors: George Uhl, Tomas Drgon, Molecular Neurobiology Research Branch, NIDA
Also pictured: Karolina Maciag, NCBI summer intern, whose "BLAST Optimization: Towards Speedier Sequence Searches" (preceptor: Alejandro Schaffer) was also featured that day

Genetically Modified Mouse Strains Available

The network of Mutant Mouse Regional Resource Centers (MMRRC), established to accept mutant mice from donating investigators for the purpose of transferring the strains to requesting investigators or institutions, now has six *available* strains. These genetically modified strains include models for studies of cardiovascular disease, cancer, diabetes, obesity, and epilepsy. Strains are supplied either from a production colony or from a colony recovered from cryopreservation.

Details of *available* strains as well as a list of *new* strains currently under development can be found at the MMRRC website—<**http://www.mmrrc.org/index.html**>—where investigators may now register their interest in new strains.

The site includes information on distribution policies and fees. Fees are intended to defray the costs of specialized mouse breeding, genetic quality control, animal health monitoring, and cryopreservation. Material Transfer Agreements, also reviewed at the website, are required to ensure fair and reasonable balance for donors and recipients in the sharing of these mouse strains among researchers for internal noncommercial research.

The MMRRC network is supported by NCRR and currently includes four repository-distribution facilities located at the University of North Carolina at Chapel Hill, the University of California at Davis, Taconic Farms in New York, and Harlan Sprague Dawley, Inc., in collaboration with the University of Missouri. Contact information for each MMRRC is available at the NCRR website at <**http//www.ncrr.nih.gov**> (linked from "announcements").

Each MMRRC facility is equipped to cryopreserve embryos or gametes, rederive strains as needed, and characterize the genetic and phenotypic makeup of the mutants so that models are validated and may optimally serve as models of human disease.

Efficient facility systems provide genetic quality control and disease safeguards. The MMRRCs offer expertise in the biology of laboratory mice—covering areas of cryobiology, genetics, comparative pathology, behavioral science, and infectious disease. ■

Recently Tenured

Thomas Dever *received his Ph.D. from Case Western Reserve University in Cleveland in 1990 and did postdoctoral work in the Laboratory of Molecular Genetics, NICHD, before joining NICHD's Laboratory of Eukaryotic Gene Regulation in 1994. He is now a senior investigator in the Laboratory of Gene Regulation and Development, NICHD.*

My research interest is the mechanism and regulation of cellular protein synthesis—what I like to call the ultimate step of gene expression. As a graduate student, I used biochemical techniques to characterize translation initiation factors—proteins that facilitate binding of the ribosome to an mRNA and selection of the AUG start codon for protein synthesis.

Fran Pollner

Thomas Dever

As a postdoc with Alan Hinnebusch, I continued my studies on translation initiation, investigating the roles of the factor eIF2 in control of *GCN4* expression in the yeast *Saccharomyces cerevisiae.*

We discovered that the yeast protein kinase GCN2 phosphorylates the α subunit of eIF2 to downregulate general translation while paradoxically stimulating *GCN4* mRNA translation. We went on to show that the human dsRNA-activated, antiviral kinase PKR could substitute for GCN2 in yeast, phosphorylate eIF2α, and stimulate *GCN4* expression.

In my lab, we continued to study the phosphorylation of eIF2α, focusing on the mechanism of kinase-substrate recognition. To overcome the inhibitory effects of PKR, most viruses express inhibitors of the kinase. We found that high-level expression of PKR in yeast is toxic and that co-expression of the vaccinia virus K3L protein, a pseudosubstrate inhibitor of PKR, suppresses this toxicity.

Mutational analyses demonstrated that a sequence motif shared between the K3L protein and eIF2α, and located around 30 residues from the Ser-51 phosphorylation site in eIF2α, is critical for eIF2α phosphorylation and for K3L protein inhibition of PKR. These results reveal an unexpected contribution of remote sequences to kinase-substrate recognition and indicate that phosphorylation site consensus sequences are not sufficient to characterize all kinase-substrate interactions.

In related studies, we used our yeast system to identify a novel eIF2α kinase inhibitor from baculovirus. This inhibitor resembles a truncated protein kinase. We are currently extending these studies using molecular genetic, biochemical, and structural techniques to identify the residues in PKR and GCN2 that contribute to the recognition of eIF2α and selection of Ser-51 as the phosphorylation site.

A second research focus in my lab is the GTP-binding protein IF2/eIF5B. In bacteria, the factor IF2 binds the initiator methionine tRNA to the ribosome, a function carried out by eIF2 in eukaryotic cells. We discovered an IF2 ortholog in yeast and humans and demonstrated that this protein, now called eIF5B, is a translation initiation factor.

Together with Tatyana Pestova at the State University of New York, Brooklyn, we showed that eIF5B is a ribosome-dependent GTPase that promotes subunit joining in the final step of translation initiation.

In collaboration with Stephen Burley at The Rockefeller University in New York, we determined the X-ray structure of eIF5B, revealing a chalice-shaped protein that undergoes lever-type domain movements upon GTP binding.

Our recent genetic and biochemical analyses revealed that GTP-binding regulates the ribosome affinity of eIF5B, and we are currently conducting structure-based mutational analyses to further our understanding of eIF5B function and the mechanism of GTP hydrolysis by eIF5B.

Protein synthesis is a somewhat underappreciated step in gene expression; however, recent studies have revealed the importance of translational regulation in cell growth, development, and human diseases.

By combining yeast genetics, molecular biology, biochemistry, and structural studies, we hope to provide new and critical insights into this final step of gene expression.

Eric Freed *received his Ph.D. from the University of Wisconsin–Madison in 1990. He did postdoctoral work at UW-Madison before joining the Laboratory of Molecular Microbiology (LMM), NIAID, in 1992. He is now a senior investigator in LMM.*

For a number of years my work has focused on understanding the molecular biology of HIV replication. When I began at NIH, the functional properties of most HIV proteins were poorly understood.

Our initial efforts were therefore focused on characterizing viral protein function. We were particularly interested in the Gag proteins, which direct virus assembly and release, and the envelope glycoproteins, which bind receptor and co-receptor and catalyze the membrane fusion reaction as the virus enters a host cell. We identified key regions of the Gag and envelope glycoproteins involved in the targeting and binding of Gag to the plasma membrane, Gag multimerization, membrane fusion, envelope glycoprotein incorporation into virions, and particle budding from the cell.

Fran Pollner

Eric Freed

As we learned more about the viral determinants of particle assembly and release, our work shifted to a greater emphasis on the complex interplay between viral and host factors. We are currently focused largely in two major areas: 1) elucidating the role that lipid rafts and other plasma membrane components play in HIV replication, and 2) defining the host cell machinery involved in virus particle budding and release from infected cells.

The plasma membrane, rather than being a uniform sea of lipid, contains a variety of microdomains with specific lipid and protein compositions. This concept sparked excitement in my lab. We have appreciated for many years that HIV virions contain high levels of cholesterol and glycosphingolipids relative to the host cell plasma membrane. Since cholesterol and sphingolipids are components of the so-called "lipid rafts," we asked whether HIV-1 Gag associates with these microdomains during virus assembly.

We found that a large portion of membrane-bound Gag is recovered in rafts

and that cholesterol depletion, which disrupts raft structure, markedly and specifically inhibits virus release. These results identify the association of Gag with lipid rafts as an important step in HIV-1 particle production and suggest a link between rafts and virus assembly. Ongoing studies will define the role of rafts throughout the virus replication cycle and explore the possibility that the Gag-raft association may be a target for the development of novel antivirals.

Early work from my lab indicated that deletion of the p6 domain of Gag markedly inhibits virus particle production from Gag-expressing HeLa cells. Examination by electron microscopy reveals that p6 mutation blocks a very late step in virus release, such that p6-mutant particles fail to pinch off and instead remain tethered to the plasma membrane.

It was recently demonstrated that the host protein TSG101 binds HIV-1 Gag in a p6-dependent fashion. We examined the impact of overexpressing a transdominant negative form of TSG101 on HIV particle assembly and release. Intriguingly, we observed that this truncated protein potently and specifically inhibits virus production by blocking budding. These results indicate that TSG101, which functions in the endosomal sorting pathway, plays a central role in HIV-1 budding. The results also demonstrate that TSG101 derivatives can act as potent and specific inhibitors of HIV replication.

A high priority for my lab's future research will be to understand fully the role that TSG101 and the endosomal sorting pathway play in HIV-1 release and to apply this knowledge to develop antivirals that block virus budding. We will also study in detail the role that host endosomal sorting pathways play in the budding of other enveloped viruses. Understanding the mechanism by which enveloped viruses have co-opted cellular machinery to promote budding from the plasma membrane will likely contribute important information to the fields of cell biology and virology.

Okihide Hikosaka *received his M.D. and Ph.D. from the University of Tokyo in 1973 and 1978 and did postdoctoral work at the NEI Laboratory of Sensorimotor Research (LSR) from 1979 to 1982. He held faculty positions at Tobo University School of Medicine in Tokyo, the National Institute of Physiological Sciences in Okazaki, and Juntendo University School of Medicine in Tokyo before returning to the LSR in 2002 as a senior investigator.*

Fran Pollner

Okihide Hikosaka

My original interest in neuroscience was to discover the neural mechanisms for "voluntary movement." This is still my major interest and goal. However, it became clear to me that voluntary movement includes or is related to many brain functions. Voluntary movement is a final outcome of brain functions, including attention, intention, learning, memory, and motivation, in addition to reflexes and fixed motor patterns. Accordingly, I have studied neuronal mechanisms underlying the following functions: 1) brainstem and basal ganglia networks, 2) procedural and motor skill learning, 3) attention and response selection, and 4) motivational control of behavior. My early research with Hiroshi Shimazu at the University of Tokyo involved brainstem mechanisms for saccadic eye movement (or simply saccade). The eye typically makes saccades two to four times per second when a person is awake—for example, as you are reading this article. We discovered and characterized a group of saccadic burst neurons that are inhibitory burst neurons. These neurons are essential for reading this article, for example.

I then studied the neuronal mechanisms of the basal ganglia with Bob Wurtz at the LSR. We demonstrated that the basal ganglia use inhibitory mechanisms to control movements: Neurons in the substantia nigra pars reticulata (output of the basal ganglia) normally exert tonic inhibitory effects on the superior colliculus (a command area for saccadic eye movement) and remove the inhibition when a saccade is necessary.

Wurtz and I found that the basal ganglia mechanism is especially critical when a saccade is guided by memory, not by vision. The behavioral paradigm to induce memory-guided saccades, which we devised, is now widely used. We also devised a now-widely-used method for reversible blockade of local brain function by muscimol injection. In Japan, working with Satoru Miyauchi and Shin Shimojo, I devised a new psychophysical method to measure the spatial distribution of attention, which is called "line motion effect." Using this method, we characterized the time course and spatial extent of stimulus-induced (bottom-up) and voluntary (top-down) attention.

I then turned my interest to more complex motor functions. Almost any kind of movement or procedure is at first difficult to perform and requires volitional control. But after repeated practice, it becomes easy and eventually nearly automatic. This is usually called procedural or motor skill learning. With many people in Japan, I studied the neural mechanisms of procedural learning and memory involved in learning a new task. Based on behavioral and physiological experiments, we proposed a parallel neural network model in which a sequential procedure is acquired and stored independently by two loop networks, including the cerebral cortex, basal ganglia, and cerebellum.

My current research focuses on the neuronal mechanisms of decision-making. Probably the most fundamental reason for making a decision is based on biological needs or expectation of reward, as in the pursuit of food and sex. This kind of decision-making may be described as "motivational," while decision-making based on rules may be described as "cognitive."

Using a new saccade task, we found that neurons in the basal ganglia are specialized for, if not exclusively involved in, motivational decision-making. We now plan to investigate more detailed mechanisms underlying motivational decision-making by combining pharmacological and neurochemical methods. We also plan to investigate how the two different kinds of decision-making mechanisms conflict, interact, or negotiate with one another in the brain.

Stephanie London *received her M.D. degree from Harvard Medical School in Boston in 1983. After completing an internal medicine residency at Massachusetts General Hospitalin Boston, she earned a D.P.H. degree in epidemiology from Harvard School of Public Health in 1989. She was an assistant professor in the Department of Preventive Medicine at the University of Southern California School of Medicine, Los Angeles,*

Recently Tenured

before joining NIEHS in 1995. She is currently an investigator in the Laboratory of Pulmonary Pathobiology, NIEHS.

My work deals with how genetic and environmental factors interact in the etiology of diseases of the lung. I began with the study of lung cancer over 10 years ago. During my six years at NIEHS, I have extended this effort to asthma—the major nonmalignant respiratory illness. I have developed a research program that is international in scope, taking advantage of variation in disease rates, allele frequencies, environmental exposures, and potential protective factors.

Stephanie London

Although smoking is the major cause of lung cancer, diet and genetics may influence how an individual responds to tobacco carcinogens. When I began my research in this area, there was little work on genetic susceptibility to lung cancer. In 1990, I initiated a case-control study of genetic susceptibility to lung cancer among African-Americans and Caucasians in Los Angeles. I have published on several genetic polymorphisms in pathways relevant to lung cancer with early findings on myeloperoxidase, which may influence oxidative stress in the lung, and *XRCC1*, a gene involved in DNA repair.

I was also interested in dietary and hormonal factors that can best be tested in a prospective study where samples and other data are collected prior to development of cancer. To test these hypotheses I developed a relationship with the Shanghai Cohort, a study of 18,244 followed since the late 1980s. We found a novel gene-diet interaction. Subjects with higher levels of a urinary biomarker of isothiocyanate from dietary intake of cruciferous vegetables were at reduced risk of lung cancer, but this preventive effect was limited to subjects null for *GSTM1*, who would be predicted to excrete these beneficial compounds more slowly (*Lancet* **356**:724–729, 2000). In these Shanghai samples I have also found that subjects with higher levels of insulin-like growth factor binding protein-3 are at reduced risk of lung cancer (*J Natl Cancer Inst* **94**:749–754, 2002).

In the past few years, I have concentrated most of my efforts on developing a coherent program of research into environmental and genetic factors in asthma, an area central to the NIEHS mission. At the University of Southern California, I was part of a small group of investigators who established a cohort study of respiratory effects of air pollution in Southern California children. After coming to NIEHS, I established a genetic component to this study. This subsequently has become a large extramurally funded project.

Childhood asthma is notable for wide geographic variation in rates–with lower rates in developing countries. This variation in rates does not appear to be due to differences in diagnostic access. Taking advantage of this variability, I have also developed studies of genetic and environmental factors in childhood respiratory illness among school-aged children in Wuhan, China, and Mexico City, Mexico. I am also planning a birth cohort study in Mexico City to examine the role of early life factors in the etiology of asthma. In addition, I have recently begun a collaboration to study genetic, dietary, and environmental factors in adult asthma and chronic bronchitis in an NCI-funded cohort study of Chinese Singaporeans.

Constantine Stratakis *received his M.D. and Doctor of Medical Sciences (Ph.D.) degrees from the National & Capodistrian University of Athens, Greece, in 1989 and 1994, respectively; he did predoctoral work there in the Unit of Endocrinology, Department of Experimental Pharmacology, before joining the Developmental Endocrinology Branch, NICHD, first as a student and then as a postdoctoral fellow in 1988. In 1990, he continued his postgraduate medical education at Georgetown University Medical School, Washington, D.C., where he finished a residency in pediatrics and two fellowships, in pediatric endocrinology (as part of the NICHD/GU training program) and in medical genetics and clinical dysmorphology. In 1996, he returned to the Developmental Endocrinology Branch, where he is now a senior investigator and chief of the Section on Genetics and Endocrinology.*

My interests are in the area of endocrine tumor cell development and function. This follows a long-time interest in how hormones and cancer relate.

During my research as a predoctoral student in Greece, I became interested in the regulation of growth hormone secretion and its function as a "growth factor." This work became the subject of my doctoral thesis.

During a subsequent medical clerkship in the Hospital Cochin, in Paris, France, I was introduced to adrenal gland genetics and physiology through Professor Jean-Pierre Luton, internationally known for his clinical studies on adrenal tumors.

I strengthened my ties to adrenocortical research in the late 1980s in the Developmental Endocrinology Branch, where pioneering research in adrenal development, oncology, and pharmacology was underway. As a postdoc, I was part of the team that identified the first mutations in the human glucocorticoid receptor in familial glucocorticoid resistance. I also was involved in some of the clinical studies on Cushing syndrome.

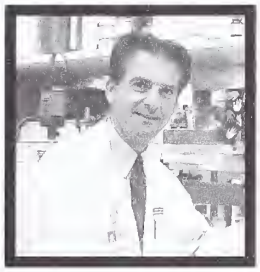
When I began my own laboratory in the branch, it was natural for me to pursue the work on adrenal tumor genetics. At this fortuitous time, the Human Genome Project (HGP) had just started providing geneticists with the tools to investigate questions that could not even be asked 20–30 years ago. These tools complemented NIH's unique resources and access to patient populations.

One of the first patient groups that attracted my attention had a relatively unknown, newly described syndrome, called Carney complex (CNC). These patients had inherited adrenal tumors, but they also had a variety of other manifestations, including pigmented spots on the skin and the mucosae; skin, breast and heart tumors, known as "myxomas"; and other endocrine and nonendocrine neoplasms. The disease was inherited as an autosomal dominant.

There were only a few known kindreds with this disorder in the entire world, but I had already been to two of the three places where most of these families had been seen: the NIH Clinical Center and Hospital Cochin. The third place, and the one with the largest collection of patients, was Mayo Clinic in Rochester, Minn., where J. Aidan Carney worked.

Collaboration with Carney allowed us to apply the tools of the HGP to DNA of

more than two dozen kindreds and led to the identification of the genetic loci of this disease in my lab. More recently, we cloned *PRKAR1A* as the gene that is mutated in approximately half of the patients with CNC (*Nat Genet* **26**:89–92, 2000).



Fran Pollner

Constantine Stratakis

CNC's complex clinical presentation and the involvement of many different organs suggested that the genetic defects responsible for CNC are important for basic functions of the human cells that are common among several tissues and organs. Indeed, the *PRKAR1A* gene that is mutated in CNC patients is present in almost all mammalian cells. It participates in the structure of an enzyme, protein kinase A (PKA), that regulates one of the most important cellular signaling pathways—that of cAMP. The defective gene encodes the most common regulatory subunit regulating PKA.

In the normal physiologic state, this regulatory subunit appears to act as a tumor suppressor (albeit not a classic one). When its action is abolished (as in patients with CNC who have inactivating mutations of that gene [*Hum Mol Genet* **9**:3037–3046, 2000]), tumors of various organs ensue.

This knowledge added significantly to what was known about PKA and its possible involvement in tumorigenesis, but it also raised important questions. Currently, two animal models constructed by our laboratory are addressing the participation of *PRKAR1A* in endocrine cell growth and neoplastic development. We are also trying to find what other genes are mutated in CNC patients. Preliminary evidence suggests that two (or more) genes interact in the process of tumorigenesis in CNC tissues.

In addition, we are screening several sporadic tumors to identify mutations or functional dysregulation of the *PRKAR1A* gene and/or the PKA system. We recently found downregulation of this gene in thyroid carcinomas from patients who had no genetic syndromes (*Genes, Chromosomes & Cancer*, in press). We are also using microarray technology to identify genes that interact with *PRKAR1A* in mouse and human cell lines, as well as to investigate the genetics of noninherited adrenocortical tumors. We are studying forms of bilateral adrenal hyperplasia (both cortisol- and aldosterone- producing), adrenocortical cancer, and single adrenocortical adenomas.

We have identified a locus for idiopathic hyperaldosteronism on chromosome 7 (*J Med Genet* 37:831–835, 2000). Recently, in collaboration with a group in Brazil, we identified a novel *TP53* genetic defect that predisposes individuals to the development of adrenal tumors (*Proc Natl Acad Sci USA* **98**:9330–9335, 2001) in a unique way: Functional effects of this mutation depend on the pH of the cellular microenvironment.

Our work on adrenal cortex would not be complete without looking at patients with the opposite defects, namely, those with adrenocortical hypoplasia. The identification of genes with a role in fetal adrenal development is an important addition to the understanding of the neoplastic processes affecting this gland. Our group has identified mutations in both isolated glucocorticoid deficiency and triple A syndrome (*J Clin Endocrinol Metab* **86**:5433–5437, 2001).

We hope that this work will lead to better molecular elucidation of endocrine cell development and neoplastic evolution and, ultimately, to better treatments for patients, especially those with adrenal cancer, currently a disorder with dismal prognosis. ■

Salzman Award

The Foundation for the NIH and the NIH Virology Interest Group announce the Fourth Annual Norman P. Salzman Memorial Award in Virology. This award has been established to recognize an outstanding research accomplishment by a postdoctoral fellow or research trainee working in the field of virology at NIH. The award honors Salzman's 40-year career in virology research and his accomplishments in mentoring young scientists. The winning fellow will receive a plaque and an unrestricted gift of $2,500; the mentor will receive a plaque. Information about the award and the Norman P. Salzman symposium to be held at NIH on **November 7th** can be found at the interest group website:

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

Application deadline for the award is **September 21, 2002**. ■

Grand Rounds With Great Teachers

The 2002–2003 series of NIH/CC Grand Rounds in Contemporary Clinical Medicine opens September 18 and continues monthly through June—**12 noon to 1:00 p.m., Wednesdays**, in the Lipsett Amphitheater, Building 10.

- **September 18: Thyroid Disease**, Daniel Federman, Harvard Medical School, Boston
- **October 9: Developmental Disabilities**, Martha Bridge Denckla, Johns Hopkins University School of Medicine, Baltimore
- **November 13: Arthritis**, Nathan Zvaifler, University of California, San Diego
- **December 11: Osteoporosis**, Clifford Rosen, Maine Center for Osteoporosis Research and Education, Bangor
- **January 15: Pain**, Kathleen Foley, Memorial Sloan-Kettering Cancer Center, New York
- **February 12: Asthma**, Jeffrey Drazen, Harvard Medical School
- **March 12: Surgery with Extracorporeal Membrane Oxygenation**, Robert Bartlett, University of Michigan Medical Center, Ann Arbor
- **April 9: Electrolyte Disorders**, Robert Narins, American Society of Nephrology
- **May 14: Depression**, Charles Nemeroff, Emory University School of Medicine, Atlanta
- **June 11: Thinking about Infectious Disease**, John Bennett, NIAID

This CME series carries a maximum of 48 hours in category 1 credit toward the AMA Physician Recognition Award.

For reasonable accommodations, call 496-2563 at least five business days in advance. Lectures will be videocast: **<http://videocast.nih.gov>**.

Honored Mentors

Nominees for the 2002 NIH Distinguished Clinical Teacher's Award (DCTA) will be honored at the Clinical Center Grand Rounds, **September 25, 12:00–1:00 p.m.**, in the Lipsett Auditorium. The DCTA is the highest honor bestowed collectively by the NIH Clinical Fellows on an NIH senior clinician, staff clinician, or tenure-track/tenured clinical investigator for excellence in mentoring, teaching, and research. Clinical Fellows from nine institutes nominated 14 individuals. They are:

- NCI: H. Richard Alexander, Maria Merino, Thomas Walsh
- NHLBI: John Barrett, Cynthia Dunbar
- NIA: Josephine M. Egan
- NIAID: Steve Holland
- NIAMS: Gregory Dennis
- NICHD: Lynnette Nieman, Owen Rennert
- NIDDK: Jay Hoofnagle
- NIMH: Trey Sunderland
- NINDS: Mark Hallett, Barbara Karp

Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: the IRP's special resources, the IRP role in advancing CAM research, NIHers' response to 9/11 and the anthrax mailings, and what happens after summer students go back home. **Send your responses on these topics or your comments on other intramural research concerns to us via e-mail: <catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2W23.**

In Future Issues...

- Emerging Center For Emerging Diseases
- GME: Rising To New Demands
- Building 50 Revisited

1) How can intramural scientists take maximal advantage of the special resources of the IRP?

2) What special role can the IRP play in advancing research in complementary and alternative medicine?

3) Are you aware of other ways NIH staff responded to the events of 9/11 and the anthrax mailings?

4) From time to time, the *Catalyst* learns that a former NIH summer student has been honored in one way or another for research that began during their summer "vacation" here. We'd like to collect vignettes for a story in an upcoming issue. Do you have any such items to send us?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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