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news & notes

November 17, 1995 Volume 6, Number 10

The Rockefeller University

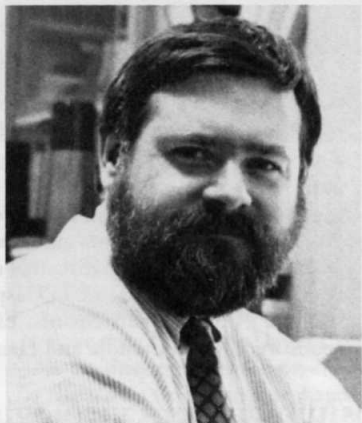
Trustees approve promotions



Fred Cross (left) is now professor and James Krueger, associate professor and head of lab.

At its fall meeting Wed., Nov. 15, the Board of Trustees promoted to professor molecular geneticist and head of lab Frederick R. Cross and appointed immunologist James G. Krueger associate professor and head of lab.

"We are pleased that the trustees have endorsed the accomplishments and the promise of these young scientists," said President Torsten Wiesel. "Fred Cross is a creative researcher who has made significant contributions to our knowledge of cell control. Jim Krueger has played a leadership role in our clinical research efforts, particularly in the cause and treatment of skin disease."



Left: Carlsson

Cross

Cross and his colleagues study the control of the cell cycle in yeast. Specifically, his lab looks at the beginning of the cell cycle, called START, a critical step toward the replication of DNA and eventual division of the cell. Mechanisms of cell cycle control in yeast are similar to those in higher organisms.

Cross, a graduate of Swarthmore College (1978), completed his Ph.D. at Rockefeller (1984) in the Hanafusa lab. He held a postdoctoral fellowship at the Hutchinson Cancer Center in Seattle, Washington, for four years, then

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Memorial symposium honors late RU virologist Igor Tamm

A memorial symposium in honor of the late Professor Emeritus Igor Tamm, entitled "A Day of Virology and Cell Biology," will take place Thurs., Nov. 30.

"A day of exciting research reports by friends and colleagues is a most fitting tribute to a superb scientist and wonderful man," said Purnell Choppin, president of the Howard Hughes Medical Institute (HHMI) and Tamm's scientific colleague, who organized the symposium with RU trustee Alexander Bearn, Professor Hans J. Eggers of the Institute of Virology at the University of Cologne, and Professor Emeritus James S. Murphy of Rockefeller.

A native of Tapa, Estonia, Tamm emigrated to the U.S. in 1945 after studying at the Tartu University Medical Faculty and at the Karolinska Institute in Sweden. Yale University awarded him an M.D. cum laude in 1947. In 1949, he joined Rockefeller. He became Abby Rockefeller Mauzé Professor in 1986, and emeritus in 1992.

Tamm was a pioneer in the study of the biochemistry and replication of viruses. Working with influenza viruses, he isolated and characterized the Tamm-Horsfall glycoprotein, the first pure virus receptor

and substrate for the influenza virus enzyme. Tamm obtained the first evidence that RNA plays a role in the replication of DNA-containing viruses. In the 1960s, he discovered the existence of double-stranded

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At the Friday lecture

A message about signal messengers



Angus Nairn is associate professor in the Greengard lab.

Angus Nairn, associate professor in the Greengard lab, discusses "Serine/Threonine Protein Kinases and Protein Phosphatases: Structure and Regulation" at the Friday lecture today (Nov. 17).

Cells respond to chemical signals from other cells through a process called signal transduction. In signal transduction, first messengers—hormones and neurotransmitters—bind to the outside of a cell, setting in motion a process that produces second messengers inside the cell that complete communication of the signal. Nairn and his colleagues focus on protein phosphorylation, a key enzymological mechanism by which signal transduction takes place. Recently, collaborations with the Kuriyan laboratory resulted in the first determination of the three-dimensional structures of a calcium/calmodulin-dependent protein kinase and of a serine/threonine protein phosphatase.

"Angus is one of the world's

See *Nairn*, page 4

President of natural history museum to address Cohn forum

Ellen V. Futter, president of the American Museum of Natural History, will speak on "Science: Not for Experts Only" at the Zanvil A. Cohn Forum on Health Affairs Tues., Nov. 28.

"Ellen Futter believes in commu-

nity service and contributes to many sectors of society—academia, the arts and sciences, corporate affairs, and public policy," said Alexander Bearn, forum organizer. "She has a unique understanding of the role of science in public life, and I am pleased that she has agreed to share her perspective with the forum."

President of the American Museum of Natural History since 1993, Futter previously served as president of Barnard College, her alma mater, for 13 years. She earned her undergraduate degree magna cum laude in 1971, serving in her senior year as a student representative to the Board of Trustees. She earned her J.D. degree from Columbia Law School in 1974, and then joined Milbank, Tweed,

See *Futter*, page 4



Joyce Ravitt

Ellen Futter served as president of Barnard College for 13 years before joining the American Museum of Natural History.

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will travel

3 Abl's abilities

4 RU runners in
the cold apple

Promotions

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returned to RU in 1989 as head of lab. Trustees promoted Cross to associate professor in November 1993. His awards include a National Science Foundation Predoctoral Fellowship, a Helen Hay Whitney Fellowship, and a Lucille P. Markey Scholarship.

Krueger

Krueger will head the Laboratory of Investigative Dermatology. He has been acting administrative head of the research group, which studies a variety of skin conditions, since the death of lab head Martin Carter in 1993.

Krueger studies the pathogenesis of psoriasis in patients at the RU Hospital. Recently he made discoveries about the role of the immune response in triggering outbreaks of the painful and disabling disease and has been experimenting with a lymphocyte toxin to mitigate its effects.

After completing undergraduate work at Princeton University (1979), Krueger joined RU as an M.D.-Ph.D. student (Ph.D., 1984; M.D., 1985), then held a succession of appointments in the Carter lab. He became assistant professor in 1990. In 1991, Krueger was the first recipient of the Thomas B. Fitzpatrick Award and in 1995 he was elected to membership in the American Society for Clinical Investigation.

Pieribone

The board also approved the appointment of postdoctoral fellow

Vincent Allen Pieribone to assistant professor in the Greengard lab.

Pieribone, who studies vertebrate locomotion, earned both his baccalaureate and doctorate at New York University (1986, 1992). While completing his dissertation with Gary Aston-Jones, he was a visiting scientist at the Karolinska Institute, where he worked with Tomas Hökfelt and Sten Grillner. He joined the Greengard lab as a postdoctoral fellow in 1992. New York University supported his work with five competitive awards, and he has won grants from the National Science Foundation and the Public Health Service's National Research Service.

News&Notes will carry more news from the trustee meeting in December.

Tamm memorial symposium gathers virologists and cell biologists

(continued from page 1)

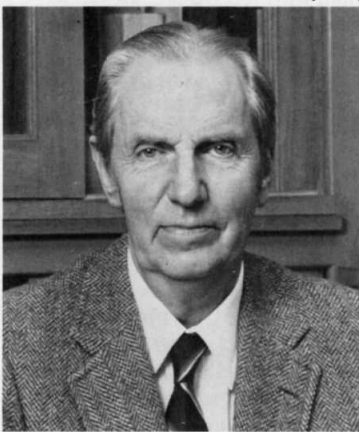
RNA as genetic material in the ubiquitous reoviruses of humans and animals and in the wound tumor virus of plants. He also studied mechanisms that regulate the production of interferons. Among other honors, the National Academy of Sciences elected Tamm a member in 1975. He died at home in Watch Hill, R.I., in February 1995. He was 72.

The symposium, which will take place in Caspary Auditorium, begins at 9:15 A.M. with opening remarks by President Torsten Wiesel and Choppin. The speakers

are: Walter Doerfler, professor, Institute of Genetics, University of Cologne; Eggers; Kathryn V. Holmes, professor of Microbiology, University of Colorado School of Medicine; Edwin D. Kilbourne, research professor, New York Medical College; James Krueger, associate professor, Rockefeller; Robert A. Lamb, professor, Northwestern University and investigator, HHMI; Murphy; Lennart Philipson, director, Skirball Institute for Biomolecular Medicine, New York University; and Pravinkumar Sehgal, professor, New York Medical College.

Choppin will give closing remarks, followed by a reception at 5:00 P.M. All are welcome.

For the program, contact the Office of Public Affairs, x8967.



Igor Tamm (1922-1995)

propulsion engines on submarines and destroyers.

Accent: Half New Hampshire, his home state, and half South Carolina, his wife's. "In the South, they say I'm from the North. In New England, they think I'm Southern. No one wants to claim me."

Progeny: Five daughters, four granddaughters.

Home: Mount Joy, PA. "The heart of Amish country. Yes, we see horse and buggies driving by."

Church: The Living Word Community Church, York, PA. "It's nondenominational. We think about how we can help each other, at home as well as in other countries."

Plans: Travel to Villa Nueva, Guatemala in

January to build a school at an orphanage for 70 children. "It's a church project. Lots of the guys own construction businesses. The concrete's been laid and the cement stacked. Our team will do the wiring, install doors and windows, and put on the roof."

"We get close to these kids, helping them. These are kids with no family. *No family.* One team leader is working to adopt one."

Motivation: "I've been given a good life, but I witnessed a lot of terrible stuff, in Vietnam and all over. I did some midlife reflection, and I want to add good to the world."

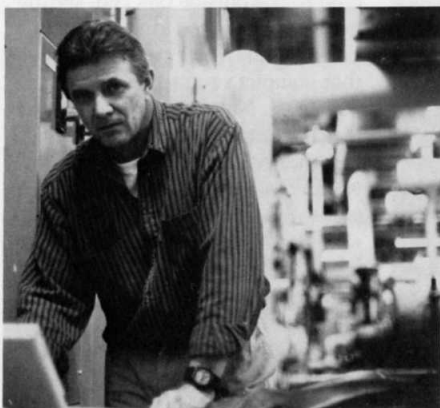
Request: "I've pledged to raise \$1,000 by the end of November, in addition to my own contributions. If members of the campus community would like to join me in giving the gift of food, shelter, and education, I can be reached at x8001."

Profile

Mike Whalen

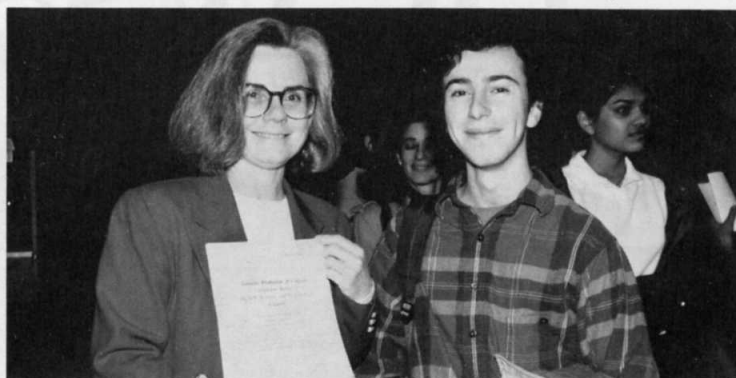
Position: Senior controls technician. Maintains automated control systems, primarily for laboratory ventilation systems.

Military service: Navy, 1965-1985. Retired as a senior chief petty officer. Responsible for main



In January, Mike Whalen will complete a school for orphans in Guatemala.

Outreach program awards certificates



Aaron Einbond of Hunter College High School (right) is first author of an article submitted for publication on work he did in the Hanafusa lab through RU's Science Outreach Program, which gives high school students and teachers laboratory experience. Bonnie Kaiser, program director, displayed the manuscript at a convocation Sat., Nov. 11 in Caspary Auditorium for last summer's program participants. Einbond and seven others were sponsored by the Camille and Henry Dreyfus Foundation.

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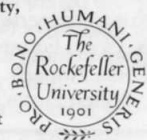
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Synthetic ligands yield real insights into signaling processes

by Susan Blum

The cells of multicellular organisms do not live in isolated splendor. Though each cell has its own specialized role to play, the way it plays that role is largely determined by messages it receives from other cells near and far. These messages are multifarious, commanding the cell to grow, differentiate, produce a particular protein, migrate, or even die for the good of the whole.

Each message arrives at the cell surface and then is sent to the cell's innermost regions through a complicated relay race involving numerous signal-transducing proteins. Many of these proteins contain conserved domains, or modules, that act as key players in sending the signal along.

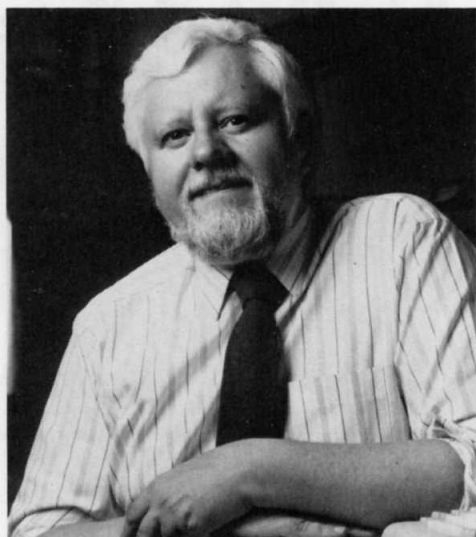
Among the most important of these protein modules are the SH2 and SH3 domains. Embedded within hundreds of proteins, and frequently found adjacent to one another, the two regions serve different functions.

SH2 domains bind phosphorylated tyrosines in proteins. Tyrosine is one of the 20 amino acids used to build proteins, and one of the first steps in signal transmission inside the cell—the flicking of a molecular switch from an off to an on position—is often the addition of a highly charged phosphate group to a tyrosine. When SH2 domains bind to phosphorylated tyrosines, they register that the molecular switch has been tripped, and move the cell further along in the process of signal transduction. The function of SH3 domains is less well understood, although they are known to bind peptides rich in proline, another of the 20 amino acids.

One example of SH2- and SH3-containing proteins is the Abl protein (abl—pronounced “able”) under study in several labs at Rockefeller, including the lab of Associate Professor David Cowburn. The protein is a tyrosine kinase, an enzyme that puts phosphates on tyrosine. When mutated in certain ways, abl can become an oncogene, or cancer-causing gene. In the protein's oncogenic form, it appears that the SH2 domain is required for transforming the cell, while the SH3 domain is required to inhibit or regulate SH2's function. Just how this happens is as yet unknown—as is the normal function of the abl protein.

Abl domains: Able to interact?

Because SH domains play such important roles in proteins, scientists want to learn more about the ways SH2 and SH3 domains may



Associate Professor David Cowburn is conducting research on signaling molecules using nuclear magnetic resonance spectroscopy.

interact with other molecules and among themselves. Structural studies of several other SH2- and SH3-containing proteins had indicated there might be some direct interaction between the two domains, and researchers in the Cowburn lab were interested to see if such interactions were present in abl. NMR spectroscopy, the lab specialty, studies protein molecules in solution, and is especially sensitive to the small structural perturbations that might be caused by the interactions.

Initially, Cowburn and his colleagues, particularly postdoctoral associate Yuying Gosser, solved the structure of the abl SH3 domain. They found that it consists of two anti-parallel beta sheets (a type of protein folding) packed against each other, as first shown for the SH3 domain of spectrin, another protein.

Having already solved the NMR structure of abl's SH2 domain in 1993, the researchers were then able to explore the relationships between the two domains in a dual domain construct, SH(32). Comparing the NMR spectra—the fingerprints—of individual abl SH2 and SH3 domains and of the domains connected together through their native linker, the researchers' results suggested that the functions of the abl SH3 and SH2 domain are relatively

independent *in vitro*, with no inherent cross talk between them. The results were reported in the Oct. 15 issue of *Structure*.

Though these NMR findings provided much information about abl, they could not resolve the issue of the relative orientation of its SH2 and SH3 domains. Such information might provide insight into the domains' function—for example, their possible propinquity to the enzyme's active site. To begin solving this problem, Cowburn and his colleagues took a chemical approach, to see what the action of ligands (or binding peptides) could

show about the orientation of the domains' binding sites.

No known binding protein contains ligands for both SH2 and SH3 domains, so Cowburn and his collaborators, including George Barany of the University of Minnesota, synthesized a series of consolidated ligands composed of multiple binding peptides of various orientations, separated by linkers of different lengths. These consolidated ligands interacted simultaneously with the

SH2 and SH3 domains of the Abelson kinase.

Close, but no interaction

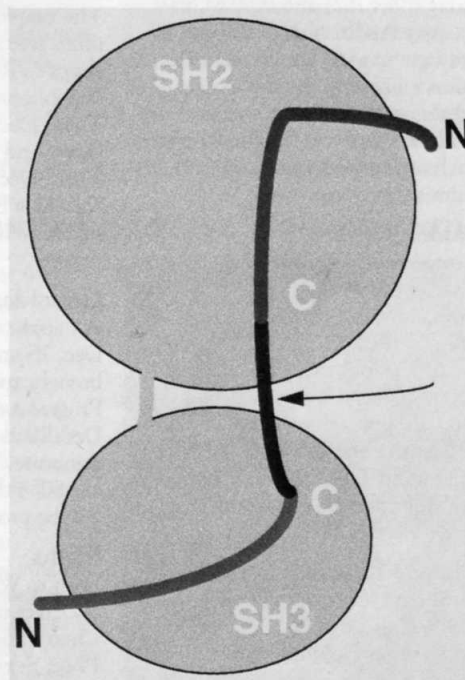
NMR engineer Jie Zheng measured the binding affinities of the various ligands by a method called quenching of intrinsic tryptophan fluorescence. Data about the affinities enabled the researchers to determine the position of the amino and carboxyl ends of the binding peptides, to learn in which orientations and separation distances the ligands bound most strongly and, thus, to learn the orientations of the binding sites within the domains themselves. Using this approach, for instance, they found that the binding sites can come moderately close to one another, even though there is no direct interaction between them.

The success of this methodology makes Cowburn optimistic about broader uses of the approach. “Consolidated ligands may be generally useful reagents for studies of the cell biology of signal transduction complexes,” he said. As such, they may help elucidate not just the roles of SH domains in individual proteins, but also their roles as participants in the multiprotein assemblies that form during signal transduction, as signals get passed along from one protein to the next.

In addition, “a major challenge in the study of intracellular signal transduction is the relatively transient nature of the complexes formed,” Cowburn said. He speculates that highly specific reagents may permit these complexes to be trapped or selectively interfered with, permitting more detailed studies of the signal transduction process.

The reagents may also provide leads into possible diagnostic and therapeutic agents for the many pathological states that can occur when signaling through SH domains is involved. For instance, cancer, diabetes, immune system disorders, and vascular problems are just a few of the conditions linked to malfunctions in signaling mediated through SH2 and SH3 domains.

High affinity ligands may permit scientists to tinker with the aberrant pathways to correct problems in signaling. At molecular weights of over 2,000 Daltons, the first generation of consolidated ligands constructed in the Cowburn lab are too big for use as small-molecule drugs. But mimetics or other target molecules based on the consolidated ligands and the structures derived using them may someday prove useful and practical in treating disease.



Researchers in the Cowburn lab made synthetic ligands, or binding peptides, to probe the relationships between domains called SH2 and SH3 in a signaling molecule called abl. Their studies disclosed the ligands' orientations, which gave the scientists clues about how the domains themselves are situated.

Courtesy of David Cowburn

For RU marathoners, warm glow follows record cold

The Manhattan entrance to the Queensboro Bridge, just a sprint from Rockefeller's 66th Street gate, marks the 17th mile of New York's annual marathon. For Raymond Birge, an assistant professor in the Hanafusa lab, it felt like home.

"I got a tremendous boost when I turned onto First Avenue that carried me through to the end," said Birge, one of a handful of Rockefeller runners that competed this year. Finishing in 3 hours, 33 minutes, Birge achieved a personal best after dropping out of last year's race from fatigue.

Another veteran from last year's race, Peter van Ophem, clocked in with his best time—3:09:38. Any special training for this marathon? "Only the regular things that are well prescribed," said van Ophem, a postdoctoral associate in the Manning lab.

Other marathon repeaters were Mark Wurfel, a postdoctoral associate in the Steinman lab, and Heather Mooney, a research nurse in the Hospital, who ran in two Boston marathons and one previous New York marathon. Wurfel finished his fourth marathon in 3:23.



A handful of Rockefeller runners were among the 26,500 who competed in the New York City Marathon Sun., Nov. 12. **Left to right:** Eric Marechal, Raymond Birge, Cecile Bougeret, Peter van Ophem, and Mark Wurfel (not shown: Heather Mooney).

"I trained quite a bit but got off to a bad start," he said.

Two newcomers to the race, Eric Marechal and Cecile Bougeret, trained together and finished with identical times of 5:06:59. "Eric watched last year's marathon and talked me into doing it," said Bougeret, a postdoctoral fellow in the Hanafusa lab.

This year's marathon, the coldest

in the history of the race, affected each runner differently. "The weather was brutal, but then I like the cold," said Birge. Mooney, who finished in 4:27, rated the weather "very tough." For Marechal, a postdoc in the Chua lab, "the weather was not a problem."

There is a familiar adage in sports: "There's always next year." Said Bougeret, "I'll be back for sure!"

Futter

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Hadley & McCloy to practice corporate law. In 1980, she took a leave of absence from the law firm to serve as Barnard's acting president, becoming president a year later.

Futter is a trustee of the Committee for Economic Development, a director of the Bristol-Myers Squibb Company, and a member of the Council on Foreign Relations, the Helsinki Watch, and the National Institute of Social Sciences. She has served as chairman of the board of the New York Federal Reserve Bank and on the boards of the Educational Testing Service, the Legal Aid Society, the Regional Plan Association, and other organizations.

Futter has received honorary degrees from Amherst College (doctor of humane letters), Columbia University (doctor of laws), Hamilton College (doctor of laws), New York Law School (doctor of laws), and Smith College (doctor of laws).

The forum will take place at 5:30 P.M. in Abby Aldrich Rockefeller dining room, preceded by sherry at 5:00 P.M. All are welcome.

Potpourri



Pianist Fazil Say, winner of the 1995 Young Concert Artists International Auditions, performs today (Nov. 17) at the noon recital in Caspary Auditorium. Admission is free and all are welcome.

Open enrollment deadline

Today (Nov. 17) is the last day of the open enrollment period, which allows employees to join or make changes to the university's health insurance and voluntary accidental death and dismemberment plans. This is also the only time to sign up for the 1996 flexible spending account (FSA). Prior FSA elections do not roll over each year. Contact Kristin Gross, x8297, or Ginny Hansen, x8299.

Friday film

Bye bye Brazil (Brazil, 1980), directed by Carlos Diegues, will be shown today (Nov. 17) at 8:00 P.M. in Caspary Auditorium. The film, in Portuguese with English subtitles, follows a small-time traveling sideshow as they ply the dusty back roads of Brazil peddling tawdry yet enchanting cardboard magic. Admission is free.

Banking offer

Representatives from Chase Manhattan Bank will be on campus Tues., Nov. 21 and Wed., Nov. 29 from 10:00 A.M. to 2:00 P.M. in the Weiss lobby to answer questions about a special workplace banking offer. Appointments are also available at the branch office at 79th Street and Third Avenue. For further information contact the Controller's Office, x7736.

Clinical Research Seminars

Li-Shing Huang, assistant professor at the College of Physicians and Surgeons at Columbia University, will discuss "Role of Apo B in Embryonic Development, Lipoprotein Metabolism and Male Infertility: Studies in Apo B Knockout Mice," Wed., Nov. 22. Marilyn M. Dammerman, assistant professor in the Breslow lab, discusses "The Apo AI/CIII/AIV Gene Locus in Common Dyslipidemias," Wed.,

Nov. 29. The seminars take place at noon in Nurses Residence 110B.

EAPC workshops

The Employee Assistance Program offers free stress-management workshops to RU employees and their dependents in Weiss 305:

Tues., Dec. 5, noon to 1:00 P.M.: Stress and Relaxation Techniques; Tues., Dec. 12, noon to 1:00 P.M.: "Holiday Blues" and Stress. Space is limited. Call 746-5890 to register.

Grant deadlines

All applications due between Mon., Dec. 25 and Mon., Jan. 1 should be brought to the Office of Sponsored Programs Administration by Wed., Dec. 20 at 3:00 P.M. for review and signature. Voice mail messages left at x8054 during the holiday week will be promptly answered.

Births

Born to Wenzhu Zhang, research associate in the Chait lab, and Chao Tang a daughter, Alice, 5 lb, 15 oz, Sept. 16.

Born to Urooj Mirza, research associate in the Chait lab, and Asra Mirza, assistant for research in the Steinman lab, a son, Talib, 6 lb, 15 oz, Oct. 13.

News&Notes schedule

News&Notes will not be published Fri., Nov. 24 due to Thanksgiving.

Nairn

(continued from page 1)

leading authorities on the enzymes involved in signal transduction pathways," said Professor Paul Greengard, who introduces Nairn today. "He has contributed greatly to our understanding of the structure and function of calcium-dependent protein kinases and serine/threonine phosphatases."

Nairn received a Ph.D. from the University of Birmingham, England, in 1979. He was a postdoctoral fellow and a research associate at Yale University School of Medicine from 1979 to 1983. He joined the Greengard lab in 1983 as an assistant professor and was promoted to associate professor in 1989.

Nairn, previously a Muscular Dystrophy Society fellow, is a member of the Society for Neuroscience and the Protein Society. He is editor of the book *Advances in Second Messenger and Phosphoprotein Research* and of the *Journal of Biological Chemistry*. Author or coauthor of more than 150 publications, Nairn has taught courses at the Institute for Advanced Studies at the Hebrew University, RU, and the Marine Biology Laboratory, Woods Hole.

The lecture will be held at 3:45 P.M. in Caspary Auditorium and preceded by tea at 3:15 P.M. in Abby Aldrich Rockefeller Lounge. All are welcome.