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The Rockefeller University

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news&notes

SEPTEMBER 24, 1999 VOLUME 10, NUMBER 3 THE ROCKEFELLER UNIVERSITY

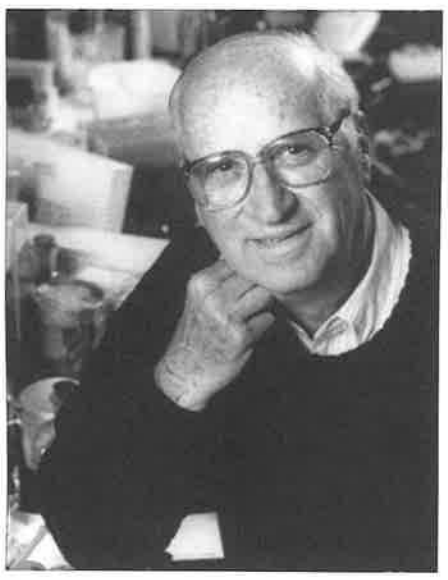
Koshland to launch Cohn Forum series Wed., Sept. 29

Daniel Koshland, professor of biochemistry and molecular biology at the University of California at Berkeley and editor emeritus of the journal *Science*, will be the academic year's first Zanvil A. Cohn Forum on Health Affairs speaker on Wed., Sept. 29.

Koshland, a distinguished scientist whose talents extend beyond doing good science to creating an environment in which imaginative research can flourish, will speak on "The Future of Biomedical Science—What We Will be Able to Do and What We Will be Allowed to Do."

Koshland is the recipient of the 1990 National Medal of Science and currently works on the chemical reactions involved in Alzheimer's disease by analyzing the changes that occur inside

see **Cohn forum,** page 3



Daniel Koshland, professor of biochemistry and molecular biology at UC Berkeley and former *Science* editor will speak at the Cohn Forum Wed., Sept. 29.

Save the date:

Mon., Oct. 18

The Molecular Flying Circus: Innovations in Biological Mass Spectrometry. *A Symposium Celebrating the 25th Anniversary of the NIH-funded National Resource for the Mass Spectrometric Analysis of Biological Macromolecules.*

President's initiative brings Ned Block to campus

NYU Professor of Philosophy and Psychology Ned Block met RU graduate students last Wed., Sept. 15 before his lecture, "Why Is It So Hard to Explain Consicousness in Biological Terms?"
Photo by Paul Schneck.

On Wed., Sept. 15, President Levine opened his house to 25 Rockefeller students and guest lecturer Ned Block, professor of philosophy and psychology at NYU, to discuss the machinery of perception and the identity of consciousness, with detours into zombies and basketball.

The lecture, entitled "Why Is It So Hard to Explain Consciousness in Biological Terms?" was the first of the Sloan Series for Graduate Fellows to tackle a 3-part question: What is known? What is unknown? And what is unknowable? Levine also emphasized that the gatherings are intended to open the intellectual gifts of New York City to Rockefeller students and to be "absolutely pure fun."

Block led the discussion by challenging the students to refine their notion of consciousness. "We're at such an early stage," he said, "we only have guesses of models." He also suggested that we are so primitive in our understanding of the connection between the brain and experience that we have no way of understanding how they might point to the same entity, something he thinks we will eventually discover. "We have concepts of consciousness, and of the brain, but our concepts are not refined enough to allow us to see that they pick out the same property," he said.

As the students became more engrossed in the debate, Block fielded questions about free will, creation myths and sleepwalking and relied on several thought experiments to try and get at a firmer understanding of consciousness. "Zombies" were proposed who were like us in every way but had no consciousness, and basketball players streaked down the court without ever "knowing" what they were doing.

Clearly enjoying the give and take with students at a pre-eminent biomedical research institution, Block confided toward the end of the evening that when he was in graduate school, "You were regarded as a little loony to be studying consciousness at all."

A lab on the move

Anyone who has ever felt overwhelmed moving from one apartment to another has to marvel at the way Angie Teresky can transport an entire scientific laboratory. Of course, she's had a lot of practice. Teresky has been President Levine's lab manager since their early Princeton days in 1968. In 1979, she moved his lab to the SUNY Stony Brook School of Medicine when Levine became chair of the Department of Microbiology. Then in 1984 she moved him back to Princeton, where, as the Harry C. Wiess Professor and chair of the Department of Molecular Biology, Levine oversaw a major expansion of Princeton's life sciences programs. Now it's on to Rockefeller, where in addition to his presidential duties, Levine will have a lab on the 8th floor of Weiss.

Teresky handles it all with aplomb, gamely showing a *News&Notes* reporter around the lab while fielding phone calls about computer installation. The key to her calm demeanor is planning and organization. A lab map on the wall identifies each bench and lab area with a letter. At Princeton, every packed box was labeled so that the movers would know exactly where things went at RU, so now each bench has its own stack of boxes—a stack for bench A, a stack for bench B, and so on. The contents, too, are listed on the outside, Teresky notes, "so we don't end up with Wonder Boxes—'I wonder what's in that box?'"

see **Lab move,** page 5

Friday lecture: Kappler to discuss presentation of antigens and T-cell recognition

University of Colorado immunologist John Kappler will present today's Friday lecture.

Immunologist John Kappler will present the Friday lecture today (Sept. 24). His topic will be "Structural Features of Antigen Presentation."

Kappler is a professor in the Department of Immunology and Pharmacology at the University of Colorado Health Sciences Center in Denver. He also is in the immunology Division of the Department of Medicine at the National Jewish Medical and Research Center, and is an investigator with the Howard Hughes Medical Institute.

Kappler has been studying the problem of antigen recognition by T cells for many years, in particular how the peptide/MHC ligand forms and how the quality of its interaction with the T-cell receptor can determine T-cell fate. His laboratory was one of the first groups to identify T-cell recognition and also showed the first direct evidence that clonal deletion is a major way to establish self-tolerance.

His laboratory has developed expression systems for alpha beta receptors and MHC molecules, which they have used to produce cell-free, soluble forms of the proteins. In order to express MHC molecules that are occupied with a single peptide, his lab has devised a way to attach sequence encoding a peptide to the MHC gene, such that the MHC mol-

see **Friday lecture,** page 2

Music News:

Baritone Scott Hendricks to perform with pianist James Lowe at today's noon recital

The Tri-Institutional Noon Recital series begins its fourteenth season today with a performance by baritone Scott Hendricks and pianist James Lowe. The duo will perform works by Ralph Vaughn Williams and Franz Schubert.

Scott Hendricks makes his debut this season at Austin Lyric Opera in the title role of *Don Giovanni*. He is also the baritone soloist in concerts with the New York Festival of Song at Weill Rectial Hall and at the Vocal Arts Society in Washinton, D.C., in recital at Roosevelt University this season. He will be in residency, sponsored by the Marilyn Horne Foundation, at the University of Arkansas at Little Rock during 1999-2000.

James Lowe is a pianist with Houston Grand Opera Studio. As a soloist he has appeared with the Rochester Philharmonic Orchestra and the University of Michigan Symphony Orchestra. In addition, as keyboardist, rythm guitarist, lead singer and songwriter for the rock ban Backwash, he has toured the Eastern United States over the past five years.

The recital takes place in Caspary Auditorium at noon. Admission is free for members of the tri-institutional community and guests.

Baritone Scott Hendricks will perform Williams and Schubert today with pianist James Lowe at the first concert of the Tri-Institutional noon recital series.

Potpourri

GSRA Seminar

Deborah Meyers from TIAA-CREF will be on campus Wed., Sept. 29 to present the Group Supplemental Retirement Annuities Seminar. The seminar will provide important information to both current and prospective participants. The seminar will be held twice in 301 Weiss from 11:45 a.m. to 12:45 p.m. and from 1 p.m. to 2 p.m. All are welcome. Please call Human Resources, x8300 with questions.

Visa Lottery

Fifty thousand immigrant visas will be offered in a lottery run by the U.S. Department of State. The filing period is from noon Mon., Oct. 4, 1999 until noon Wed., Nov. 3, 1999 and is open to natives of most countries around the world. (Only 14 countries are excluded from the lottery.) For detailed instructions about the lottery, visit the Office of Human Resources, 103 Founder's Hall.

Telecommunications

The latest edition of the Manhattan white pages is available at the Telecommunications office in B-1 Smith Hall between 9 a.m and 5 p.m.

News&Notes deadline

The deadline for submission of text for Potpourri and other *News Notes* sections is one week prior to print. Deadlines for the Oct. 1, 8 and 22 issues are Sept. 24, Oct, 1 and 15 respectively.

The Ninth Medical Complex Art Show

All faculty, staff and students of RU, MSKCC, NYPH, NYPGH Care Network, Weill Medical College and Graduate School of Medical Sciences and HSS are encouraged to submit paintings, photographs, computer-generated art, sculpture, ceramics and handicrafts. The Ninth Medical Complex Art Show, sponsored by Weill Cornell Medical Library, will open in late October and run through January 2000. Submit up to six slides or photographs until Fri., Oct. 8 to Helen-Ann Brown, Cornell Medical Library (C-115), 1300 York Ave., New York, NY 10021-4896. Call 746-6092 or e-mail habronw@mail.med.cornell.edu with your comments and questions.

Restaurant discount

Baluchi's Indian Food Restaurant (1149 1st Ave., on the corner of 63rd St.) already offers a lunch discount of 50 percent on menu items between noon and 3 p.m. In addition, the restaurant is extending a dinner discount of 20 percent off for all Rockefeller University faculty, students and staff. Just present your Rockefeller I.D., and they will take 20 percent off the food items on your check. They also offer catering, parties and takeout. (Discounts are available for eat-in meals only.)

Security

Security can be reached from anywhere on campus by dialing x8295. In the event of an emergency dial x1111.

RU Artistic?

Employee art show seeks submissions

Human Resources is hosting the first in a series of special employee events to take place on campus.

An exhibit of Employee Artwork will be featured at this year's Employee Recognition Event on Wed., Oct. 20. Artwork will be displayed in the University library from Mon., Oct. 18 through Fri., Oct. 29.

Human Resources continues to encourage University painters, sculptors and photographers to submit up to three slides of their best work. All slides should reach Kate Drake or Ron Kurtz by Mon., Oct. 4 for consideration.

The Employee Recognition Event will be held on Oct. 20 from 3 to 5 p.m. in the University library. Service awards will be presented at 3 p.m. to those employees who have served the University for ten and twenty years, followed by a cocktail reception. All RU employees, faculty, students, and guests of honorees are welcome to attend.

In future months, Human Resources hopes to sponsor a night of literary readings, cabaret performances and jazz music.

If you would like to present your work, or have any further questions, please contact Drake at x8300 or Kurtz at x8303.

Friday lecture, continued

ecule becomes occupied with the peptide during biosynthesis to the exclusion of all other peptides.

Most recently, he has concentrated on biophysical and X-ray crystallographic approaches to these questions. The crystallography allows the scientists to determine the structure of the protein structures at the atomic level.

The first experiments of this type showed the researchers in great detail how members of a group of different antigen peptides bind to the same MHC molecule, holding the peptide in a precise orientation.

Kappler's laboratory complements the studies using biophysical and crystallographic methods with experiments in transgenic mice, where the scientists can track the influence of a single peptide/MHC molecule on the development of T cells bearing a particular alpha beta receptor.

Kappler received his B.A. in chemistry from Lehigh University in Bethlehem, Penn., and his Ph.D. in Biochemistry from Brandeis University in Waltham, Mass. He did his postdoctoral work with Richard Dutton at the University of California, San Diego, and was on the faculty of the University of Rochester Medical School before moving to his present position.

Among Kappler's awards are the Royal Society Wellcome Foundation Prize, the Paul Ehrlich and Ludwig Darmstaedter Award from the Paul Ehrlich Foundation, and the Louisa Gross Horwitz Prize from Columbia University. Dr. Kappler is a member of the National Academy of Sciences.

Kappler's talk begins at 3:45 p.m. in Caspary Auditorium and is preceded by a tea in Abby Aldrich Lounge at 3:15 p.m. All are welcome.

Announcement:

JCAHO visit upcoming

The Joint Commission on Accreditation of Healthcare Organizations will conduct an accreditation survey of The Rockefeller University Hospital on Mon. and Tues., Nov. 15 and 16.

The purpose of the survey will be to evaluate the organization's compliance with nationally established Joint Commission standards. The survey results will be used to determine whether, and the conditions under which accreditation should be awarded the organization.

Joint Commission standards deal with organizational quality of care issues and the safety of the environment in which care is provided. Anyone believing that he or she has pertinent and valid information about such matters may request a public information interview with the Joint Commission's field representatives at the time of the survey.

Information presented at the interview will be carefully evaluated for relevance to the accreditation process. Requests for a public information interview must be made in writing and should be sent to the Joint Commission no later than five working days before the survey begins.

The request must also indicate the nature of the information to be provided at the interview. Such requests should be addressed to:

Division of Accreditation Operations
Accreditation Service Specialist
Joint Commission on Accreditation of Healthcare Organizations
One Renaissance Boulevard
Oakbrook Terrace, IL 60181

The Joint Commission will acknowledge such requests in writing or by telephone and will inform the organization of the request for any interview. The organization will, in turn, notify the interviewee of the date, time and place of the meeting. This notice is placed in accordance with the Joint Commission's requirements.

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Rockefeller researchers produce 3-D picture of DNA-reading molecular machine

by Joseph Bonner

A team of researchers led by Associate Professor Seth Darst has determined the first three-dimensional structure of the cellular RNA polymerase (RNAP), a molecular machine that activates individual genes by transcribing, or reading out, the instructions encoded in their DNA. The structure, published in the Sept. 17 issue of the journal *Cell*, provides scientists with a model for understanding the RNAPs of higher organisms, including humans.

"We hope that this structure will provide a more detailed framework for interpreting the existing genetic, biochemical and biophysical information, as well as guide further studies aimed at understanding the transcription process and its regulation," says Darst, who heads a Laboratory of Molecular Biophysics.

> "Now that there is a structure, everything is going to shift from the blind probing of the structure-function relationship to really understanding what's going on."

Molecular biologists often refer to the "Central Dogma," the roadmap of how information within DNA is transferred to proteins, the building blocks of all living processes. DNA passes information to RNA through a process called transcription, and the RNA carries the blueprints for making proteins. Transcription is orchestrated by a large assembly of proteins called the RNA polymerase. In bacteria, the RNAP comprises four proteins, or subunits. In humans, the RNAP consists of up to a dozen subunits. Because evolution has allowed for genomic similarities among many different organisms, scientists can study the relatively simple structures found in bacteria to understand the complex workings of this machinery in higher organisms, including humans.

Since the late 1980s, Darst's work focused on the RNAP found in the bacterium *E. coli,* a well-characterized organism, using a technique called electron diffraction, a method in which electrons are shot at a crystal and the reflected particles provide information about the shape of a molecule. However, electron diffraction only yielded structural information with a resolution of 12 angstroms, meaning that parts of the structure that are much smaller than 12 angstroms can't be resolved. (An angstrom is the approximate radius of a typical atom.) To obtain a more detailed structure, Darst needed to use a technique called X-ray diffraction, but the RNAP from *E. coli* did not give good results.

About a year ago, Darst and Gongyi Zhang (a postdoctoral fellow in the Darst lab, now an assistant professor at the National Jewish Medical and Research Center) decided to look at proteins from thermophiles, organisms that thrive at high temperatures, reasoning that proteins isolated from these organisms would be less flexible and more stable, characteristics that are desirable for crystallization.

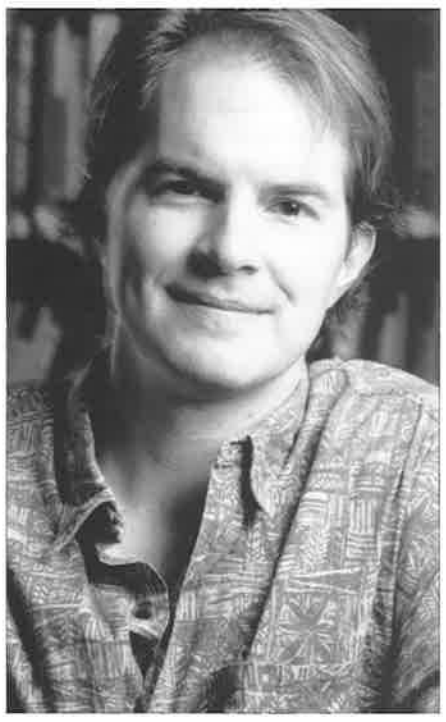
The Rockefeller team chose a bacterium called *Thermus aquaticus,* a relatively poorly studied organism whose genome has yet to be sequenced. After determining how to purify the RNAP from *T. aquaticus,* the researchers almost immediately obtained crystals that diffracted X-rays to a nearly 3 angstrom resolution, enough to begin to solve the structure.

However, the researchers still needed more information to solve the structure. They needed to clone and sequence each of the genes whose products make up the subunits. For this, Darst struck up a collaboration with Rutgers University's Konstantin Severinov, a former postdoc from his lab, to clone and sequence the subunits.

"At every step of the way we expected it would take several months or years, but everything went faster than we thought it was going to," says Darst. "We got to our current stage in a year."

The RNAP structure resembles a crab's claw, with a groove or channel that is the appropriate size for accommodating double-helical DNA. The researchers have proposed a model for how the RNA and DNA are situated in the RNAP during the elongation of the RNA chain.

Darst says that the structure is not complete and needs more work, but even at this stage it's a big advance for scientists who study transcription.



Associate Professor Seth Darst leads the group that determined the three-dimensional structure of RNAP. *Photo by Robert Reichert.*

Before the structure was available, scientists studied RNAP by using biochemical techniques, such as mutagenesis, in which individual amino acids in a protein be altered one at a time to yield information about how the protein's structure relates to its function.

"Now that there is a structure, everything is going to shift from these types of experiments—the blind probing of the structure-function relationship," says Darst. "Researchers can now look at the structure and design better experiments to really understand what's going on."

Along with Zhang, Darst and Severinov, co-authors on the manuscript are Elizabeth A. Campbell and Catherine Richter, postdocs in the Darst lab, and Leonid Minakhin of Rutgers.

This work was supported in part by a Burroughs Wellcome Career Development Award, a Pew Scholars Award in the Biomedical Sciences, and a National Research Service Award (National Institutes of Health). Campbell was a Kluge Postdoctoral Fellow.

In Memoriam
Frederick P. Rose, trustee emeritus

The university community mourns the passing of Frederick P. Rose, an emeritus trustee. Rose died Tues., Sept. 14 at age 75. A leader in New York's world of real estate, Rose was also a prominent philanthropist. He became a member of the university's board of trustees in 1984 and served as a chairman of its real estate committee.

As a trustee, Rose made lasting contributions to the university, helping to modernize its physical plant. He also supported its research programs and established the Frederick P. Rose Professorship.

In addition to his involvement at Rockefeller, Rose had served on the boards of more than 30 other institutions including Lincoln Center, the American Museum of Natural History, the Children's Aid Society and the New York Public Library.

Cohn Forum, Sept. 29

the cells of the brain. In the 1980s Koshland and his colleagues discovered essential features of signaling systems among cells.

Koshland's early work on the mechanisms by which enzymes and proteins function resulted in important conceptual advances in biochemistry. He proposed that enzymes change their shape as they react with other molecules, leading to his "induced fit theory" that had extensive ramifications not only for enzymes but also in the control and regulation of biological systems.

The Albert and Mary Lasker Foundation honored Koshland with a Special Achievement Award in 1998 for his various contributions to elevating science as a visionary biochemist as well as tireless institution builder and eloquent public communicator.

Fired by the belief that good science in the 21st century must cross disciplinary boundaries, Koshland transformed the institutional landscape at UC Berkeley by combining 12 small scientific departments into three large ones. The reorganization took 10 years, but Berkeley biologists now find it easier to collaborate with one another and with colleagues in physics, chemistry and other areas more and more crucial to solving problems in biology.

Koshland was born in New York City. He earned his B.S. degree from the University of California at Berkeley and his Ph.D. from the University of Chicago. From 1951 to 1965 he held an appointment at Brookhaven National Laboratory, adding a joint appointment at the Rockefeller University from 1958 to 1965. In 1965 he joined the faculty at UC Berkeley.

The Cohn Forum lecture will be preceded by a sherry and wine reception from 5 to 5:30 p.m. in Abby Aldrich Rockefeller Lounge. Koshland's lecture and discussion will be in the Abby Aldrich Dining Room from 5:30 to 6:30 p.m. All are welcome.

News from the Aaron Diamond AIDS Research Center:

RU Researchers say resistance to HIV drugs may be higher than previously thought

By Jim Stallard

A study of patients infected with the AIDS virus revealed that about one in six was carrying a strain that is resistant to at least one of the drugs targeting HIV, researchers report from the Aaron Diamond AIDS Research Center (ADARC), an affiliate of the Rockefeller University. Lead author Daniel Boden and 11 colleagues report the research as the cover story in the Sept. 22-29 issue of the *Journal of the American Medical Association.* The authors suggest that further research should try to establish whether AIDS therapy structured around HIV-resistance testing would be more effective than current methods.

Although the researchers caution that the analysis was limited to a subset of the AIDS population—mostly gay, white men who were recently infected—the percentage of patients in the group carrying a resistant strain was significant. The researchers found that viruses resistant to more than one drug were much less common.

"There are two important messages we should draw from this study," Boden says. "First, that we need to explore how widespread this resistance is. Is the percentage going to be the same in the AIDS population in general? Is it affected at all by means of transmission? The second message is that HIV has a much tougher time resisting three drugs than one. Until we know how much resistance there is and what is causing it, we recommend that infected patients who are able to should follow the multidrug therapy."

The study is the first to be published that attempts to measure the prevalence of transmitted drug-resistant HIV-1 in the United States during the era of combination antiretroviral therapy. Since it was implemented four years ago, the multidrug approach—in which infected patients take a combination of drugs (usually three) every day—has caused a marked reduction in AIDS cases and AIDS deaths. For example, the death rate from AIDS dropped 47 percent in the United States between 1996 and 1997. Scientists have been concerned, however, that the success of antiretroviral drugs has resulted in the increased transmission of drug-resistant strains of the virus.

To measure the prevalence of this resistance, the researchers performed genetic analysis on virus in blood drawn from 80 patients to find any HIV mutations associated with drug resistance. They found that 13 of the patients, or 16.3 percent of the total, carried strains that were less susceptible to an antiretroviral drug by a factor of three or more. The scientists said the actual percentage of patients carrying resistant strains in the group is probably higher because other mutations that confer resistance have not yet been identified. Viruses resistant to more than one drug were found in only 3 patients, constituting 3.8 percent of the total.

Assistant Professor Martin Marcowitz and ADARC physician Dan Boden suggest that AIDS therapy structured around HIV-resistance testing would be more effective than current methods in their cover story in *JAMA* this week. *Photo courtesy of ADARC.*

"Rather than jumping to any conclusions about whether resistant strains of HIV are being widely spread, we need to measure the resistance in other populations," says study co-author Martin Markowitz, an assistant professor at Rockefeller and staff scientist at ADARC. "If it appears that HIV resistance to drugs is becoming more common in the future, we may have to alter current strategies for treatment. But until we know more, we do not want patients to stop taking drugs because in most cases they are quite effective."

The scientists recommend initiation of clinical trials to determine whether therapy guided by resistance testing would work better than issuing the standard drug or combination of drugs. Such testing might lead to drug therapies tailored around the specific resistant HIV strain found in a particular patient.

This research was supported in part by the National Institute of Allergy and Infectious Diseases, part of the federal government's National Institutes of Health, and by a General Clinical Research Center grant (M01-RR00102) from the National Center for Research Resources at NIH.

No viral rebound after stopping drugs: an anomalous group of HIV patients

By Jim Stallard

An unusual group of HIV-infected patients who stopped taking antiviral drugs yet continued to suppress HIV replication may have somehow boosted their immune response against the virus by temporary therapy interruptions, ADARC researchers report. Although scientists strongly advise against halting drug therapy—because the virus usually comes surging back—this observation suggests that some HIV-infected people can suppress the virus without drugs if they have strong immune responses.

The study focuses on only six subjects, so its widespread implications for treating the general population of HIV-infected people are unclear. But if researchers can identify the mechanism by which the immune response is strengthened in patients who interrupted treatment, they might be able to design vaccines that infected patients could take to keep the virus at low levels even when medication is halted.

"We don't want people to stop taking anti-HIV drugs," says Gabriel Ortiz, a biomedical fellow and first author of the paper. "But the observation that has been made is pretty striking, because it does suggest that artificially vaccinating infected patients who are taking drugs may help maintain virus at a low level if they stop taking drugs for whatever reason."

Suppressing HIV at the lowest possible level is important because the amount of virus in an infected person is the most important factor determining how soon he or she develops full-blown AIDS. Anti-HIV drugs have proven to be effective in keeping the virus at undetectable levels, but they must be taken every day for an indefinite period. Many patients have trouble sticking to the regimen because the drugs can have toxic effects and can cause adverse events in the body. In addition, this highly active antiretroviral therapy (HAART) is unaffordable for most HIV-infected people in developing countries.

If scientists could intervene to boost the immune response, more HIV-positive patients could presumably postpone the development of full-blown AIDS. A vaccine having this effect could possibly be administered to infected populations in the Third World who do not have access to antiretroviral pills. "Our study suggests that such a vaccine will have to stimulate cell-mediated immune responses against HIV," says senior author Douglas Nixon, an assistant professor at Rockefeller and staff scientist at ADARC.

In the study, the researchers identified six patients who, for various reasons, were unable to keep taking pills for HIV; some had stopped and started again, while others had stopped the therapy altogether. All but one of the subjects had begun therapy within four months of infection with HIV, so the virus was suppressed relatively early. The researchers measured in these patients both the level of virus and the level of immune response.

In three of the six patients, the virus remained low for between four and 24 months after stopping drug therapy. The other three subjects had the virus rebound significantly. The researchers noticed that in those patients where the virus was suppressed, there was "a broad and strong" HIV-specific immune response. It appears that temporarily discontinuing drugs allowed the virus to make its presence known just enough to trigger the immune responses.

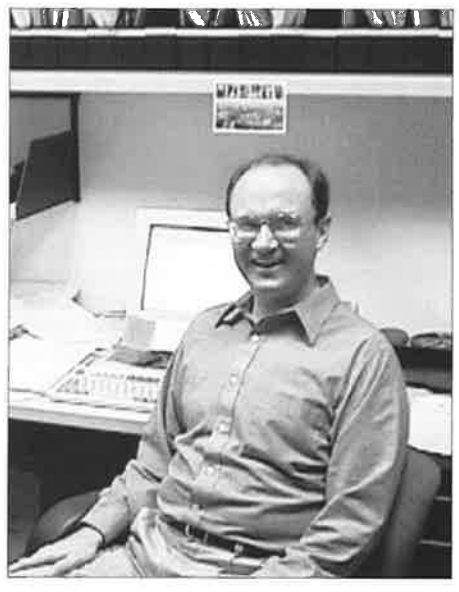
The study is reported in the Sept. 15th issue of the *Journal of Clinical Investigation* by Ortiz, Nixon and 17 colleagues at ADARC. The researchers say follow-up studies are in progress to build on the intriguing results of this study. New trials getting under way in controlled clinical settings will explore the effects of stopping and starting drug therapies for variable periods.

"Right now, we just have an association," Ortiz says. "The exact mechanism as to how these immune responses interplay with the virus is not completely understood, which is why we can't advocate that patients discontinue drug therapy."

The idea of using "pulsed" treatments is not completely new to medicine, having been part of chemotherapy treatments for cancer for quite some time. But this study represents the first sign that intermittent drug treatment for HIV might rally the immune system.

"Gabriel's study, I think, has advanced the field substantially, because we now believe that immunological mechanisms are critical in keeping the virus low after a drug is discontinued," Nixon says. "In a real-world situation where adherence to anti-HIV drugs is difficult and often impossible, it is essential to know what recourse we have to keep the virus at the lowest levels possible."

This work was supported in part by grants from the National Institute of Allergy and Infectious Diseases, part of the federal government's National Institutes of Health (NIH), and the General Clinical Research Center grant (M01-RR00102) from the National Center for Research Resources at NIH. Ortiz is a biomedical fellow and is supported by an NIH Medical Scientists Training and Minority Pre-doctoral Fellowship.



Assistant Professor Douglas Nixon worked with biomedical fellow Gabriel Ortiz studying the effects of stopping antiviral drugs in HIV patients. *Photo courtesy of ADARC*

Rockefeller researchers discover new brain gene related to snake venom toxins

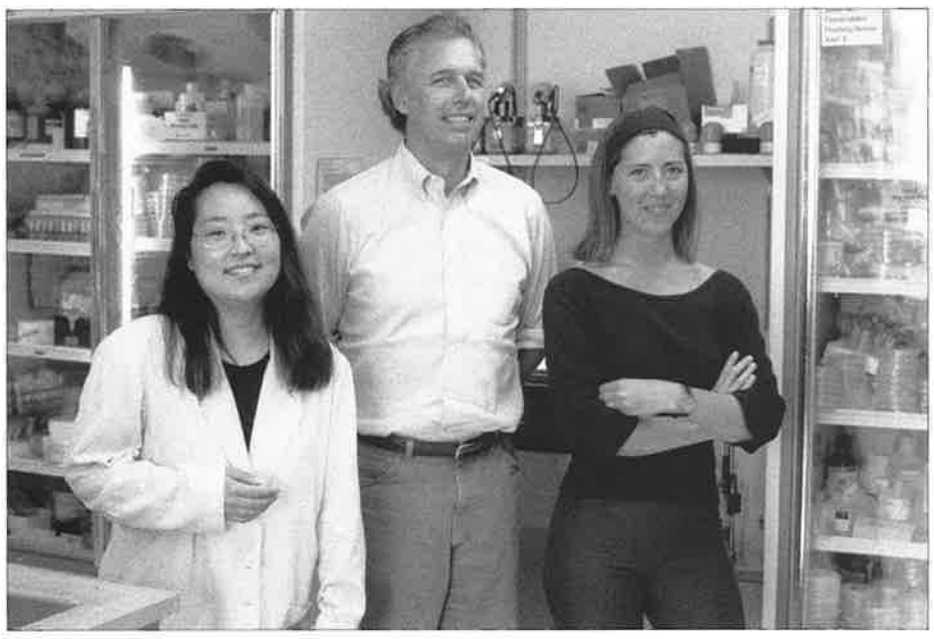
By Joseph Bonner

When Julie Miwa, a postdoctoral fellow in the Heintz lab, was cloning genes that regulate late stages of development in mice, little did she know that she and her colleagues would find a gene that shared a branch of the evolutionary tree with a snake venom toxin. As Professor Nathaniel Heintz says, "It's not everyday that you find a new genetic function in the central nervous system." And furthermore, an activity that may shed new light on such brain functions as learning and memory, attention and sleep-wake cycles and possibly offer improved strategies for treatment of cognitive disorders such as Alzheimer's disease.

Miwa and her colleagues in the Heintz lab—Postdoctoral Fellow Ines Ibanez-Tallon and Heintz—published their findings in the May issue of *Neuron*, along with Graduate Fellow Roberto Sánchez and Assistant Professor Andrej Sali of the Sali lab. The new gene, called *lynx1*, is functionally, structurally and evolutionarily related to snake venom toxins and plays a role in the function of molecules in the brain called nicotinic acetylcholine (nACh) receptors.

In the brain, nACh receptors are part of the cholinergic system. Cells called cholinergic neurons make projections from the brain stem that go to every part of the brain, secreting a molecule called acetylcholine, which attaches to the nACh receptors. Scientists think that cholinergic input from the brain stem regulates such properties as arousal, sleep/wake cycles and attention. Unlike snake venom toxins, which block the normal function of ACh receptors in the peripheral nervous system (limbs and extremities), *lynx1* shows promise as a positive regulator of ACh action in the central nervous system (brain and spinal chord).

"Snake venoms have been studied for decades because of their very specific effects on CNS receptors," says Heintz, who is an investigator at the Howard Hughes Medical Institute. "People in the field thought that they had to derive from something already present in the brain, and that there might be endogenous genes related to the snake venom toxins called prototoxin genes. However, for a large class of important venom toxins, no one had identified proteins that were evolutionarily and functionally related."



Postdoctoral Fellow Julie Miwa (left), Professor Nathaniel Heintz (center) and Postdoctoral Fellow Ines Ibanez-Tallon discovered a new genetic function in the central nerrvous system of mice. *Photo by Robert Reichert.*

The Rockefeller researchers think that snake venoms and *lynx1* share a common ancestral gene. Somewhere along the evolutionary pathway, snakes commandeered the mammalian gene, turning it into a toxic substance. The scientists call the new gene *lynx1*, after a family of genes in the immune system called *Ly-6*, which share sequence homology with the snake venom toxins but are not known to be functionally similar. *Lynx1* produces a protein in the central nervous that is closely related—both functionally and evolutionarily—to a venom toxin produced by elapid snakes. The venom of elapid snakes, such as the coral snake and others found in Australia and other parts of the world, kills by entering the blood and blocking molecules on cells called receptors, rendering the snake's prey unable to breathe. The receptors, called acetylcholine (ACh) receptors, are found in the brain and in muscle cells and relay information from essential chemicals that control muscle movement and nerve function.

Miwa's first clue that the *lynx1* gene was special came while looking at expression patterns of genes that occur in late stages of development. (The expression pattern of a gene groups all the localizations of its expression in the individual.) According to Heintz, genes that are expressed late in CNS development tend to be important in modulating the mature properties of neurons. Miwa found a very specific pattern of expression for the *lynx1* gene in multiple brain regions. By analyzing the gene's messenger RNA—the blueprint for protein synthesis—the scientists found a region that is rich in the amino acid cysteine.

"Once we saw the sequence similarity we realized that this could in fact be an evolutionary precursor or an endogenous counterpart to these small cysteine-rich a-neurotoxins and that it might have an important function for modulating CNS receptors," says Heintz.

Next, Sali and Sánchez used the computer program Modeller-5 to model the protein, and showed that it had the same structure as the snake toxins, providing important evidence that *lynx1* could be funtionally similar to the snake toxins. Ibanez-Tallon and Miwa then performed binding assays that showed that *lynx1* binds to specific sites on brain slices, which would be expected if these molecules function as modulators of nicotinic receptors. Heintz, Ibanez-Tallon and Miwa then spent a good deal of effort producing active *lynx1* for collaborative studies Gregg W. Crabtree and Lorna W. Role at Columbia to examine the effects of *lynx1* on nicotinic acetylcholine (nACh) receptor function. They showed that *lynx1* can directly modulate the same receptors that the snake toxins bind to, but with an opposite, non-toxic, effect.

Heintz speculates that *lynx1*, through its action on the cholinergic system, could offer a novel avenue for development of treatments for some of the effects of aging, such as the normal loss of memory and cognitive function, which is associated with a decrease in function of the cholinergic system. It is also noteworthy that the only drug currently approved for treating Alzheimer's disease, donepezil, works on the cholinergic system.

"Cholinergic function is lost early in Alzheimer's disease and in aging," Heintz says. "Our studies of *lynx1* and other prototoxin genes offer a novel and very specific strategy for modulation of cholinergic function, which could eventually be important for attempts to restore cholinergic function in older people with memory loss or in Alzheimer's patients."

But Heintz cautions that much more work needs to be done.

"This is an exciting discovery, " he says. "It's the beginning of a set of really interesting experiments because there is so much left to discover regarding the mechanism of action of *lynx1* and its role in CNS function."

The research was supported in part by the Howard Hughes Medical Institute; the National Institute for Neurological Diseases and Stroke and the National Institute for General Medical Science, both parts of the federal government's National Institutes of Health; the AT Children's Project; and The Rockefeller University.

Lab move, continued from page 1

The task of unpacking looks daunting, but organized.

"You should have been here yesterday, " Teresky tells *News&Notes* "The boxes were piled so high in my office I could barely get in. Today I'm just tossing everything in here," she says, gesturing to Levine's faculty office—or what can be seen of it under the boxes and bubble wrap.

Levine will continue his research on the *p53* tumor suppressor gene, and his team is moving into Weiss without making any structural changes to the preexisting space. In addition to the usual benches and office space, the lab has an area for working with radioactive material, plus a glass-cleaning facility and cold rooms for storing biological samples. Levine's new lab is smaller than the one he had at Princeton, so some things were left behind in New Jersey.

Among them were a number of laboratory mice. "It took a long time for the lab to create this mouse line, and we don't want to lose it," says Teresky, explaining that the animals left at Princeton are a kind of research insurance. Once mice leave the lab, they are no longer "clean" for experimental purposes. Male mice from Levine's Princeton lab were transported to RU, where they will breed with "clean" female mice. But once these females have been in contact with the "unclean" males, they themselves become unclean; their embryos are thus removed and implanted in a second set of clean female mice. Not until the new generation is born will the lab have any animals to work with.

Tissue samples are also tricky to transport. Numerous cell lines were brought to RU in liquid nitrogen drawers. Also, chemicals considered hazardous by the moving company remained at Princeton.

In the recent move, Teresky has also had to concern herself with safety inside the new lab. "Because of the biological materials and radioactive materials we work with, federal and state regulations forbid any food or drink in the main lab," she says. She made sure that the Weiss blueprints included a conference room for lab meetings and breaks. "Here in the conference room, you can have a cup of coffee while you read a journal article. It gives people a comfortable place to sit and exchange ideas."

This concern for staff happiness seems to come from the top. "Arnold Levine is such a wonderful person to work with," says Teresky, who, after 31 years, ought to know. "He really takes an interest in the people in his lab, both professionally and personally. The only time I've ever seen him tough on people is if they aren't working hard enough."

It's obvious, though, that Teresky herself is not a target of such disapproval. When *News&Notes* returned a few days later to photograph her among the moving boxes, every bench but one had been organized and unpacked. Levine's office was spotless.The major equipment was in place. Graduate students and postdocs were already working productively in the lab. Apparently, our photo team made it just in time.

Levine lab manager Angie Teresky has had a lot of practice moving scientific equipment safely and efficiently. *Photo by Pavani Thagirisa.*

SEPTEMBER 24 | 8 OCTOBER

calendarofevents

http://wwww.rockefeller.edu/rucal

THE ROCKEFELLER UNIVERSITY—*Please post*

FRIDAY, SEPTEMBER 24
12:00 p.m. **Role of Transcription Factors in Blood Cell Commitment.** Thomas Graf, Professor, Albert Einstein College of Medicine. Molecular Biology Seminar. **116 Rockefeller Research Laboratories, MSKCC, 430 East 67th St.** *Open to RU/CUMC/NYPH/MSKCC community and guests only.*

MONDAY, SEPTEMBER 27
4:00 p.m. **NMR Studies of T-Cell Protein Interactions.** Gerhard Wagner, Dept. of Biological Chemistry and Molecular Pharmacology, Harvard School of Medicine. NMR Structural Biology Seminar. **301 Weiss.**

5:00 p.m. **Don't Take Your Medicine Like a Man.** Robert Lipsyte, Sports Columnist, New York Times, and host, *The Health Show*. E. Darracott Vaughan, James J. Colt Professor and Chairman of Urology, NYPH-WMCCU. Humanities and Medicine Lecture. **C-2, Weill Education Center Auditorium, WMCCU, 1300 York Ave.** *Reception to follow in Archbold Common.*

TUESDAY, SEPTEMBER 28
11:00 a.m. **The Structure of the Bacterial Flagellum and a New Mechanism For Its Rotary Motor.** David DeRosier, Professor, W.M. Keck Institute for Cellular Visualization, Rosentiel Basic Medical Center, Department of Biology, Brandeis University. Pels Family Center for Biochemistry and Structural Biology Seminar. **305 Weiss.**

4:00 p.m. **Agonist Gating and Isoflurane Potentiation in the Human $GABA_A$ Receptor Determined by Volume of a TM2 Residue.** Neil Harrison, Associate Professor, Dept. of Anesthesia and Critical Care, U. of Chicago. Pharmacology Seminar. **Weill Auditorium, WMCCU, 1300 York Ave.**

4:00 p.m. **From Single to Many Molecular Motors.** Frank Julicher, Institut Curie, Paris. Center for Studies in Physics and Biology Seminar. **B Level Conference Room, Smith Hall Annex.** *Contact Matthew Turner, 327-8184. Tea, 3:30 p.m.*

WEDNESDAY, SEPTEMBER 29
12:00 p.m. **p53 and TRAIL Signaling Pathways: Novel Insights into Apoptosis and Chemosensitivity.** Wafik El-Deiry, Assistant Professor, U. of Pennsylvania. Seminars in Clinical Research. **110B Nurses Residence.**

4:00 p.m. **Foreign DNA in Mammalian Systems.** Walter Doerfler, Professor of Genetics, Institute of Genetics, U. of Cologne. Pharmacology Seminar. **Weill Auditorium, WMCCU, 1300 York Ave.**

5:30 p.m. **The Future of Biomedical Science—What We Will be Able to Do and What We Will be Allowed to Do.** Daniel E. Koshland, Former Editor, *Science* Magazine; Professor of Biochemistry and Molecular Biology, UC Berkely. Zanvil A. Cohn Forum on Health Affairs. **Abby Dining Room.** *Sherry at 5:00 p.m. in the Abby Lounge.*

THURSDAY, SEPTEMBER 30
4:00 p.m. **Erythropoietin Receptor Transgene Effects on Hematopoiesis and Stem Cell Physiology.** Suzanne L. Kirby, Associate Professor of Medicine, UNC School of Medicine. LFKRI Research Seminar. **Lower Level Conference Room, New York Blood Center, 310 East 67th St.** *Tea at 3:45 p.m. Contact Rosanna Martinez, 570-3357.*

6:30 p.m. **Reinventing Medicine: Beyond Mind-Body to a New Era of Healing.** Larry Dossey, Physician and Author. Moderator: Mitchell L. Gaynor, Director of Medical Oncology, Strang Cancer Prevention Center. Integrative Medicine Lecture. **Uris Auditorium, WMCCU, 1300 York Ave.** *Contact 987-8862.*

FRIDAY, OCTOBER 1
12:00 p.m. **APP, Presenilins and the Genesis of Alzheimer's Disease.** Dennis Selkoe, Professor of Neurology, Harvard Medical School, and Co-director, Center for Neurologic Diseases, Brigham and Women's Hospital. Cellular Biochemistry and Biophysics Seminar. **116 Rockefeller Research Laboratories, MSKCC, 430 East 67th St.**

MONDAY, OCTOBER 4
11:00 a.m. **Gene, Peptide and Circadian Behavior-Lessons from Misexpressing Neuropeptide Pigment-dispersing Factor in *Drosophila melanogaster*.** Marcus Taeuber, U. of Regensburg. Lecture. 305 Weiss.

4:30 p.m. **Using GFP-tagged Molecules to Report on the Assembly of MHC Class I Molecules in the Endoplasmic Reticulum.** Michael Edidin, Professor of Biology and Medicine, Johns Hopkins University. PBMM Research Seminar. Weill Auditorium, WMCCU, 1300 York Ave.

6:30 p.m. **Breast Cancer Diagnosis and Treatment at the Millennium.** Alexander Swistel, Moderator, WMCCU. Seminar. **Uris Auditorium, WMCCU, 1300 York Ave.** *Contact Marcelle Kaplan, 746-4708. Seating available for the first 250 people on a first come, first served basis.*

TUESDAY, OCTOBER 5
4:00 p.m. **0-1 Laws for Single Molecules.** Bud Mishra, Professor, Courant Institute, NYU. Center for Studies in Physics and Biology Seminar. **B Level Conference Room, Smith Hall Annex.** *Tea at 3:30 p.m. Contact Matthew Turner, 327-8184.*

4:00 p.m. **Recent Advances in Nutrition and Cancer Prevention.** Richard S. Rivlin, Program Director, CNRU, GI-Nutrition Service, MSKCC; Professor of Medicine, WMCCU; Chief, Nutrition Division, NYPH. CNRU Monthly Meeting. **103 Rockefeller Research Laboratories, MSKCC, 430 E. 67th St.**

MONDAY, OCTOBER 18
9:00 a.m. – 5:00 p.m. **The Molecular Flying Circus: Innovations in Biological Mass Spectrometry.** A Symposium Celebrating the 25th Anniversary of the NIH-funded National Resource for the Mass Spectrometric Analysis of Biological Macromolecules. Co-Sponsored by the Pels Family Center for Biochemistry and Structural Biology. **Caspary Auditorium.**

9:30–10:30 a.m. **Introductory Remarks**
Arnold J. Levine, President, RU; Brian T. Chait, Camille and Henry Dreyfus Professor and Director, National Resource for the Mass Spectrometric Analysis of Biological Macromolecules, RU; Stephen K. Burley, Richard M. and Isabel P. Furlaud Professor and Director, Pels Family Center for Biochemistry & Structural Biology, RU; Frank H. Field, Camille and Henry Dreyfus Professor Emeritus and Founding Director, National Mass Spectrometry Research Resource, RU; Joshua Lederberg, Professor Emeritus and Past President, RU; Marvin Cassman, Director, National Institute of General Medical Sciences, NIH.

10:30 – 11:00 a.m. Coffee Break
11:00 a.m. – 12:30 p.m. Scientific Session I

Measurement of Molecular Associations by Time-of-Flight Mass Spectrometry. Kenneth G. Standing, U. of Manitoba.

Gene Function via the Analysis of Multi-protein Complexes. Matthias Mann, U. of Southern Denmark

Tandem High Resolution Mass Spectrometry of Biomolecules. Fred McLafferty, Cornell U.

12:30 – 2:00 p.m. Lunch Break
2:30 – 3:30 p.m. Scientific Session II

Proteomics: Automated Identification of Peptides and Proteins at the Attomole Level in Complex Mixtures by Mass Spectrometry. Donald F. Hunt, U. of Virginia.

A Mass Spectrometry Approach for High Throughput Tertiary Structure Determination. Bradford W. Gibson, UC San Francisco.

MS on the Critical Path to Drug Discovery and Development. Steven A. Carr, SmithKline Beecham Pharmaceuticals.

3:30 – 4:00 p.m. Coffee Break
4:00 – 5:00 p.m. Scientific Session III

High Throughput Identification and Characterization of Proteins by MALDI-TOF-MS and -MS/MS. Marvin Vestal, PerSeptive Biosystems.

Quantitative Proteome Analysis: Methods and Applications. Ruedi Aebersold, U. of Washington.

Contact Gladys McMilleon, 327-8847, mcmillg@rockvax.rockefeller.edu.

THE ROCKEFELLER UNIVERSITY Friday Lectures

These events are held in Caspary Auditorium at 3:45 P.M. Tea is served in Abby Aldrich Rockefeller Lounge at 3:15 P.M. All are welcome.

FRIDAY, SEPTEMBER 24
Structural Features of Antigen Presentation. John W. Kappler, Member, Dept. of Medicine, National Jewish Medical and Research Center, and Professor of Immunology and of Medicine, U. of Colorado Health Sciences Center, Denver; Investigator, HHMI..

FRIDAY, OCTOBER 1
Structure and Function of Prokaryotic RNA Polymerases. Seth Darst, Associate Professor, RU.

FRIDAY, OCTOBER 8
Mechanisms of pre-mRNA Splicing. Magda Konarska, Associate Professor, RU.

WEDNESDAY, OCTOBER 6
9:00 a.m.–5:00 p.m. **Under a Woman's Control: Biomedical Means for Preventing Sexual Transmission of HIV.** AMFAR Research Symposium. **Caspary Auditorium.** *Admission is free, but reservations are required. For more information and to reserve a space, call AMFAR at 806-1621 or visit the web site at http://www.amfar.org.*

The Arts and Other Events

FRIDAY, SEPTEMBER 24
12:00 p.m. **Tri-Institutional Noon Recitals.** Scott Hendricks, baritone, and James Lowe, piano, performing works by Ralph Vaughan Williams and Franz Schubert. **Caspary Auditorium.** *Open to RU/NYPH/WMCCU/HSS/MSKCC community and guests.*

FRIDAY, OCTOBER 1
12:00 p.m. **Tri-Institutional Noon Recitals.** Gould Piano Trio (violin, cello, piano) from London, performing works by Haydn and Beethoven. **Caspary Auditorium.** *Open to RU/NYPH/WMCCU/HSS/MSKCC community and guests.*

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