



news & notes

MARCH 17, 2000 VOLUME 21, NUMBER 16

THE ROCKEFELLER UNIVERSITY

Board elects two new trustees

The board of trustees elected Georges C. St. Laurent Jr. and Robin Neustein as new trustees at its meeting Wed., March 8.

St. Laurent serves as a director for the National Academy of Sciences, President's Circle; Baxter International, Inc. and Perkin-Elmer Corp. and is a trustee for the Sabin Foundation. He is a graduate of Harvard Business School, where he received his master of business, administration-finance. Among St. Laurent's current business interests are Evans



The board of trustees elected Georges C. St. Laurent Jr. (top) and Robin Neustein as new members. Photos courtesy of Georges C. St. Laurent and Robin Neustein.

Forest Products Limited, St. Laurent Evans Canada Corp., St. Laurent Realty, Inc., St. Laurent Land and Cattle Co. and Snowy Butte Aviation, Inc.

Neustein is a managing director and co-head of the Private Equity Group at Goldman Sachs. She also is a member of the firm's management and investment committees. Neustein joined Goldman Sachs in 1982, becoming partner in 1990. The following year she moved to the executive office, where she served as the firm's chief of staff until the first half of 1999. In this role she was advisor to the Chairman/CEO, managed the broad agendas of the firm's governance bodies and had oversight responsibility for many supporting functions including Global Human Resources. She has served on more than a dozen of the firm's major

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RU board promotes three faculty at spring meeting



The board of trustees promoted Seth Darst (left) to professor, Ali Hemmati-Brivanlou (center) to professor and Andrej Šali to associate professor. Photos by Robert Reichert.

At its spring meeting Wed., March 8, RU's board of trustees approved the promotions of Seth Darst, Ali Hemmati-Brivanlou and Andrej Šali.

"These promotions in the areas of developmental, structural and computational biology are in keeping with the goals of the new Academic Plan, building on our strengths and expanding into the future," says President Arnold J. Levine. "These young scientists were brought to the university as heads of laboratories and given the opportunity to grow and do great science, and we are delighted to promote them."

Darst, head of a Laboratory of Molecular Biophysics, and Hemmati-Brivanlou, head of the Laboratory of Molecular Vertebrate Embryology, were promoted to professor. Šali, head of a Laboratory of Molecular Biophysics, was promoted to associate professor.

Darst studies the mechanism and regulation of transcription by determining the three-dimensional structures of RNA polymerase and transcription complexes. He joined the university in 1992 as an assistant professor and was promoted to associate professor in 1997. As an

undergraduate, Darst studied chemical engineering at the University of Colorado, Boulder, receiving his bachelor of science degree in 1982. He continued his studies at Stanford University, where he earned a master of science and doctorate in chemical engineering and worked with Roger D. Kornberg in the Department of Cell Biology.

Darst has been a Pew Scholar in Biomedical Sciences since 1995 and a Career Scientist of the Irma T. Hirschl Charitable Trust since 1994. Other honors he has received include an American Cancer Society Postdoctoral Fellowship from 1987 to 1990 and the Lucille P. Markey Award in Biomedical Science since 1990.

Using classical experimental embryology and molecular biology, Hemmati-Brivanlou studies the mechanisms responsible for the formation and patterning of the vertebrate embryo. He came to Rockefeller in 1994 as assistant professor and was promoted to associate professor in 1997. He received his bachelor of science degree in biochem-

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Women & Science breakfast meeting



On Wed., March 15, more than 120 guests attended a morning *Women & Science* program hosted by RU Council member Alair Townsend, publisher of *Crain's New York Business*. As part of a series of lectures at Rockefeller on issues relating to women's health concerns, RU Professor Jeffrey Ravetch and Robert Lahita, chief of rheumatology at St. Vincent's Medical Center, spoke about gender differences in immunity and susceptibility to lupus, rheumatoid arthritis and other autoimmune disorders. Pictured from left: 1999 *Women & Science* Postdoctoral Fellows Esther Bell and Giulia Celli, Ravetch, Lahita and Townsend. Photo by Paul Schneck.

Friday lecture: Inhibiting HIV entry

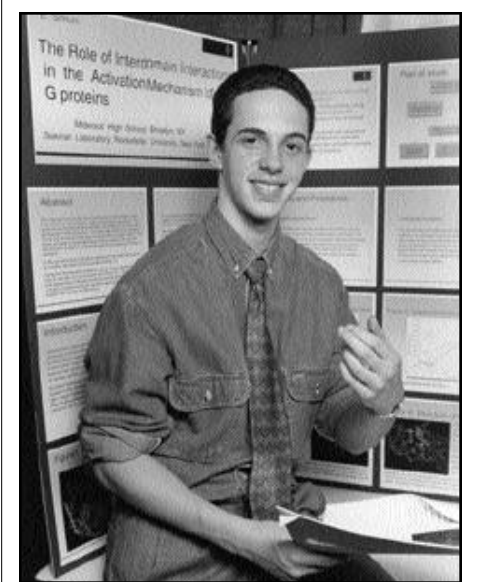
Peter S. Kim, associate head of biology at the Massachusetts Institute of Technology (MIT) and an investigator at the Howard Hughes Medical Institute (HHMI), will present today's Friday lecture (March 17). His topic will be "HIV Entry and Its Inhibition."

Kim's lab focuses on identifying and understanding the biological mechanisms that exist both within and between proteins. The lab is also interested in the folding, stability, structure and function of proteins. Using a protein-dissection approach, the lab is able to study the key substructures of a protein. The work contributes to the discovery of new drugs.

Work done by Kim's lab uncovered a spring-loaded mechanism for the activation of membrane fusion in the influenza virus. They found that the flu protein undergoes a large-scale conformational change in which loop structures in the protein rearrange to form a three-stranded coiled coil. As a result, the hydrophobic "fusion peptide" regions of the protein are propelled in a harpoon-like manner toward the target cell membrane. Recent

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Science Outreach Student in top 10 of Intel Science Talent Search



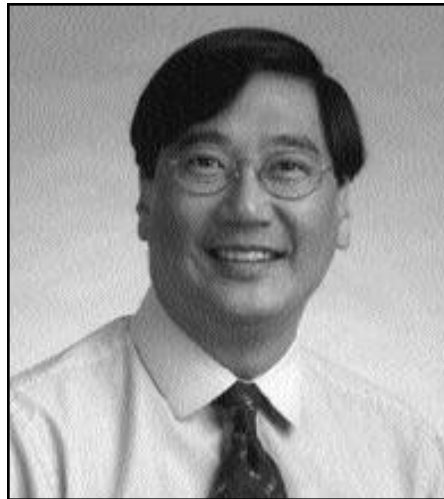
Science Outreach student Eugene Simuni was awarded a \$25,000 scholarship for his fifth-place win in the Intel Science Talent Search. A senior at Midwood High School in Brooklyn, N.Y., Simuni was mentored by Biomedical Fellow Ethan Marin of the Sakmar lab. His project explored protein transmission of visual signals to the brain. Simuni was also chosen by his fellow finalists to receive the Glenn T. Seaborg Award for his commitment to scientific cooperation and communication. Photo courtesy of Intel FPS.

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work from Kim's as well as other labs has shown remarkable similarities between the fusion-active states of the flu protein and the analogous membrane-fusion proteins from other viruses, including human immunodeficiency virus (HIV) and Ebola virus. In particular, a common trimer-of-hairpins motif has emerged, in which a central three-stranded coiled coil is surrounded by supporting helices packed in an antiparallel manner. This structure is thought to bring the viral and cellular membranes together, so the identified structural similarities imply that several virus families share similar mechanisms for cellular invasion. Remarkably, coiled-coil structures have also been implicated in cellular membrane-fusion events, such as those involved in synaptic transmission in the nervous system.

In today's talk, Kim will discuss the lab's current work on the mechanisms of HIV membrane fusion and its inhibition. The pre-hairpin intermediate, a transiently populated intermediate state of the HIV envelope protein, appears to be a particularly attractive therapeutic target for the development of inhibitors of HIV entry. The lab is currently pursuing this possibility using mirror-image phage display. The lab is also trying to develop pre-hairpin mimics to elicit antibodies against HIV infection.



Peter S. Kim will present today's Friday lecture (March 17). Photo courtesy of Peter S. Kim.

Kim received his bachelor of arts degree in chemistry from Cornell University and his doctorate in biochemistry from Stanford University. From 1985 to 1988 he was a Whitehead Fellow at the Whitehead Institute for Biomedical Research. Since 1988 he has been a faculty member of MIT. Among the many honors and awards Kim has received are the Protein Society's Hans Neurath Award in 1999 and Ohio State University's Mack Award in 1995. He is a fellow of the American Association for the Advancement of Science and of the Biophysical Society.

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

Philip Levine Memorial Lecture:
Diane Mathis to discuss engineering arthritis

Diane Mathis, a professor of medicine at the Joslin Diabetes Center at Harvard Medical School, will present the Philip Levine Memorial Lecture next Friday, March 24. Mathis's topic will be "Engineered Arthritis."

Joint destruction in rheumatoid arthritis is believed to be caused by an immune system attack against self-tissue, although the antigen that provokes this response has not been identified. In a recent Sciencepaper, Mathis and her Harvard Medical School colleagues Isao Matsumoto and Christophe Benoist found an endogenous protein that is the target of an autoimmune response in arthritic mice. The protein does not reside specifically in joints, as many researchers had suspected, but is a ubiquitously expressed enzyme—glucose-6-phosphate isomerase (GPI)—in the glycolysis pathway. The researchers believe that some unusual physiological features of joints may be responsible for focusing the autoimmune destruction in this area.

Mathis received her bachelor of science degree in biology from Wake Forest University and her doctorate in cell biology from the University of Rochester. Except for a postdoctoral stint at Stanford Medical School, she spent the next two decades at the Laboratoire de Génétique Moléculaire des Eucaryotes in Strasbourg, France, first as a postdoctoral fellow and then as a senior investigator. She was a sabbatical visitor at the Walter and Elisa Hall Institute in Melbourne, Australia in 1997-98 before moving to Harvard in 1999.



Diane Mathis will present the Philip Levine Memorial Lecture next Friday (March 24). Photo courtesy of Diane Mathis.

The lecture series was established in 1977 by Philip Levine (1900–1987) to bring speakers in the areas of cancer, genetics and immunology to The Rockefeller University. A member of the scientific staff at The Rockefeller Institute for Medical Research from 1925 to 1932, Levine studied human blood groups with Nobel laureate Karl Landsteiner.

The lecture begins at 3:45 p.m. in Caspary Auditorium and is preceded by a tea at 3:15 p.m. in Abby Aldrich Rockefeller Lounge. All are welcome.

Potpourri

92nd Street Y Events

The 92nd St. Y is pleased to offer complimentary tickets to students and employees of Rockefeller University for the Sun., March 26, engagement of "Extraordinary Vistas: The MacDowell Colony Project" at the Kaufmann Concert Hall on Lexington Ave. between 91st and 92nd Streets. The concert will feature soprano Susan Narucki, pianist Alan Feinberg and narrator Cynthia Lohman. The performance will include excerpts from such authors as Willa Cather, May Swenson and Elizabeth Bishop, as well as musical settings of the poetry of Robert Burns, Goethe and James Joyce among others. Tickets will be available one hour before each performance at the theater box office. Call 415-5740 for more information.

On Tues., April 11, the 92nd Street Y will present a panel discussion on the legacy of Marilyn Monroe in Caspary Auditorium. Panelists include authors Joyce Carol Oates and Dominick Dunne, columnist Liz Smith and film critic Molly Haskell. Tickets are \$20 and can be purchased at the 92nd Street Y's box office or by calling 996-1100. A number of free tickets will be available for RU students. Call x8072.

Purchasing corner

| RU stock # | Description | Vendor | Catalog # |
|------------|--|--------|-------------|
| 89380 | Tip aerosol 10ul (Rainin Inst.) | RT-10F | |
| 17810 | Respirator technol sm (Fisher Sci) | | 18-999-1444 |
| 16100 | Tube rd base 12*75 5ml pp str (Sarstedt) | | 55.526.006 |
| 16105 | Tube rd base 16*100 (Sarstedt) | | 62.515.006 |
| 31200 | Cesium chloride plasm (Fisher Sci) | | BP1595-500 |
| 31900 | SDS 500g (Fisher Sci) | | BP166-500 |
| 23000 | Formamide super pure (Fisher Sci) | | BP228-100 |
| 17250 | Tube MCT grad nat 1.7 (Fisher Sci) | | 11-842-17 |

1999 FSA deadline

Sat., April 15, 2000 is the 1999 Flexible Spending Account (FSA) reimbursement request deadline for dependent care and health care expenses. Please submit all 1999 FSA eligible expenses to 21st Century for reimbursement by this date. Any unclaimed balance after this date will be forfeited. FSA Reimbursement claim forms are located in Human Resources. If you have questions, call x8300.

Lottery opens for RU cottages

If you would like to enter the reservations lottery for RU's two upstate cottages, do so before Fri., March 24, at 3 p.m. The rustic cottages are located on 10 wooded acres near Bear Mountain, West Point and the Hudson River. MacInnes Cottage sleeps six in three bedrooms; Hostage Cottage accommodates four in two. RU employees may request two-day weekend stays (\$90 for the weekend) or weekday stays of two to five days (\$43 per night). Complete information, along with reservation request forms, can be found in the entrance hallway of Founder's Hall. The lottery will be drawn by the Housing Office after Sat., April 1.

News&Notes schedule

There will be no News&Notes published next week. The next issue will be Fri., March 31.

AwardsCorner

RU writer-in-residence, Jonathan Weiner has been awarded the National Book Critics Award for best general non-fiction for his book *Time, Love, Memory: A Great Biologist and His Quest for the Origins of Behavior*. The book chronicles the life and work of Seymour Benzer, who helped found the field of molecular biology.

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istry from the Université des Sciences et Techniques du Languedoc in Montpellier, France. He then completed his doctorate in molecular biology at the University of California, Berkeley. Before coming to Rockefeller, Hemmati-Brivanlou was a postdoctoral fellow in Richard Harland's laboratory at the University of California, Berkeley, and then worked at Harvard University's Department of Biochemistry and Molecular Biology in Douglas Melton's laboratory.

Among the many awards Hemmati-Brivanlou has received are the John Merck Award in 1997, the Presidential Early Career Award for Scientists and Engineers in 1996 and the McKnight Scholar Award in 1996.

Šali's lab studies the principles of protein structure, using software to compar-

atively model a protein's structure, from which its function can be ascertained. He joined Rockefeller in 1995 as an assistant professor. He received his bachelor of science degree in chemistry from the University of Ljubljana in Slovenia and completed his doctoral work in the Department of Crystallography at Birkbeck College and at Imperial Cancer Research Fund in London, England. Šali was a postdoctoral fellow in the chemistry department at Harvard University, where he worked with Martin Karplus.

Šali was an Alfred P. Sloan Research Fellow from 1998 to 2000 and a Sinsheimer Scholar from 1996 to 1999. Other awards and honors he has received include a Merck Sharp & Dohme academic scholarship and a postdoctoral fellowship from the Jane Coffin Childs Memorial Fund for Medical Research.

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operating committees. In mid-1999 she moved to the firm's Private Equity Group. Prior to Goldman Sachs, Neustein worked as an attorney for Altheimer & Gray in Chicago.

Neustein received her J.D. and master's in business administration from Northwestern University. She serves as vice-chairman and board member of the American Women's Economic Development Corporation; trustee and member of the executive committee of the American Ballet Theatre; and as a trustee of Brown University, Mount Holyoke College, the Mount Sinai-NYU Medical Center and Health System, and the Mount Sinai School of Medicine. She is also a member of the Women's Forum.

news&notes is published each Friday

throughout the academic year by
The Rockefeller University,
1230 York Avenue,
New York, NY 10021-6399
Phone: 212-327-8967
http://www.rockefeller.edu/pubinfo/news_notes.html



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Ideas and submissions can be sent interoffice (Box 68), by electronic mail (newsno), or by fax (212-327-7876).

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Rockefeller researchers characterize yeast nuclear pore complex

by Joseph Bonner

As the sole points of passage between the nucleus and the cytoplasm for macromolecules such as proteins, nuclear pore complexes (NPCs) form gateways that regulate the import and export of cargo to the nucleus. Cylinder-shaped and embedded in the nuclear envelope, NPCs determine what macromolecules are allowed to cross and ensure that the cargo proceeds in the right direction.

The NPC is one of the largest multi-protein complexes in the cell. Because of its size, it was thought that as many as 200 proteins, called nucleoporins or nups, would be found to contribute to its architecture. (By comparison, the ribosome, which directs protein synthesis, is one-twentieth the size of the NPC and comprises about 80 different proteins.) Recent research published in the Feb. 21 issue of the *Journal of Cell Biology* by two Rockefeller University laboratories and a laboratory at the University of Alberta in Canada, provides significant insights into this important organelle.

In a commentary in the journal *Nature*, RU Professor Günter Blobel and Richard Wozniak write that "this work will point the way towards unveiling the secrets of other giant molecular machines... Not only does the work of Rout and his collaborators provide us with a vast amount of information on the molecular organization of the nuclear pore complex, it also gives us an inkling of the future of cell biology... Cell biologists can now enjoy the riches of our post-genomic era."

About four years ago, while a research associate in Blobel's lab, Michael Rout, now an assistant professor and head of the Laboratory of Cellular and Structural Biology, embarked on a project to obtain a comprehensive inventory of the proteins in the NPC to better understand how the NPC functions in transport across the nuclear envelope. He chose an approach that he had used to study another organelle called the spindle pole body (SPB), when he was a graduate student at the MRC Laboratory of Molecular Biology in Cambridge. Rout developed methods to isolate SPBs, and he generated antibodies that recognized and helped him to identify several distinct protein components in the SPB.

Rather than starting from single components of the NPC and working outward, the team sought to identify and characterize all the components together. This then allowed them to produce a comprehensive picture of the nuclear pore complex.

"Whenever you isolate a complex structure such as the NPC, a lot of other proteins, as well as nucleoporins, come along for the ride," says Rout. A major problem the team had to confront was sorting through these proteins to find the real NPC components.

To characterize the NPC, Rout and his colleagues took yeast cells, separated the nuclei from the cytoplasm and then removed the NPCs from the nuclear envelope to produce an NPC-enriched solution. Working with Professor Brian Chait's lab, Rout used a variety of chromatographic and mass spectrometric methods to identify 30 genuine NPC proteins from the hundreds of proteins that were present in their preparation.

The average mass of the nucleoporins is quite large, about four times the size

of a ribosomal protein, and unlike ribosomal proteins, they exist in multiple copies in each NPC.

"It was somewhat surprising that so few proteins could make up a complex the size of an NPC," says Tari Suprpto, a graduate fellow in Rout's lab and one of the authors of the paper. "But if you take multiple copies of large proteins, it's easily done."

During the four-year-long project, three advances in the field occurred to dramatically speed up the identification and characterization of nucleoporins. First, the completion of the yeast genome project enabled the rapid mass spectrometric identification of yeast proteins.

Second, Rout and co-author John Aitchison, a former Blobel lab postdoctoral fellow who is now at the University of Alberta in Canada, developed a technique called genomic tagging to rapidly identify nucleoporins. Genomic tagging allows researchers to attach a molecular label to a protein, but in a way that doesn't usually disrupt the normal expression of the gene that codes for the protein. This is important, says Suprpto, because any changes in protein synthesis would have skewed their results.

The third development was the refinement of mass spectrometric techniques by Professor Brian Chait and his Laboratory of Mass Spectrometry and Gaseous Ion Chemistry, whose team Rout credits with greatly decreasing the time required to identify proteins.

"We needed something that could give us an answer in days to hours," says Rout. "That's where Brian Chait's fabulous technology came into play: the very rapid, very accurate identification of proteins, which he has been pioneering for years now."

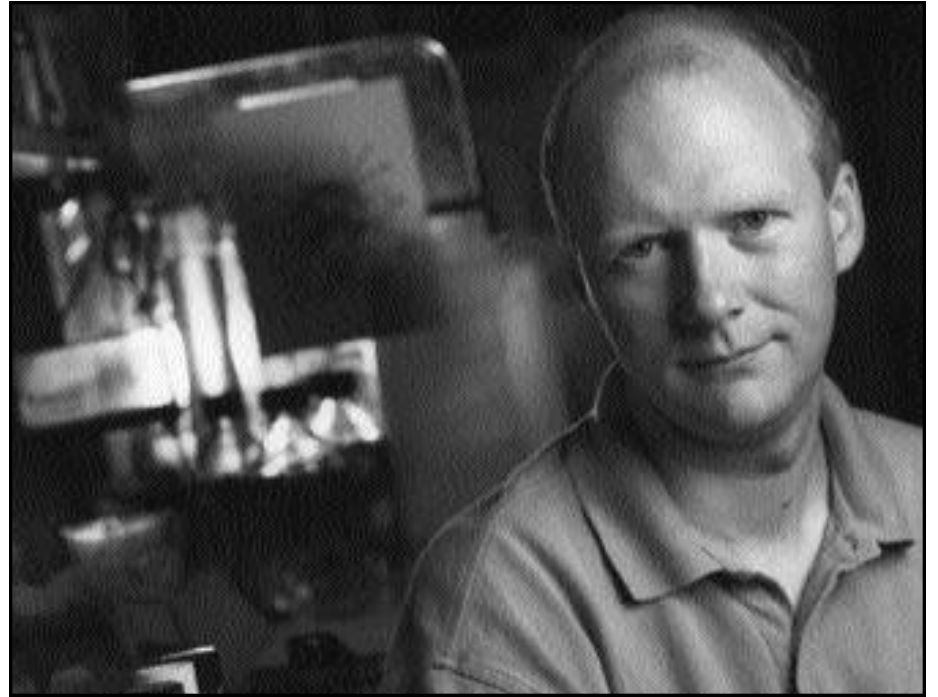
According to the researchers, the mass spectrometry techniques were 10 to 100 times more sensitive than they really needed, but this ensured that their identification of nucleoporins would be comprehensive.

Chait says this study stands out because it was among the first to rapidly and comprehensively identify all the components of a multiprotein complex, and it was done by six people working in three labs. In the past, he says, "something on this scale might have been considered virtually impossible." Also, previous work on protein machines took decades or was not comprehensive. And completeness is of key importance, says Chait, to understanding function. "If you miss an essential component, you could get it all wrong."

Chait says during the four years his lab worked with Rout, it continually improved and refined its mass spectrometric techniques. The technology, he says, is considerably better today than it was when they started.

"The real heroes are Mike and his lab," Chait says. "It's one thing to find a lot of proteins, but it's quite another to identify them as part of a machine. They did an extraordinarily thorough study."

In addition to Rout, Suprpto, Chait and Aitchison, other co-authors of the paper are graduate student Kelly Hjertaas from the University of Alberta and Yingming Zhao, a former graduate fellow in the Chait lab who now runs his own laboratory at the Mount Sinai School of Medicine. The research was funded in part by the National Institutes of Health, The Rockefeller University, the Howard Hughes Medical Institute, the Medical Research Council of Canada and the Alberta Heritage Foundation for Medical Research.



Assistant Professor Michael Rout led a team of researchers in obtaining the first comprehensive inventory of the yeast nuclear pore complex.
Photo by Robert Reichert.

A model for nuclear transport

With a list of nucleoporins and their locations in the structure, Michael Rout and his colleagues set forth to understand how the NPC regulates transport across the nuclear envelope. Because the NPC must be both selective (discriminating what cargo can pass and what cannot) and directional (once something crosses the barrier it must stay there) it was thought some type of mechanochemical gating mechanism was at play. But they found no obvious motor proteins to support that theory.

Instead, the team proposes a "virtual gate," called a Brownian affinity gate, to explain how the NPC regulates protein traffic into and out of the nucleus.

NPC is thus a "virtual gate"—because proteins that can bind the NPC pass the diffusion barrier of the central channel much more freely than those that do not, gating selectivity is achieved without necessarily invoking a gate composed of any moving parts.

"Binding to the NPC is essential," says Graduate Fellow Tari Suprpto. "Once the transport factor-cargo complex binds to it, the complex can access both sides of the nuclear envelope because binding sites are found on both sides."

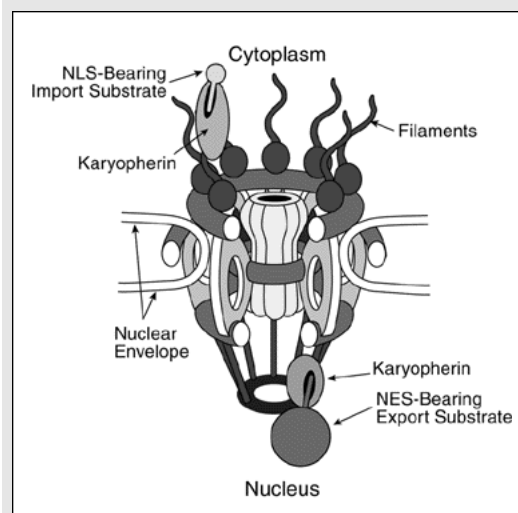
The binding sites are symmetrically localized, says Suprpto, meaning that they are located on either side of the nuclear envelope in a similar distribution. Further out from the nuclear envelope are

asymmetrically localized binding sites, or sites that are found on one side or the other, but not both. These asymmetric binding sites provide a target for transport factors to aim at in the compartment—nucleus or cytoplasm—they need to go to.

But how do the transport factors know which is the correct target compartment to dump their cargo? Previous work from many groups, including the Blobel lab, showed the molecular environment in the target compartment promotes the termination of transport. An enzyme called Ran provides the directionality, telling the transport factors where they are. Ran exists in two

forms. Inside the nucleus, Ran is bound to a nucleotide called GTP. When a cargo-laden transport factor reaches the nuclear side of the NPC during nuclear import, it is exposed to Ran-GTP, which promotes break up of the complex. On the cytoplasmic side of the NPC, Ran-GTP is converted to Ran-GDP, which promotes complexes to break up there, releasing the cargo in the right place.

The model still needs to be tested, says Suprpto, and more work needs to be done to determine the molecular architecture. But, she says, "we have a whole battery of techniques that we can use to answer these questions."



Researchers in the Rout lab propose a possible mechanism for transport of macromolecules through the NPC.
Illustration courtesy Michael Rout.

Cargo cannot pass through the NPC unescorted; it must be attached to a transport factor. The researchers suggest proteins that do not bind the NPC can only transit the NPC by the unfavorable process of diffusion through the constricted central channel; this will bar most proteins from passage. However, transport factor-cargo complexes that specifically dock the NPC can offset this with the energetically favorable process of binding. This promotes the specific diffusional exchange of transport factors—laden with cargo—on and between the nuclear and cytoplasmic sides of the NPC through the central channel. The