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news & notes

FRIDAY, OCTOBER 11, 2002 | THE NEWSLETTER FROM THE ROCKEFELLER UNIVERSITY'S OFFICE OF COMMUNICATIONS AND PUBLIC AFFAIRS

TODAY'S EVENTS

Jenuwein on histone methylation

Thomas Jenuwein, senior scientist at the Institute of Molecular Pathology (IMP) in Vienna, will give the Friday lecture today (Oct. 11). His talk, "Epigenetic Control by Histone Methylation," begins at 3:45 p.m. in Caspary Auditorium.

According to Jenuwein, great progress has been made within the past two years in understanding the functional implications of histone methylation, particularly through the characterization of histone methyltransferases (HMTases) that direct the site-specific methylation of lysine positions in the histone H3 N-terminus. Diverse post-translational modifications of histone N-termini represent an important epigenetic mechanism for the organization of chromatin structure and the regulation of gene activity.

Histone lysine methylation has been linked with pericentric heterochromatin formation, X inactivation, Polycomb-group (Pc-G) dependent repression and epigenetic gene regulation at euchromatic positions.

Moreover, studies on the stability of histone lysine methylation also revealed the surprising involvement of an RNA component in the higher-order structuring of pericentric heterochromatin. Together, these regulatory roles strongly establish histone lysine methylation as a central epigenetic modification for the organization of eukaryotic chromatin with far-reaching implications for proliferation, cell-type differentiation, overall development, gene expression, genome stability and cancer.

Jenuwein completed postdoctoral training in the Department of Microbiology and Immunology at the University of California, San Francisco. From 1990 to 1993 he was special fellow of the Leukemia Society of America and, from 1994 to 2001, group leader at the IMP.

"CAF" protein mystery solved by AIDS researchers

HIV-thwarting blood proteins provide clues to potential new treatment

AIDS researcher David Ho, The Rockefeller University's Irene Diamond Professor who heads the Aaron Diamond AIDS Research Center (ADARC), and his research team, have discovered that several natural proteins — alpha-defensins 1, 2 and 3 — can be manufactured and released by killer T cells to inhibit HIV.

The research, reported in the September 26 issue of *Science Express*, begins to unravel a 16-year-old mystery in the field of HIV research about how a small proportion of HIV-positive

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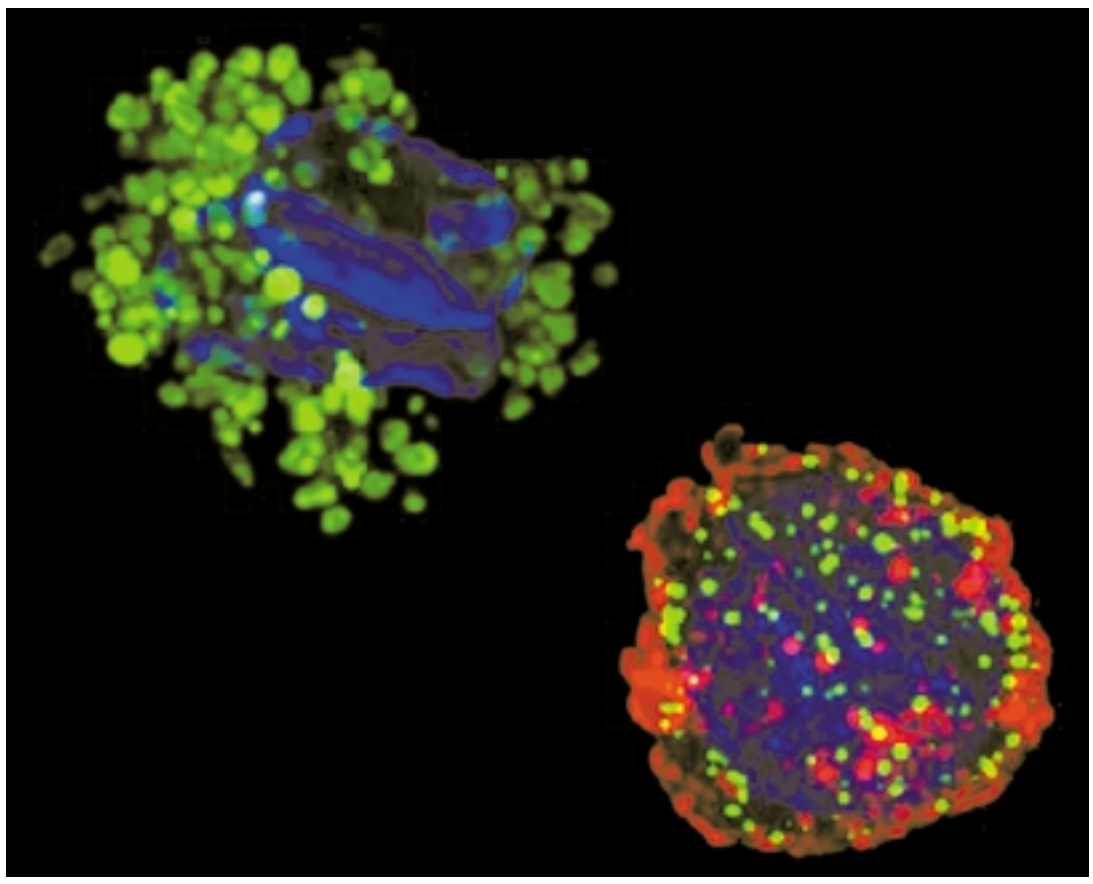


Rockefeller University/ADARC scientists recently have shown that CD8+ T cells produce alpha-defensins. At right, two immune system cells, a neutrophil *(left)* and a CD8+ T cell, are shown producing the alpha-defensin proteins *(green)*. Neutrophils have long been known to produce the proteins.

Cellular inhibitor to HIV may explain "species-specificity" of infection

Humans share over 90 percent of their genes with other primates. Yet some of our primate cousins defy infection with HIV-1, the primary source of immunodeficiency disease in humans. Other lentiviruses such as SIVmac and HIV2 afflict non-human primates, but afflict us to a lesser extent or not at all. What explains the puzzle of lentivirus susceptibility?

The "species-specificity" of infection is likely due to subtle biochemical differences in a host organism's response to a virus. These subtle variations add up to the difference between an epidemic that has claimed 25 million human lives, versus localized outbreaks of immunodeficiency disease among some non-human primates.

Rockefeller assistant professor Paul Bieniasz, a staff investigator at the Aaron Diamond AIDS Research Center (ADARC), and his research team, discovered a cellular inhibitor to HIV in non-human primates. The findings, published in the July 29 issue of *Proceedings of the National Academy of Sciences* (*PNAS*), may help explain how primate lentiviruses occasionally jump species.

Calling the inhibitor Lv1, for "lentivirus susceptibility factor 1," the researchers learned that proper reverse transcription, the stage of infection in which viral RNA is converted to viral DNA, does not occur in the presence of Lv1. Failure of reverse transcription helps researchers identify that the inhibitor works after the virus has entered a cell (post-entry), but before it has a chance to mix its viral DNA with the host cell's DNA (pre-integration).

A similar inhibitor in mice, called Fv1, blocks murine leukemia virus. This inhibitor was discovered in 1970 by Frank Lilly at Albert Einstein College of Medicine.

"It's been years since we've known that monkeys are resistant to HIV-1. This is something we should have discovered before. But I didn't think of looking for such an inhibitor until, by coincidence, I read the Fv1 literature," says Bieniasz.

To determine the cause of resistance, Bieniasz and his colleagues Simone Cowan, a research technician, and Theodora Hatziioannou, a postdoctoral associate, fused an HIV resistant monkey cell with a susceptible human cell — a kind of "poor man's" genetic cross — and challenged it with HIV. The hybrid cell remained uninfected, suggesting the presence of an inhibitor rather than a lack of permissive condition in the monkey cell. Further experiments traced the target of the inhibitor to a specific domain of the virus, called capsid.

Cells from owl monkey, African green monkey, rhesus monkey *(above)* and squirrel monkey revealed the HIV inhibitor "Lv1."
Photo courtesy of Yerkes Primate Research Center.

Follow-up research will determine whether human cells have a Lv1-like inhibitor that protects, or fails to protect, from infection by other lentiviruses. This knowledge could help predict the likelihood of other immunodeficiency virus epidemics in humans.

In addition to answering this and other related questions suggested by their findings, the scientists want to develop a better primate model (ideally rhesus monkeys) for HIV vaccine research — one that would support HIV-1 infection, as opposed to the lentivirus strains currently used.

Additional Rockefeller/ADARC authors on this publication include graduate fellow Tshaka Cunningham and assistant professor Mark Muesing.

This research was supported by the Donald A. Pels Charitable Trust, The Aaron Diamond AIDS Research Center and the National Institute of Allergy and Infectious Diseases.

— *Lynn Love*

"Tools of trade" on exhibit

Instruments play an important — and sometimes underappreciated — role in scientific research, going hand in hand with the development and testing of new ideas. Rockefeller's rich history of scientific achievement includes landmarks in the development of instrumentation. Many of these objects are on display in Caspary Gallery beneath Caspary Auditorium in an exhibit titled *Tools for Discovery*.

"Old instruments are a snapshot of the way science was done in the past," says Professor Vincent A. Fischetti, advisor to the collection. "It is a reflection of human ingenuity to answer complex questions with equally complex, yet crude, instrumentation."

Among the instruments on display are several associated with Nobel Prize winners: an early peptide synthesizer from Bruce Merrifield's laboratory; microtomes that played an important role in the development of cell biology at Rockefeller; and a fraction collector built by Stanford Moore and William Stein.

These and many other items in the gallery have a particularly close connection to Rockefeller's history because they were developed in the university's glass blowing, instrument and electronics shops.

"The display is a tribute to the instrument makers and glass blowers who help the scientists accomplish their goals," says Fischetti.

"The university was one of the first of its kind in this country doing biomedical research," adds Fischetti. "To accomplish this successfully it needed instrument makers and glass blowers to design and build the scientific equipment for the resident scientists. This unique capability placed the university at the cutting edge of scientific exploration, and is probably one of the major factors responsible for the university's extraordinary success."

Rockefeller owes its collection of more than 300 historic instruments to the efforts of Professor Emeritus Merrill W. Chase, who took over a collection that workers in the Office of Purchasing had rescued from a Dumpster. Chase initially organized and documented the collection, which has been managed for the last several years by Peter Sellers, an adjunct faculty member. Sellers continues to add pieces to the collection.

Some instruments given away before the collection was started now are making their way back to Rockefeller. In the 1950s, Theodore Malinin at the University of Miami became interested in the pump developed by Rockefeller Nobel Prize winner Alexis Carrel and Charles Lindbergh to perfuse organs in a nutrient bath and thus keep them alive outside a living organism — a precursor to organ transplant.

Instruments on display in the *Tools for Discovery* exhibit include the Van Slyke manometric apparatus (Donald Van Slyke, early 1920s); some of the earliest portable cardiac pacemakers (Alexander Mauro and Lawrence Eisenberg, early 1960s); and a peptide synthesizer (Bruce Merrifield, 1960s).

Malinin acquired about a dozen of the perfusion pumps from Detlev Bronk, then president of Rockefeller, and worked with Lindbergh, the aviator and engineer, and later on his own, using the pumps for research. Malinin recently has given the perfusion pumps back to Rockefeller, along with a large collection of manuscripts and printed material pertaining to Carrel, to be saved at the Rockefeller Archive Center.

In addition to their historical significance, the instruments are remarkable for their beauty, and the display is designed and lighted to accentuate their form. The exhibit also features photographs of the instruments by Rockefeller alumnus Barry Dworkin (class of 1973).

— *Elizabeth Hanson*

Elizabeth Hanson, curator of Tools for Discovery, *is a historian of science and director of special projects in the President's Office.*

"CAF" proteins *continued*

Research technician Wenjie Yu *(right)* confers with Assistant Professor Linqi Zhang on the mass spectrometry read-out of "CAF" proteins.

individuals avert the virus's destructive effects.

The elusive substance in the blood of "long-term non-progressors" — people who test positive for the virus, but do not get sick — has been studied since 1986, when it was discovered by leading scientist Jay Levy of the University of California, San Francisco. Since then, HIV research teams have tried to identify the proteins. But the CD8+ Antiviral Factor (CAF) proteins, as they are called, yielded little information to scientists, until now.

"Many renowned scientists have tried to clone and express these proteins," says lead scientist for the study Linqi Zhang, assistant professor at Rockefeller and an ADARC staff scientist. "But they've been unsuccessful because not every cell has the correct machinery to process the protein once it's translated." The proteins are hard to identify using traditional approaches.

"Alpha-defensins are promising as a future addition to the HIV treatment arsenal," says Ho. "Researchers at ADARC already are pursuing new therapeutic approaches based on the current research results."

Alpha-defensins 1, 2 and 3, members of a family of so-called "natural peptide antibiotics," work in combination — if the host immune system can produce them — to prohibit the virus's replication, or copying, in the body.

Defensins, which come in approximately a dozen known forms, first were described by scientists Tomas Ganz and Robert Lehrer at the University of California, Los Angeles, in 1985. The proteins were thought to be made exclusively by neutrophils, specialized immune system cells, to kill bacteria. The Rockefeller/ADARC researchers have learned that they also are made by CD8+ T cells and inhibit the replication of HIV by an as-yet-undefined mechanism.

In the *Science* study, Zhang, Ho and their ADARC colleagues Winjie Yu, Tian He, Jian Yu and Wenyong Zhang used traditional biochemical methods combined with a novel, chip-based protein analysis system, called ProteinChip, to compare long-term non-progressors' CD8+ cells with cells from HIV patients whose immune systems had begun to fail. Ciphergen Biosystems, Inc., of Fremont, California, developed ProteinChip.

The technology, which measures the qualities of a protein via simple mass spectroscopy analysis, yielded immediate results, and brought the first tangible sense of direction to identifying CAF proteins.

"Until that point, we and all the other scientists working on the project were almost blind to the proteins' identity," says Zhang. "ProteinChip suddenly put a mountain range in our line of sight."

Ho, Zhang and their colleagues scoured those "mountains" — literally the peaks of spectroscopy read-out from six different kinds of analysis — to make molecular sense of the data.

The scientists then compared their data with that of known proteins in publicly available databases, hoping for clues that would help them define the CAF proteins. To their surprise, the Rockefeller/ADARC scientists came up with an exact match: alpha-defensins 1, 2 and 3.

The remaining months of research were spent studying the proteins' efficacy. Since only very small quantities of the proteins exist, obtained from samples of human blood, Zhang's research team used synthetic defensin, alone and in combination, to try to further understand why the T cells that do manufacture the proteins make three versions.

In their experiments, the scientists learned that individual defensins alone don't perform well. A combination of at least two, and possibly all three, is required to confer inhibitory effects.

The three alpha-defensins published in the *Science* study are active against all strains of the virus.

"This discovery is a major step forward in our understanding of how the body fights HIV," says Zhang. "By understanding how some people's immune systems are able to control HIV infection, we may be able to develop new treatments that take advantage of this phenomenon."

Research in 1995 found a family of proteins called beta-chemokines that could account for some of the viral suppression in non-progressors, but beta-chemokines were ineffective against many strains of the virus and could not fully account for the CAF activity.

Additional authors of the *Science* paper include Rebecca Cafferey, Enrique Dalmasso, Siyu Fu, Thang Pham and Jianfeng Mei, all Ciphergen researchers or technicians.

This research was supported by the Campbell Foundation and the Irene Diamond Fund.

— *Lynn Love*

Curtain rises on new season of "Peggy Concerts"

For music lovers on the Rockefeller University campus and beyond, a delightful autumn ritual is the start of the university's Peggy Rockefeller Concerts Series.

And, as part of a pilot program organized this year in collaboration with The Gift of New York, 10 tickets to each concert in the 2002-2003 series will be donated to families who lost loved ones on September 11, 2001.

Founded by Professor Theodore Shedlovsky in 1958, the concert series features monthly chamber music performances in Caspary Auditorium. With a wide range of musical styles and a roster of internationally acclaimed artists, this year's series offers something to every concertgoer.

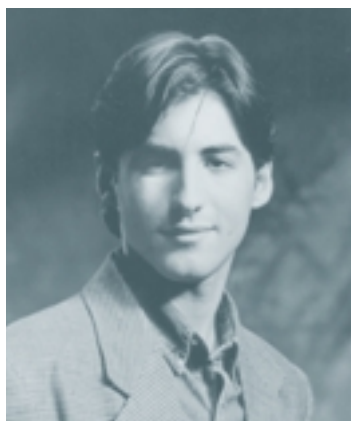
The season kicks off October 23 with a recital by young Russian-born violinist Philip Quint, whom the *Chicago Tribune* calls "a virtuoso whose many awards are fully justified by the brilliance of his playing."

German Romantic *Lieder* will be performed March 4 in a recital by baritone Wolfgang Holzmair, accompanied by pianist Russell Ryan. Holzmair has been hailed by *The New York Times* as "an intensely focused singer who uses his... keen intelligence to animate the songs he sings."

On April 30, the Guarneri String Quartet returns. The quartet are one of the world's most acclaimed chamber music ensembles and a beloved tradition on the Caspary stage, having appeared at Rockefeller each year since their inception in 1964.

Further highlights include performances by pianist Louis Lortie and renowned American and international chamber ensembles: American Chamber Players, Brahms Trio, Osiris Piano Trio and Camerata Sweden.

The Peggy Rockefeller Concerts Series (affectionately dubbed "The Peggy Concerts" by attendees) was renamed in 1996 to honor the wife of longtime chairman of the university's Board of Trustees David Rockefeller. The concerts provide a unique opportunity to hear world-class artists at affordable prices, and are an important facet of the university's commitment to the fine arts.



Violinist Philip Quint

"I'm pleased that the series has been so well appreciated in the past, and hope newcomers to campus will try it out and find it to be an important part of their lives in New York," says George N. Reeke Jr., head of Rockefeller's Laboratory of Biological Modeling and faculty coordinator of the series.

Subscriptions still are available. The cost is $145; Rockefeller graduate fellows and postdocs may purchase up to two subscriptions for their own use at a special rate of $60. Concerts are held Tuesday or Wednesday evenings at 8 p.m. For additional information, call 327-8437.

— *Holly Teichholtz*

PEOPLE IN THE NEWS

Muir receives protein award

Professor Tom Muir received the Leonidas Zervas Award from the European Peptide Society at a ceremony in Sorrento, Italy, in September. The award is given to a scientist under the age of 40 who has made the biggest impact in understanding the chemistry of peptides or proteins during the preceding five-year period. Muir was honored "in recognition of the excellent results achieved in the development and application of original and fundamental novel methods of protein synthesis." Zervas was a peptide/protein chemist whose seminal work on synthesis and enzymology was conducted at Rockefeller in the 1930s.

Joel Cohen speaks to black caucus

Abby Rockefeller Mauzé Professor Joel E. Cohen spoke at the National Town Hall meeting of the Congressional Black Caucus in Washington, D.C., last month. In addition to presenting demographic facts about the developing world and Africa in particular, Cohen emphasized the role of infectious diseases as an obstacle to human well-being and economic development. Other panelists were the Reverend Jesse Jackson, Reps. Charles Rangel (D-NY) and Richard Gephardt (D-MO), and Hilary Inyang, Duke Energy Distinguished Professor and director of the Global Institute for Energy and Environmental Systems at the University of North Carolina, Charlotte.

Rockefeller hosts discussion on stem cell research

A panel of Rockefeller senior administrative staff spoke at an October 1 inter-institutional conference for administrators working on issues relating to human embryonic stem cell research. The meeting was attended by 60 senior administrators representing such areas as technology transfer, grants management, legal, finance and research support from 16 research universities and scientific institutions throughout the country. Hosted by Acting President Thomas P. Sakmar, the conference was organized by the Development Office and the Office of the General Counsel. The panelists were *(l-r)* Rockefeller administrators Amy Wilkerson, associate vice president, Research Support; Michael Vitale, director, Finance and Audit; Kathleen Denis, associate vice president, Technology Transfer; and Harriet Rabb, vice president and general counsel.

Talent on display at RU art show

Self Portrait and *Mimi*, oils on canvas by Edward M. Jones of the Media Resource Center, were among the works on display as part of the 2002 Rockefeller University Art Show.

The annual show, which is organized by Human Resources, offers Rockefeller scientists, students and administrative staff a forum to display their photography, painting, knitwork, weaving, crochet and all manner of visual art and crafts.

The show, located in the lobby of the Weiss Research Building, opened Thursday evening, September 19, with a reception hosted by Acting President Thomas P. Sakmar. Art was exhibited through October 3.

Anniversary and Retirement Dinner honors exceptional service to RU

The Rockefeller University Anniversary and Retirement Dinner, honoring retirees and employees with 25, 40 or 50 years of service to the university, was held Thursday evening, October 3, in Weiss Café.

Among those recognized by Acting President Thomas P. Sakmar were John D. Rockefeller Jr. Professor Emeritus Norton D. Zinder for 50 years of service, and Erika Mueller, manager in Plant Operations, marking 40 years at the university.

Among those honored for 25 years of service were senior research associate Maggi Pack *(near right photo, second from right)* of the Steinman lab, celebrating with *(l-r)* retiree Grace Silvestri, Henry G. Kunkel Professor Ralph Steinman and Claudia Steinman; and Security Operations Manager Michael John *(far right photo)* with *(at left)* retiree Wilwyn Clarke.