

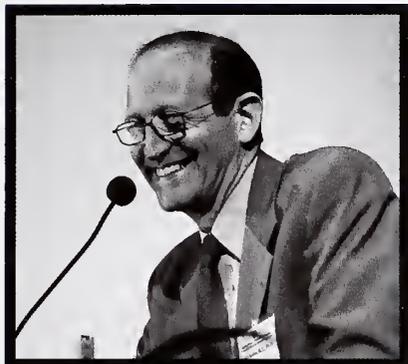
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VRC Celebrates 5th MOVING VACCINOLOGY FROM BASIC SCIENCE TO GLOBAL HUMAN TRIALS

by Fran Pollner



Bill Branson

VRC Director Gary Nabel

By the tender age of five, the VRC had launched 14 clinical vaccine trials and generated 14 clinical-grade vaccines that entailed 31 vaccine runs, one for each of the individual components of the tested vaccines.

Eight of the vaccines were anti-HIV candidates, and the other six were targeted against the likes of the Ebola, West Nile, and SARS viruses, VRC Director Gary Nabel recounted as he took stock of the VRC's accomplishments and the road ahead on the occasion of the center's fifth anniversary.

That disease breakdown reflects the VRC's original and continuing focus on HIV and AIDS, as well as its early, logical expansion into related emerging challenges.

The scope of VRC activities also reflects the concept behind its creation—to house in one facility the human and physical resources to develop vaccines from start to finish, from basic research to vaccine production and clinical trials, ob-

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Building 33 Dedicated May 2 BIODEFENSE AND EMERGING INFECTIOUS DISEASES RESEARCH BUILDING READIED FOR PRIME TIME



Ernie Branson

On Deck: (left to right) Rep. C.W. Bill Young (R-Fla.), for whom the new building is named, is joined by NIH Director Elias Zerhouni and NIAID Director Anthony Fauci alongside the Building 33 commemorative plaque, which reads:

"By Act of Congress This Building is Dedicated as the
C. W. Bill Young Center

The C.W. Bill Young Center for Biodefense and Emerging Infectious Diseases is the first NIH facility to focus exclusively on the challenge of biodefense and research on new or re-emerging infectious diseases that pose significant public health risks. Representative Young's service in the U.S. Congress for more than 35 years includes six years as Chairman of the House Committee on Appropriations, two separate terms as chairman of the Subcommittee on Defense, eight years as Chairman of the Health Appropriations Subcommittee, and 14 years on the House Permanent Select Committee on Intelligence. Founder of the national registry of bone marrow donors, Representative Young has been tenacious in his support of patients and scientists, the biomedical research enterprise, and all those who defend the Nation.

Dedicated May 2006"

The vision of the building dedicated on the NIH campus in May 2006 started taking shape in the fall of 2001—it rose from incinerated buildings and powdery envelopes in the New York and Washington, D.C., areas.

Accelerating research to defend against bioterrorism was a driving force behind the concept of Building 33.

But its development—like that of the NIAID biodefense research agenda and strategic plan, issued in early 2002—was firmly grounded in the context of emerging and re-emerging infectious diseases.

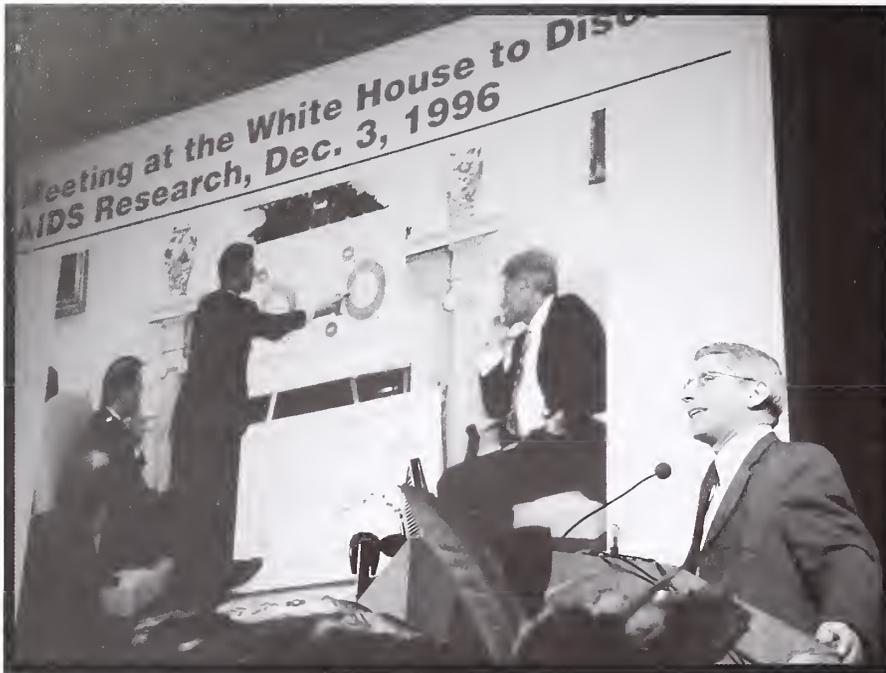
The science does not turn on whether the involved pathogens "are naturally continued on page 3

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VRC'S FIFTH

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Bill Branson

The Dawn of Creation: NIAID Director Anthony Fauci (right) traces the beginnings of the VRC to December 1996, when he and then-NIH Director Harold Varmus were invited to the Oval Office to explain HIV science to President Bill Clinton and Vice President Al Gore. The historical photo shows Fauci describing the CCR5 receptor to Clinton (right) and Gore (left), with Varmus (far left) looking on. By the end of the session, Fauci quipped, "Vice President Gore was wondering whether he had actually discovered the CCR5 receptor"—and Clinton was convinced of the need to create a center that would encompass all aspects of developing an AIDS vaccine, from basic research through vaccine production. It was five months later, in May 1997, that Clinton announced that the VRC was on the drawing board.



Bill Branson

Harmonic Convergence: (left to right): VRC Director Gary Nabel, Pontiano Kaleebu, assistant director of the Uganda Virus Research Institute, Entebbe, and president of the WHO AIDS vaccine program; Barney Graham, chief, Viral Pathogenesis Laboratory and Clinical Trials Core, VRC; and Stanley Plotkin, world-renowned vaccinologist

served NIAID Director Anthony Fauci, who triggered the memories of the assembled celebrants with a bit of VRC history.

Homing in on AIDS vaccinology, Nabel discussed the details of the VRC's recent advance into Phase II clinical testing of its multigene, multiclade DNA-prime/adenovirus-boost AIDS vaccine.

The six-plasmid construct contains versions of HIV genes *gag*, *pol*, and *nef*, as well as three modified *env* genes, one from each of clades A, B, and C.

Designed to cover the major subtypes found throughout the world, the vaccine will be tested at sites in the United States, Brazil, Haiti, Jamaica, Botswana, and South Africa.*

Each component underwent testing alone and in combination in the DNA construct, in the adenovirus vector, and then in the prime-boost sequence. "The DNA-adenovirus plat-



Bill Branson

Engineering Immunity: Two of the guest speakers—Stephen Harrison (left), Howard Hughes investigator and Harvard structural biologist, and David Baltimore, president of the California Institute of Technology in Pasadena, discussed strategies to bring neutralizing antibodies to bear against HIV, a quest VRC Director Gary Nabel called the "Holy Grail" of AIDS vaccine development

form proved to be an effective immunogen in humans, which we did not know before," Nabel said, noting that the prime-boost response is "greater than the sum of its parts."

Eliciting broadly neutralizing antibodies remains a challenge, which is being addressed in ever more sophisticated ways, he said.

Another global priority, Fauci noted, is to develop a vaccine that would obviate the need to reconstruct the flu vaccine each year. Such a universal vaccine for seasonal, or standard, flu would also obviate the need to respond in a crisis manner to potential pandemic flu, he observed. ■

* The VRC vaccine is also being tested by the International AIDS Vaccine Initiative in Phase I studies in Kenya and Rwanda and by the U.S. Military HIV Research Program in Phase I and II studies in Uganda, Kenya, and Tanzania.

BUILDING 33 DEDICATION

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occurring or deliberately perpetrated," NIAID Director Anthony Fauci observed in a speech during the ceremony to dedicate the brick, glass, and steel structure where that research will now be concentrated.

The new facility, Fauci noted, will enable the "gathering under one roof of a critical mass of researchers currently scattered in many buildings around this campus," whose work with a variety of respiratory viruses and bacteria will benefit from the "creative synergies" fostered by the new infrastructure.

The building houses animal care-areas, conference rooms, offices, and biosafety level 2 and 3 laboratories—adding another 14,300 square foot of BSL-3 lab space to NIAID's current 4,700 square feet. Researchers



Ernie Branson

Building 33, NIH Director Elias Zerhouni noted with pride, emerged "on time, on budget," but had obstacles to overcome, not the least of which was the concern of the surrounding Bethesda community about potential environmental risks. Detailed explanations of the building's design, security, and safeguards were not quite convincing enough, Zerhouni recalled. "But then I told them that I guarantee that Tony Fauci will have his office right in the middle of that building—and that won the day!"

working in the BSL-3 labs will wear special protective equipment and receive specialized training in state-of-the-art techniques for handling BSL-3 pathogens.

The new center will consolidate and expand NIAID's existing research programs on

- Respiratory viruses (such as influenza and avian flu)

- Respiratory bacteria, such as multidrug-resistant TB and anthrax)

- Insect-borne viruses (such as West Nile and dengue)

- Immunology of infectious diseases

- Development of vaccines for infectious diseases

A new program focusing on innate immunity will also be established in Building 33. Fauci noted that pathogens requiring BSL-4 facilities will not be studied in the new center.

—Fran Pollner



Fran Pollner

The latest addition to the NIH research complex. Building 33 will house about 250 laboratory, administrative, and support staff within its four stories and 12 intramural research laboratories. Construction was begun in November 2003 and completed in December 2005; move-in is anticipated throughout the summer of 2006.



Bill Branson

Flanked by NIAID Director Anthony Fauci and NIH Director Elias Zerhouni, Rep. C.W. Bill Young receives gifts of gratitude for his "unwavering support for biomedical research"—an artist's rendering of Building 33 and a certificate commemorating the day's event

NEW NCCAM FELLOWS TO CREATE BRIDGE BETWEEN CAM AND CONVENTIONAL RESEARCH

by Leikny Johnson, NCCAM



Fran Pollner

The Upside of Three on a Match: NCCAM fellow Marni Silverman (center) and her two mentors, NIMH's Esther Sternberg and NCCAM's Patrick Mansky. "Marni," says Sternberg, "is the glue between us."

The first two winners of the NCCAM Director's Fellowship have been named: Marni Silverman, whose doctorate is in neuroscience, has already arrived at NIH, and Patrick McCue, whose degree is in molecular and cellular biology, is due in July.

Silverman began work at NIH in February after receiving her Ph.D. in neuroscience from Emory University in Atlanta.

Her motivation in applying for the NCCAM fellowship, she says, was to examine the "physiological and molecular mechanisms by which CAM therapies, or mind-body interventions, are effective in alleviating depressive symptomatology in the medically ill."

She is based in the lab of Esther Sternberg, head of the Section on Neuroendocrine Immunology and Behavior, NIMH. Her selection in the NCCAM competition was based not only on her own qualifications and the nature of the proposed research but also on the capabilities and relevance of the lab she designated as her desired base. "There had to be a good match between the postdoctoral fellow and the lab," Sternberg notes.

The Cortisol Connection

Silverman's fellowship comprises two

research projects: One explores the relationship of glucocorticoid resistance and inflammation vulnerability to genetic variants in the glucocorticoid receptor

(GR); the other explores the effects of tai chi on the quality of life of cancer survivors.

Glucocorticoids such as cortisol are

Fellowship Promotes Evidence-based CAMaraderie

Complementary and alternative medicine (CAM) is used by 36 percent of American adults to treat a spectrum of diseases and conditions. Because of the breadth of health conditions for which CAM is used, NCCAM has collaborated in its research efforts with many of the NIH institutes and centers (ICs).

Recently, NCCAM created a new collaborative program—the NCCAM Director's Fellowship—to promote the training of promising young CAM investigators by supporting their work in the intramural laboratories of senior scientists in other ICs. Ultimately, the fellows will serve as a bridge between their mentor's laboratory and NCCAM.

The fellowship, says NCCAM Director Stephen Straus, "exemplifies our approach to promoting the integration of evidence-based CAM practices into conventional biomedicine."

It also provides an innovative means through which NCCAM can recruit and train the next generation of CAM researchers, he observes, noting that the program has gained wide support throughout NIH. That support has been rewarded, he observes, by the "excellence" of the program's inaugural awardees—Marni Silverman and Patrick McCue.

The fellowship provides full research support for two years of clinical, translational, and/or laboratory research. It is funded by NCCAM in partnership with the Prince of Wales Foundation through the Foundation for the NIH.

—Leikny Johnson

the brain's messengers in mediating the body's stress response and are potent modulators of the immune system, Silverman notes.

"Intriguingly," she says, "we can study both ends of the workings of cortisol, from the [mechanisms by which] cells receive the cortisol signal to the effect of tai chi on cortisol levels."

Noting that her dissertation centered on neuroendocrine-immune interactions—cytokine activation of glucocorticoid responses—Silverman says she is eager to piece together the genetic component of this dynamic and the related behavioral interventions that can have a clinical effect.

The project, observes Sternberg, "fulfills both objectives" of the NCCAM director's fellowship—"basic research relevant to the [patient-care] issue and clinical research central to the issue."

In the basic-research project, Silverman is hoping to substantiate a role for genetic variants of GR in the susceptibility to inflammatory syndromes that could be extended to immune-re-



Patrick McCue

James Phang

lated diseases, such as asthma and rheumatoid arthritis.

This research might also shed light on reasons for individual differences in responsiveness to CAM therapies, Silverman says.

A Step Beyond Cancer Survival: Comparing Tai Chi And Physical Exercise

In her second project, Silverman plans to explore changes in neuroimmune markers in cancer survivors practicing a mind-body intervention such as tai chi compared to physical exercise.

For this project, she is collaborating with NCCAM's Patrick Mansky, who is

studying the efficacy of Tai Chi versus moderate exercise to reduce stress and improve metabolic parameters and physical and psychological well-being in adult cancer survivors.

The NCCAM Director's Fellowship served as the vehicle for the first collaborative contact between Mansky and Sternberg. Without that vehicle, Sternberg observes, this valuable exploration might have been viewed as a diversion of lab resources.

Botanical Extracts And Cancer Prevention

McCue received his Ph.D. in molecular and cellular biology from the University of Massachusetts at Amherst and is currently at the Genome Research Facility at the NASA Ames Research Center, Moffett Field, Calif., where he is investigating herbal antioxidants as countermeasures for radiation injury.

In July, he will be joining the Laboratory of Comparative Carcinogenesis, NCI-FCRDC, where he will work with James Phang, who heads the Metabolism and Cancer Susceptibility Section.

When asked what attracted him to CAM research, McCue pointed to the "challenge of applying cutting-edge research techniques to the study of CAM modalities" and contributing to a science-based perspective that generates a better understanding of how such therapies work.

He plans to investigate the chemopreventive mechanisms of action of botanical extracts against cancer cells using a functional genomic approach.

The underlying hypothesis is that phenolic antioxidants in the extracts may promote apoptosis by modulating the link between the proline and pentose phosphate pathways.

He will enlist high-throughput technologies, high-density DNA microarrays, computational biology, and bioinformatics in the investigation of this hypothesis. ■



Fran Pollner

Good Fellowship: (left to right): Patrick Mansky, NCCAM clinician; Marni Silverman, NCCAM director's fellow; Esther Sternberg, NIMH section head; and Andrea Deak, NIMH postdoc in Sternberg's lab, chose a photogenic place in the Clinical Research Center to hold a meeting to discuss Silverman's NCCAM fellowship projects, which connect the research interests of both ICs

For more information about the NCCAM Director's Fellowship, see http://nccam.nih.gov/about/jobs/dir_fellowship.htm.

*Bench-to-Bedside Journey to Morocco***NOVEL STRATEGY TO VANQUISH INTRACTABLE CANCER PAIN: RESINIFERATOXIN AT THRESHOLD OF CLINICAL TRIAL**

by Karen Ross



Karen Ross

Michael Iadarola

Michael Iadarola, chief of the Neurobiology and Pain Therapeutics Section, NIDCR, and anesthesiologist Andrew Mannes, who works both in Iadarola's laboratory and in the Clinical Center, are leading an effort to bring a new pain-relieving drug, called resiniferatoxin or RTX, to the clinic.

RTX is intended for patients with advanced cancer whose pain is not alleviated by morphine or other currently available drugs. It is almost ready for a Phase I clinical trial, thanks in part to Iadarola's 2001 Bench-to-Bedside Award that funded critical parts of the translational work.¹

Opioids and Cancer Pain

Patients with advanced cancer often experience severe pain. Many, but not all, patients can control their pain with high doses of morphine and other opioids—but at the cost of a host of debilitating side effects, including impaired consciousness, nausea, vomiting, and constipation. And for patients who do not get relief from morphine, there are not a lot of options.

Iadarola estimates that there are currently 50,000–100,000 cancer patients who either cannot control their pain or have a dismal quality of life because of the side effects of their pain medication. Iadarola and Mannes hope that their novel strategy for pain relief can help this population. “We want to take pain

out of the equation,” says Mannes.

Opioids work by binding to receptors on pain-sensitive neurons and inhibiting transmission of pain signals to the brain. However, animals have evolved to remain sensitive to pain as long as the tissue injury remains and the pain-sensing neurons are intact. “If [the painful stimulus] is still happening at the periphery, it's going to get through the spinal cord and up to the brain one way or another,” says Iadarola.

With long-term use, opioids gradually lose their effectiveness and patients need progressively higher doses to get pain relief.

Killing the Messenger

In contrast, RTX is a non-opioid, nonaddictive analgesic that works by selectively killing the neurons that are responsible for cancer pain while leaving other neurons intact. RTX, explains Iadarola, “is like a molecular scalpel.”

RTX is a naturally occurring substance found in a species of a Moroccan cactus-like succulent plant. People have used latex from this cactus for topical pain relief and other medicinal purposes for thousands of years.

The molecular structure of RTX resembles that of capsaicin, the active ingredient in hot peppers.² RTX and capsaicin both bind to the same neuronal receptor, an ion channel called TRPV1 or the vanilloid receptor-1, but RTX binds 500 to 1,000 times as tightly.

Capsaicin binding causes the TRPV1 channel to open briefly, allowing a limited amount of calcium and sodium ions to flow into the cell and generating the burning sensation associated with eating hot peppers. RTX, in contrast, holds the channel wide open for a long time, flooding the cell with a toxic level of calcium ions. It can also cross the plasma membrane and release calcium ions from

intracellular storage compartments.

Within an hour of exposure to RTX, neurons expressing TRPV1 die, and they do not grow back. Cells that do not express TRPV1 are unaffected. Only a few types of neurons in the body express TRPV1, so the effects of RTX treatment are quite specific.

The cell bodies of TRPV1-positive neurons are found in the dorsal root ganglion, and their nerve endings are in the skin, where they respond to sensations of moderate heat, and in the internal organs, where, importantly, they appear to be the main mediators of cancer and inflammatory pain.

Early Findings

Iadarola and his colleagues have long been interested in clinical treatments for severe pain and in the basic science behind the sensory detection of painful stimuli (nociception) and the transmission of pain signals to the brain. (Pain in humans is a combination of nociception and higher-order sensory, psychological, and emotional responses.) Their experience in both of these areas put them in an ideal position to recognize the potential of RTX for pain relief.

On the clinical side, they were already testing strategies for specifically killing pain neurons. On the basic-science side, they were interested in TRPV1's role in the early stages of nociception.



Fran Pollner

Andrew Mannes

In an effort to better understand signaling through the TRPV1 receptor, Zoltan Olah and Laszlo Karai, scientists then in Iadarola's lab, treated cells that expressed a fluorescently labeled form of TRPV1 with RTX and examined them under the microscope. To their amazement, the cells underwent a dramatic death. These studies "gave us the insight" into how RTX could work as a painkiller, says Iadarola.

After completing studies in rats that suggested that RTX was effective at reducing pain, Iadarola's lab teamed up with Dorothy Cimino-Brown, a veterinarian at the University of Pennsylvania in Philadelphia, to try RTX as a pain reliever in dogs with naturally occurring bone cancer.

Preempting Euthanasia in Dogs

The dogs enrolled in the study had severe pain that was not well controlled by available analgesic medications, and their owners were considering euthanizing them. They received a single injection of RTX into the fluid around the spinal cord so the drug would bathe the dorsal root ganglia. RTX is very painful for the first hour or so after administration, so the dogs were placed under general anesthesia for treatment.

The results were impressive. All of the dogs experienced significant pain relief that lasted for the rest of their lives. One dog that had only walked on three legs due to pain from a large tumor on his foreleg trotted almost normally through the clinic with his tail wagging several weeks after treatment. Moreover, RTX did not negatively affect locomotion, coordination, bowel and bladder function, or behavior in any of the animals.

Encouraged by the results in dogs, Iadarola and Mannes are currently developing RTX for testing in humans, which has immersed them in the complex and sometimes frustrating world of translational medicine.

Going by the Book

Before a new drug can be used in humans, researchers must obtain a very high quality batch of the drug and conduct formal toxicology studies that meet the FDA's specifications, and they must design a clinical protocol for administering it.

To meet the first requirement, the team has relied heavily on the assistance of James Terrill, of the Division of Phar-

macotherapies and Medical Consequences of Drug Abuse at NIDA, who has extensive experience with the FDA's procedures and requirements for new drugs, says Iadarola. In this realm "definitions of words [such as "impurity"] are a little bit different from the way we normally think of them," he says.

After some false starts, the group now has a batch of RTX that qualifies for use in humans. Their clinical protocol is also well on its way, awaiting final approval from the NCI's Institutional Review Board.

They expect to begin toxicology studies in the animals this summer, and if all goes well they will move on to a Phase I clinical trial in humans. Mannes is the PI and Iadarola the associate PI on the protocol, entitled "A Phase I study of the intrathecal administration of resiniferatoxin for treating severe refractory pain associated with advanced cancer."

They plan to enroll patients at NIH who have advanced cancer and are no longer seeking curative therapy. Although the purpose of the Phase I trial is to establish the safety and optimal dose of RTX, they hope that some of the patients in the study will also get relief from their pain.

A Fine Translation

Iadarola emphasized the importance of having a supportive environment in which to do translational research.³ Studies that are essential to preparing a drug for the clinic are not the types of research that are rewarded by the basic-science community, he says. Iadarola praised the members of his laboratory for their independence and their ability to advance the lab's basic-science projects while he was busy with tasks such as importing 40 liters of cactus resin from Morocco's Atlas Mountains.⁴

Iadarola and Mannes are cautiously optimistic about RTX's future. "There's a [saying] around the NIH that if there was ever a mouse or a rat that had cancer or pain, we'd be able to treat it," says Mannes. While many of these seemingly successful therapies do not live up to their promise in humans, the investigators observe they have reason to hope that the therapeutic effects of RTX will be more extrapolatable.

The dramatic relief it afforded dogs with naturally occurring cancer—the clinical correlate of what could be expected based on its mechanism of ac-

tion—informs their very best guess that the drug will also be safe and effective in patients with heretofore severe intractable pain. ■

Footnotes

1. The Bench-to-Bedside program funded some of the initial animal work, the purchase of the initial *Euphorbia resinifera* latex from Morocco, and the costs of drug purification to meet FDA regulatory guidelines. Additional funding came from Iadarola's laboratory budget and, importantly, from the NIDA division headed by Frank Vocci, with which the Iadarola lab collaborated in preparing the drug for toxicologic studies.

2. The fact that RTX is a capsaicin analog was discovered in unrelated research by NCI's Peter Blumberg (see *The NIH Catalyst*, March-April 1997, "The Capsaicin Story: Some Like It Hot"). Blumberg was working with tumor-promoting phorbol esters and found that the non-capsaicin part of RTX has structural similarity to phorbols, though it does not have tumor-promoting actions.

3. In addition to the Bench-to-Bedside program, the primary facilitator of the research, and their NIDA collaborators, Iadarola and Mannes cite the Pharmaceutical Development Section of the NIH Pharmacy, run by George Grimes, and the NCI Protocol Review and Monitoring Committee and the NCI IRB for their help with issues related to cerebrospinal fluid volume in humans, starting-dose justification in extrapolating from animals, and dose escalation.

4. The team worked with Ahmed Benharref, of the Laboratory of Natural Chemical Products at the Université Cadi Ayyad in Marrakech, and Charles Dahhan, of the United States and Morocco, who handled international coordination and export licensing. Although the plant is not endangered and the latex-collection procedure involves a gentle scoring of the skin surface that does not damage the plant, the investigators had to secure phytosanitary clearances in accordance with the Cooperative International Treaty on Endangered Species. ■

ON THE ROAD TO DOCTORAL DEGREES: NIH GRADUATE STUDENTS EMERGE FROM THEIR LABS TO REVEAL THEIR RECENT FINDINGS

The Graduate Partnerships Program (GPP) is NIH's contribution to the training of graduate students who are working toward a degree in the biomedical sciences at accredited universities in the United States and abroad. The university partners provide the coursework and the degree, and, in some cases, research advisors; NIH provides the labs, NIH research mentors, and hands-on research training.

There are now about 370 students in the GPP, and that number will top 400 when the new students arrive this summer. The students come from more than 100 universities—about 62 percent based in the United States and 38 percent elsewhere.

The third annual GPP graduate student research symposium took place May 5. Seventy-six of the students presented posters; 11 gave talks on their research.

Judged on the basis of "organization, clarity, and scientific significance," 20 of the posters were designated "finalists." From this cohort, three were selected as winners (see footnote, next page).

Following are brief reports on two of the 76 posters.

HARNESSING THE ANTITUMOR EFFECT OF AN IMMUNOSUPPRESSANT FOR LUNG CANCER PREVENTION

"Rapamycin, an inhibitor of mTOR, decreases tobacco carcinogen-induced lung tumorigenesis"

Courtney Granville, George Washington University, Washington, D.C., Graduate Program in Genetics

NIH research advisor: Phillip Dennis, investigator, Medical Oncology Branch, NCI-CCR

Granville's research project, which was one of 14 selected for oral presentation at the GPP Research Symposium, explored further the role of tobacco-activated mTOR in the induction of lung cancer, as well as the inhibition of mTOR in the prevention of lung cancer and the amelioration of existing tumors.

The Dennis lab had previously shown that tobacco components activate the Akt/mTOR pathway.

In the current project, the team treated mice that had been exposed to a specific tobacco carcinogen with rapamycin, an mTOR inhibitor that is also an immunosuppressant approved by the FDA to prevent post-transplantation graft rejection and to coat arterial stents.

Rapamycin works as an immunosuppressant by squelching T-cell proliferation and function, Granville noted; it has been studied in tumor models and found to shrink existing tumors.

In the current study, Granville and her colleagues showed that to-



Fran Pollner

Courtney Granville

bacco carcinogen-induced lung tumorigenesis depends on mTOR and that rapamycin-mediated inhibition of mTOR prevented the development of lung lesions in carcinogen-exposed mice. The action of rapamycin before the emergence of observable lesions had not previously been demonstrated, Granville noted.

This ability to suppress tumorigenesis "provides a rationale to test mTOR inhibitors in smokers at high risk for lung cancer," Granville wrote in her abstract. She noted in an interview, however, that the immunosuppressive action of rapamycin would necessarily inspire

Now a fourth-year student in the graduate genetics program at George Washington University in Washington and already the holder of a master's degree in public health, Courtney Granville has been working in the NCI lab of Phillip Dennis for three years, drawn there, she says, by the lab's "emphasis on tobacco-related lung cancer and the environmental causes of disease in general." Equally important is the "translational nature of the lab's research." The science, Granville says, "is very real and very applicable." She wants to focus her career on chemoprevention and can envision working in academia or a regulatory agency.

great caution in considering it as a preventive agent, even in heavy smokers.

That rapamycin might be useful as a cancer preventive was suggested, however, in a study reported last year: Transplant patients who received rapamycin exhibited a decreased incidence of de novo malignancies, compared with transplant patients who had received other immunosuppressive drugs.

Figuring out how to maximize rapamycin's antitumor effect while minimizing its immunosuppressive effect would be a worthy pursuit for future studies, Granville said.

—Fran Pollner

PARENTAL ALCOHOL USE REFLECTED IN BRAIN MEASUREMENTS OF ADULT ALCOHOLICS

"Influence of parental alcoholism on brain volumes in alcoholics"

Jodi Gilman, Brown University, Providence, R.I. Graduate Program in Neuroscience

NIH research advisor: Daniel Hommer, chief, Brain Electrophysiology and Imaging, Laboratory of Clinical and Translational Studies, NIAAA

Images of the brains of alcoholics pose general questions regarding cause and effect and particular questions regarding genetic versus environmental causes.

Jodi Gilman and her NIAAA co-workers aimed to tease out the effects of alcoholism and the influence of parental history on brain structure and function in adult alcoholics.

Study volunteers were alcoholics seeking inpatient treatment at the NIH Clinical Center. Sixty-four men and 27 women had no family history of parental alcoholism; 96 men and 60 women had at least one heavy-drinking or alcoholic parent.

Using MRI, the team measured intracranial volume (ICV), cerebral brain volume, and white and gray matter volume.

Consistent with reported findings in previous studies, the entire cohort of alcoholics had smaller-than-average brain volumes. Beyond that, however, the alcoholics with a positive family history had significantly smaller ICVs than those with

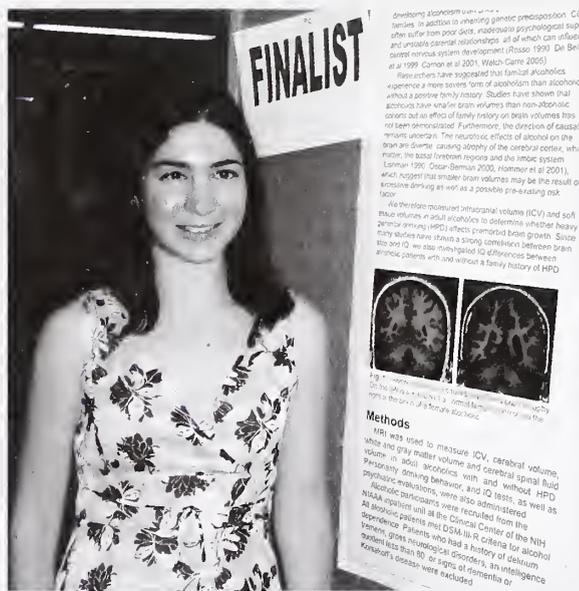
unaffected parents, a finding not previously demonstrated.

Unlike the cerebral cortex, which is subject to alcohol-induced atrophy, ICV is a particularly intriguing measure, Gilman said, because it reaches its permanent size by about age 12 to 16. Factors operating during the time between conception and puberty, therefore—not the individual's alcoholism—would be in play.

"We have a lot more to study," Gilman noted, listing functional MRI studies; looking at the influence of family history on the size of different parts of the brain, such as the frontal lobe; looking more deeply at the cognitive and emotional impact of family history; analyzing the impact of age at drinking onset on measures; and, of course, "everyone is still looking for genetic factors."

The fact, however, that people have been looking for genetic factors for decades inclines Gilman to accord a greater role to environmental reasons to account for why children of alcoholics are at a fivefold increased risk of becoming alcoholics themselves.

The stress of growing up in an environment where heavy alcohol consumption is a fact of daily life might account,



Fran Pollner

Jodi Gilman

The field of neuroscience, Gilman says, is "awesome." One of the 20 or so finalists among the 76 graduate students who presented posters at the GPP Graduate Student Research Symposium, Gilman is in her second year of doctoral training at Brown University in Providence. Eventually, she says, she would like to work at NIH or in academia.

too, for the physical brain findings, she remarked.

Not only does stress affect brain growth and development in animals, she observed, but there are studies showing that children subjected to abuse and other experiences associated with post-traumatic stress disorder have reduced ICVs.

—Fran Pollner

*At the end of the GPP poster day, three of the 76 graduate student poster presenters were declared winners. In alphabetical order, they are:

■ **Kristina Buac**, George Washington University graduate program in genetics, Washington, D.C., "**Wireless, a novel ENU-induced allele of ErbB3 gene exhibiting neural crest defects distinct from the null allele.**" NIH research advisor, Bill Pavan, senior investigator, Genetic Disease Research Branch, NHGRI.

■ **Daniel Spellman**, New York University School of Medicine graduate program in structural biology, "**Stable isotopic labeling of amino acids in cultured primary neurons for the study of protein turnover and neuronal signal transduction.**" NIH research advisor, Alfred Yergey, Head, Section on Mass Spectrometry and Metabolism, NICHD.

■ **Honghong Zhu**, Johns Hopkins University School of Public Health graduate department of epidemiology, Baltimore, "**Secondhand smoke and breast cancer risk: a population-based prospective cohort study.**" NIH research advisor, Kenneth Cantor, senior investigator, NCI-DCEG.

RECENTLY TENURED

Steven Libutti received his M.D. from the College of Physicians and Surgeons of Columbia University in New York in 1990 and completed a residency in general surgery at the Presbyterian Hospital in New York in 1995. He then joined the Surgery Branch, NCI, as a clinical associate and after completing his surgical oncology fellowship in 1996 joined the senior staff. In 2001, he became a tenure-track investigator with a focus on tumor angiogenesis and the tumor microenvironment. He is currently a senior investigator and the chief of the Tumor Angiogenesis Section in the Surgery Branch, Center for Cancer Research, NCI.

In order for a tumor to grow larger than a few millimeters, it must develop a blood supply. This process of new vessel growth from pre-existing vessels is termed "angiogenesis," and it is important not only for the growth of the primary tumor but also for tumor invasion and spread to distant sites.

Aiming to identify novel targets for cancer therapy, my laboratory has focused on understanding the tumor microenvironment, the molecular processes involved in the development of new vessels, and the complex interactions between the tumor and host cells.

We have developed some new techniques and assays to help us model and measure these processes.

We contributed to the creation of a technique for isolating endothelial cells from tissues that have been fixed or frozen. This adaptation of a novel laser capture approach termed expression microdissection, or xMD, has allowed us to study DNA, RNA, and protein changes in tumor-associated endothelial cells *in situ*.

We were able to demonstrate that tumor endothelial cells exhibit differential patterns of promoter methylation compared with endothelial cells in adjacent normal tissues.

This provided the first definitive evidence *in vivo* of epigenetic alterations in tumor neovasculature. We hope this observation will lead to a better understanding of the mechanisms that result in phenotypic alteration of endothelial cells and thus facilitate the identifica-

tion of new therapeutic approaches.

The use of angiogenesis inhibitors in the clinic has faced several challenges. Although the anti-VEGF antibody Avastin (bevacizumab) has recently been approved by the FDA for the treatment of colon cancer, many other antiangiogenic agents have shown mixed results. This may be due, in part, to the need to deliver such agents directly to the tumor microenvironment to exert sustained paracrine effects.

We have therefore explored the use of targeted gene therapy to deliver antiangiogenic gene products to tumor vessels. In collaboration with investigators at the University of Texas M.D.

Anderson Cancer Center, Houston, we have been developing a phage-based vector system that is capable of targeting tumor vessels selectively.

We are now testing this vector in animals within the NCI Comparative Oncology Program by delivering vascular-targeted, TNF-expressing phage to dogs with spontaneous cancers. Data from this study will be

submitted to the FDA to support an IND (investigational new drug application) to conduct the first clinical trial of this vector.

Along with others in the angiogenesis field, we have pursued the identification of unique targets in the tumor vasculature.

Utilizing genomic and proteomic approaches, we have attempted to elucidate common pathways involved in the response of endothelial cells to angiogenesis inhibitors.

This work has enabled us to characterize more completely the activity of two important mediators of endothelial cell apoptosis.

We recently elucidated the mechanism by which EMAP-II (endothelial cell monocyte-activating polypeptide-II) gets into endothelial cells and exerts its effects via an HIF1- α -mediated pathway. By enhancing HIF1- α degradation, EMAP-II induces endothelial cell apoptosis.

We have also identified the putative tumor-suppressor gene *DOC1* as an im-

portant mediator of endothelial cell apoptosis and a common link between the effects of several different angiogenesis inhibitors.

Recently, our laboratory became a part of the new Tumor Angiogenesis Section in the Surgery Branch, opening up new opportunities to better translate our findings to the clinic. We believe the next one to two years will bring the translation of several new vascular-targeted therapies to our patients with cancer.

Xinzhuan Su received his Ph.D. in parasitology from the University of Georgia in Athens, Ga., in 1990. He did postdoctoral training at the University of Georgia before coming to the Laboratory of Parasitic Diseases, NIAID, in 1992. He is currently the head of the Malaria Genomics Section and a senior investigator in the Laboratory of Malaria and Vector Research.

Lack of an effective vaccine and widespread parasite resistance to multiple antimalarial drugs have led to a resurgence of malaria worldwide. Indeed, after decades of research and much progress in molecular biology, we are not much better off in treating and controlling

malaria than we were 50 years ago. Dynamic and rapidly evolving parasite populations present tremendous problems for developing effective control measures.

Under the guidance of Thomas Wellems, my initial research as a postdoctoral fellow at NIH involved genetic mapping of a gene linked to chloroquine resis-

tance in *Plasmodium falciparum* parasite.

I developed various tools and methods, including a high-density microsatellite map, and mapped the locus of resistance to a 36-kb region. I realized then how much remained to be discovered in malaria genetics and genomics and decided these were areas I wanted to explore for years to come.

My laboratory applies genome-wide approaches to fundamental problems of parasite biology and evolution.

Current goals are to develop genome-wide single-nucleotide polymorphism (SNP) and microsatellite genetic maps and to use these maps to identify genes affecting such phenotypes



Fran Pollner
Steven Libutti



Xinzhuan Su

as parasite drug resistance, red blood cell invasion, and sexual development.

Collections of genome-wide polymorphisms from malaria parasites worldwide will also provide a useful database for studies of parasite origin, transmission, and evolution.

Using malaria parasite lines adapted to *in vitro* culture and large numbers of genotypes obtained from both nuclear and mitochondrial genomes, we studied parasite population structure, recombination rate variation, linkage disequilibrium, and evolutionary history. We have shown that *P. falciparum* probably migrated with humans out of Africa to other parts of the world about 50,000–100,000 years ago.

Our studies also found that parasite population expansions probably occurred in Africa 5,000–10,000 years ago, along with changes in mosquito ecology and species distribution from agriculture and its impact on the environ-

ment.

Malaria parasites can be grouped into populations according to their continental origins, yet no obvious population structure exists in Africa due to high transmission and recombination rates.

We have collected thousands of SNPs from geographically diverse parasite isolates and are in the process of developing a microarray chip to genotype additional isolates from field sites, including a new field site in Cambodia. Our plan is to perform association studies with well-characterized parasite phenotypes.

For example, to map important drug-resistance genes, we will look for loci with signatures of selection such as chromosomal regions with reduced polymorphism.

Indeed, we have already shown reduced diversity in a large chromosomal region surrounding a gene for a chloroquine-resistance transporter on chromosome 7, suggesting spread of

drug-resistant parasites from one or two foci.

Malaria parasites have a complex life cycle, with asexual replication in the human host and mandatory sexual recombination in the mosquito host. The sexual stages are vital phases in malaria parasite transmission and are the targets of various interventions such as transmission-blocking vaccines.

Malaria parasites have a haploid genome in the human host. The switch from asexual replication to sexual differentiation is therefore likely to involve signal transduction and gene regulation.

Recently, we used genetic mapping to identify a candidate gene that plays an important role in parasite sexual development. We are now using genetic mapping, microarrays, and other approaches to study the regulation of this complicated process and gain knowledge to inform the development of strategies for malaria control. ■

NEW PERFORMANCE MANAGEMENT APPRAISAL PROGRAM

by Sue Fishbein

What is the PMAP? Who Will Be Affected?

Efforts are underway at NIH to implement the new HHS-wide performance management appraisal program (PMAP).

All NIH employees—including all research fellows and investigators, but excluding SES and Commissioned Corps employees—are to be placed on new performance plans incorporating PMAP requirements by the end of June. Basically, employees who served under performance plans and contracts before will now serve under one program—the PMAP—and will use the PMAP forms, rating methodologies, and processes.

The PMAP program aims to enhance organizational and individual accountability and results; provide clear information concerning performance expectations; and reward employees who perform exceptionally well. The program shifts employees from a two-level (pass/fail) system to a four-tiered rating system.

General Schedule and Title 42 appointment categories, including both extramural and intramural researchers, are included in the program.

Performance Liaisons

Working with the staff of the NIH Office of Human Resources (OHR), the ICs have designated individuals to serve as “Performance Liaisons.”

These individuals have gone through

orientation provided by OHR and are now helping to train supervisors and employees in their respective ICs, assist with the development of employee performance plans, and track PMAP progress. They are the first point of contact for questions about the PMAP.

Customized Performance Plans For Varied Types of Researchers

Also, to expedite performance plan development, OHR is collaborating with subject-matter experts across NIH to develop generic performance plans for various occupations, such as senior investigator, investigator, senior scientist, and senior clinician. These generic plans can be customized and are available on the OHR PMAP website:

<http://hr.od.nih.gov/PerfMgmt/default.htm>

Other prototype plans for targeted NIH occupational groups include staff scientist, staff clinician, research fellow, clinical fellow, senior research assistant, and research assistant.

Additional Support

The website also includes the list of NIH Performance Liaisons; detailed information on the PMAP program; suggestions for supervisors who would like to fine-tune their managerial skills, including the provision of feedback; and links to other related websites. ■

New Vision Research Lecture Series/Award

The first Sayer Vision Research Lecture—“Stemming Vision Loss with Stem Cells”—took place **May 25, 2006**. It can be viewed at <http://videocast.nih.gov> under “Past Events.”

Martin Friedlander, professor of cell biology at Scripps Research Institute and chief of Retina Services at Scripps Clinic in La Jolla, Calif., kicked off this new lecture series in vision research.

The lecture series is sponsored by NEI in collaboration with the Foundation for the NIH. Its focus is interdisciplinary research with special relevance to vision. Investigators chosen to deliver a Sayer lecture may work within or outside NIH.

Additionally, the Sayer Vision Research Fund will award a grant-in-aid to a promising new intramural NIH investigator to pursue his or her current research. This individual will be asked to deliver the Sayer lecture during the year in which the award is given. More details about this award are forthcoming.

NIH research chemist Jane Sayer established the fund to honor her family and in memory of her parents, Winthrop and Laura Sayer. ■

CATALYTIC REACTIONS?

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

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

In Future Issues...

- More Bench To Bedside
- Nobel Experience For GPP Students
- IG Directory

Kids' Catalyst: Spring Break -- Enjoy Nature



Jennifer White

Kids' Catalyst creator and writer Jennifer White was so enchanted by the spring sights on the NIH campus that she took time out to capture some of them in her digital camera. You can see a few more of her NIH nature photos (in color, including the one above) in the online edition of *The NIH Catalyst* at <http://www.nih.gov/catalyst/2006/06.05.01>.

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