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news & notes

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The Rockefeller University

Nobel laureates Brown and Goldstein lecture today on feedback regulation of LDL receptors



Nobel laureates Michael S. Brown (left) and Joseph L. Goldstein give today's Friday lecture (Mar. 17), which is part of the cell biology celebration.

Michael S. Brown and Joseph L. Goldstein, Paul J. Thomas Professors of Medicine and Genetics at the University of Texas Southwestern Medical Center, will discuss "Membrane-bound SREBP: Sterol Sensor and Transcriptional Regulator" at the Friday lecture today (Mar. 17). The molecular geneticists, who shared the 1985 Nobel Prize in Medicine, will lecture in the culmination of today's celebration of the 50th anniversary of electron microscopy and modern cell biology at Rockefeller.

Brown and Goldstein, scientific collaborators since 1972, elucidated the biochemical and genetic mechanisms that regulate chole-

sterol level in blood and cells. In 1974, they discovered that human cells possess a protein on their surfaces called the low density lipoprotein (LDL) receptor, which binds a cholesterol-carrying protein—LDL—that circulates in blood. This work provided strong evidence for the theory that cholesterol-carrying particles are a major cause of heart attacks. Brown and Goldstein also discovered the fundamental processes by which cells take up molecules from blood, and isolated the gene for the LDL receptor, tracing the mutations to the molecular level. Today they will discuss their work on sterol-mediated feedback regulation of

LDL receptors.

"Brown and Goldstein always manage to come up with something exciting," said Professor Günter Blobel, who will introduce the speakers today. "The concept of a membrane-bound protein serving as a cholesterol sensor and, after being cleaved, as a transcription factor is fascinating and beautiful."

Brown, who received an M.D. from the University of Pennsylvania School of Medicine in 1966, met Goldstein, a graduate of the University of Texas Southwestern Medical School, at the Massachusetts General Hospital when both were interns. In 1968, they went to the National Institutes of Health (N.I.H.), with Brown working in the laboratory of Earl R. Stadtman and Goldstein assigned to Marshall W. Nirenberg's laboratory. In 1971, Brown joined the Department of Internal Medicine at the University of Texas Southwestern Medical School as an assistant professor. He became professor in 1976, and director of the Center for Genetic Disease in 1977. He holds the W.A. (Monty) Moncrief Chair in Molecular Genetics.

Goldstein continued his post-doctoral studies as an N.I.H. fellow at the University of Washington School of Medicine in Seattle. He joined the faculty of the University of Texas Southwestern Medical School in 1972 as assistant professor and head of the Division of Medical Genetics. He became professor in 1976 and, in 1977, was named chairman of the new Department of Molecular Genetics.

See Friday lecture, page 4

Public lecture on Saturday closes cell biology celebration



Rockefeller alumnus Peter Satir will give a public lecture on cell biology Saturday morning (Mar. 18).

Peter Satir, chairman of the Department of Anatomy and Structural Biology at the Albert Einstein College of Medicine, will give a talk entitled, "Inventing the Cell" Sat., Mar. 18.

The general public is invited to his lecture, which will be aimed at nonscientists. The lecture is the final event in the university's three-day celebration of electron microscopy and modern cell biology, which began yesterday (Mar. 16).

Satir will discuss the origins of cell biology and overview its development in the 50 years since the first electron micrograph of an intact cell. He will discuss how the work of Rockefeller researchers and others contributed to the organelle doctrine, which states that every organism more complex than a bacterium contains the same cell components that perform the same functions.

Satir graduated from Rockefeller in 1961 after working under Keith Porter, who collaborated with Albert Claude and Ernest Fullam on the historic micrograph, which was published in *The Journal of Experimental Medicine* (J.E.M.) in 1945. The J.E.M. is also celebrating the landmark in its March issue with an article reprising the discovery by Rockefeller research associate Carol Moberg. Reprints are available from Public Affairs, x8967.

The lecture will begin at 11:00 A.M. and will take place in Caspary Auditorium. All are welcome.

2 Tarantula defense

3 The biochemical chamber

4 Hostage Brain wins design award

Campus blossoms, welcoming spring



Irises (left) bloomed for the first time in the Mary Lasker Gardens alongside Abby Aldrich Rockefeller Lounge. Crocuses poked up from the garden on the 66th St. Drive.

Who babysits the tarantulas when the heating fails?

Presentation given at L.A.R.C. on reptiles and arthropods

by Kay Locitzer



Robert Blackburn, who recently lectured at Rockefeller, displays his furry friend at the Liberty Science Center in New Jersey.

Tarantulas, their bad reputation notwithstanding, have never been convicted of killing a soul.

This datum comes from Robert Blackburn, a self-trained expert on some of the animal kingdom's less-loved creatures and a regular volunteer at the "Touch-A-Bug" desk of the Liberty Science Center, who recently gave a talk at Rockefeller on "The Handling and Care of Anoles, Iguanas, Millipedes, and Tarantulas."

Arranged by the university's Laboratory Animal Research Center (L.A.R.C.), Blackburn's lecture was one in an occasional lecture series that has featured veterinary surgeons and a mouse geneticist. "I choose topics that will be interesting or useful," said Michael Hayre, director of L.A.R.C.

Blackburn devoted part of his talk to anoles, a type of lizard that some scientists at Rockefeller have worked with. He gave advice on how to house, feed, domesticate, and reassure anoles as well as chameleons, iguanas, snakes, and Madagascar hissing cockroaches.

But he talked mostly about the infamous tarantula, his "personal favorite," he said, though he admitted, "Caution is the word when handling them."

"I was once bitten on the hand by one of my tarantulas. I rinsed the wound for 20 minutes, though I was also hoping I got a little venom," he said. "I didn't get any. My theory is that fangs are the primary defense—that venom contains a digestive enzyme, which is cumbersome for the spider to regenerate. She wasn't going to

waste it on me." The American Tarantula Society, Blackburn said, has confirmed this theory.

To avoid bites, begin handling tarantulas when they are young, do it often, and do it gently, Blackburn said. "My hand was really a kind of substrate for her. She bit me only because someone poked her."

Blackburn can tell you if a tarantula is nervous—she'll show her fangs. He can tell you how long it takes for a tarantula to digest a mouse: "Not as long as you'd think." If you want to witness the miracle of birth in tarantulas, he said, get the young ones out of the cage fast after birth—otherwise their parents may devour them. And be prepared to find good homes for 75 spiderlings.

Blackburn is a lifelong aficionado of all creatures that creep, scoot, and slither. "I was always interested in reptiles and arthropods, but when I was a child, my mother wasn't happy about keeping them at home." Now that he's a grown-up, his basement is a verita-

ble zoo, heated to a temperate 88°F, which keeps his three tarantulas and two snakes comfortable.

His two children help him out downstairs; it's a hands-on science education for them. When Blackburn's Royal python suffered a respiratory infection, he said, "I could not get a hypodermic into her. My son suggested we put the antibiotic into a mouse and feed the mouse to the snake. It was a great idea, but she was so sick by then, she wouldn't eat." The snake died several days later. "We were all pretty sad."

How does his mother feel about her grandchildren doing what she didn't want her son to do several decades ago?

"Well, my heating system broke one day when it was really cold outside. It was some crisis," said Blackburn. "But I brought the menagerie to my mother's house and said, 'Here Mom, babysit my tarantulas.'" She couldn't say no, after all, to a respected member of the American Tarantula Society.

Students select representatives

New members of the Student Representative Council (S.R.C.), which represents Rockefeller's 99 graduate fellows and 33 biomedical fellows on issues of common concern, were officially appointed at the S.R.C. meeting last month. Representatives are elected by a ballot sent out to all students.

The new S.R.C. representatives are Jorge Muñoz (for the first-year class) and Catherine Friedman (for the third-year class). Firdaus Dhabhar, a member since his first year, will represent fifth-year students. Adrian Rothenfluh (second year), Xiaofeng Qin (fourth year), and Julie Miwa (sixth year) are serving the second year of their two-year terms. Other members

of the S.R.C. include Philip De Jager (M.D.-Ph.D. student representative), Natalie DeSouza (single-student housing representative), and Sabine Hilfiker-Rothenfluh (married-student housing representative).

S.R.C. members discuss such matters as housing, graduate study, student events, and special student facilities. Meetings, open to all graduate students, are held on the first Thursday of every month at 9:00 A.M. on the 17th floor of Tower. The agendas are posted in student residences before the meetings. The S.R.C. encourages students to attend meetings and to contact their representatives with comments, suggestions, and concerns.



Student Representative Council members for the next year include (from left): Jorge Muñoz, Xiaofeng Qin, Firdaus Dhabhar, Catherine Friedman, Philip De Jager, Julie Miwa, and Adrian Rothenfluh.

Silicon Graphics' magic bus parks at Rockefeller



Silicon Graphics, Inc.'s 48-foot tractor-trailer pulled up curbside on Monday, laden with \$1.4 million of their latest computer imaging equipment, for perusal by members of the Rockefeller community. Three new biological imaging programs were on display. Over 80 people browsed through the "Magic Bus," which tours the country continuously throughout the year. "We were at Morgan Stanley last Friday and 600 people dropped in, but here the people who visit are decision makers, people who really use this technology," said Joseph Rizzi (above), Silicon Graphics sales representative. Armand Gazes, Rockefeller's associate director of Computing Services, who arranged the visit, said, "Silicon Graphics not only sports the best blend of integrated high-quality graphics and computer power, but they are a leader in multiprocessor technology and high speed scalar processors. We are really pleased that they brought this display to our door."

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A tradition of traveling through the cell

Rockefeller researcher advances studies in membrane biogenesis

by Susan Blum

The journey into a new intracellular world began half a century ago, when Albert Claude, Keith Porter, and Ernest Fullam peered at an intact cell through an electron microscope. Thanks to this wondrous instrument, the cell no longer appeared as a cytoplasmic sea interrupted by dimly defined inlets and islands, but was rather revealed as a complex city full of highly differentiated domains. In the years that have passed since then, countless insights into the cell have been disclosed by researchers who headed labs at Rockefeller or who were educated here. Günter Blobel, Christian de Duve, George Palade, David Sabatini, Philip Siekevitz—these are among the researchers who have made essential contributions to our understanding of the structure and function of intracellular organelles, and of the processes they control.

This research tradition has informed the work of Associate Professor Sanford Simon, first as a postdoc in the Blobel lab and now as head of his own lab since 1992. In the early '90s, for instance, Blobel and Simon published a series of papers on how proteins destined to be secreted from the cell take one of the first steps in their intracellular voyage—the movement, or *translocation*, across the membrane of an organelle called the endoplasmic reticulum (ER) by means of an aqueous channel. Now, Simon is turning his attention to the voyage of another type of protein: the integral membrane proteins that stud the plasma membrane surrounding the cell. His aim is to elucidate the biogenesis of these proteins—the process by which they are synthesized, partially translocated, folded, inserted into the membrane, and then directed to the cell surface.

Membrane biogenesis

He and his colleagues use opsin and the P-glycoprotein as models for membrane protein biogenesis. Like many integral membrane proteins, these two molecules weave through the membrane more than one time, and thus pose some particularly perplexing problems. Do their transmembrane domains translocate separately, or in groups? How do they manage to move only partially through the membrane? How do they fold? And how are they stitched through the membrane's fatty bilayer?

To answer such questions, Simon and his colleagues have used the



Associate Professor Sanford Simon studies membrane proteins and the process by which they are synthesized, translocated, folded, inserted into the membrane, and directed to the cell surface.

techniques of molecular biology to take "snapshots" of the proteins at various stages of biogenesis. The picture emerging so far is that each transmembrane domain seems to translocate across the membrane separately, but that none is fully integrated until all the protein has been synthesized on the ribosome, the workbench upon which proteins are forged. Until then, the nascent protein appears to be held and stabilized in some intermediate configuration—perhaps by chaperone proteins.

Powerful as these studies are for a basic understanding of cell biology, they are also important for insights into disease. So vital are plasma membrane proteins—they serve as receptors and as channels, for instance—that a hitch anywhere in their biogenesis can spell disaster for a cell.

Opsin, the protein component of the retina's rod cell receptors, is a case in point. More than 60 different mutations in this molecule can cause retinitis pigmentosa (RP), the most common form of inherited blindness. Studies in the Simon lab in collaboration with the Scripps Institute's Martin Friedlander (a Rockefeller M.D.-Ph.D. who also studied with Blobel) have shown that some cases of RP are due to snarls in the intracellular trafficking of the opsin molecule. They have already found that two RP-causing opsin mutations reduce by 30 percent the amount of protein that is targeted to the ER. The scientists are now studying other opsin mutations implicated in the disease to

learn what effects they may have on the molecules' biogenesis. (RP is not the only condition to be caused by protein trafficking problems. For example, faulty biogenesis is often at the root of cystic fibrosis, as well.)

The P-glycoprotein—the lab's other model molecule—has also been implicated in disease. Simon's initial interest in this protein stemmed from its membership in a family of proteins—the ABC proteins—that act as transporters. While investigating how the molecule works in normal cells, Simon became intrigued by published studies on its role in cancer cells that develop resistance to many chemotherapeutic drugs. The P-glycoprotein is highly overexpressed in such cells, and the majority view holds that the molecule serves as a pump that rids cells of the anticancer drugs. Unconvinced by the evidence for this scenario, Simon has now expanded his studies to explore the role of the P-glycoprotein in both normal and cancerous cells.

The acid test

He is also studying resistant cancer cells as a whole, with particular emphasis on their acidity. Normally, tumor cells are more acidic than healthy ones—a fact scientists have exploited by designing chemotherapy drugs that need an acidic environment to work. But resistant cancer cells are less acidic than drug-resistant ones, thereby thwarting the drugs' therapeutic effect.

This much had been known

since the '80s, but Simon and his colleagues have refined the field by showing that the changes in acidity are subtly distributed within the resistant cell. Thus, while the cytosol is less acidic than in normal tumor cells, certain organelles—including the lysosomes and the Golgi complex—are more acidic, and the drug accumulates there. In the "classic" secretory pathway elucidated by Palade, vesicles budding off from the Golgi can carry the drug up to the cell's surface membrane, from which it can then be secreted. In vitro studies by Simon and colleagues, conducted in collaboration with Melvin Schindler at Michigan State University, have already shown that drugs that reduce the acidity of the Golgi complex can resensitize resistant tumor cells. The next step is to test this potential therapy in mice—a project that will soon get under way with collaborators at other institutions.

Progress is instrumental

Studies such as Simon's on intracellular acidity have only become possible thanks to the development of dramatically new microscopes, some of which Simon is helping to devise, and one of which is due to arrive in his lab momentarily. This new generation of microscopes uses lasers, hitherto unexploited light ranges (infrared and ultraviolet), and other advances to maintain the cell within its normal physiologic environment; to track changes in its metabolism, acidity, and the localization of small ions; and even to tweeze out individual organelles for exploratory intracellular surgery.

With such microscopy, the promise of electron microscopy has, in a sense, come full circle. As Simon explained, "The pioneers in cell biology went from looking at a nonliving intact cell, to breaking the cell apart and isolating its organelles, to reconstructing the organelles' components in vitro in order to study their functions. Now, we can actually start to use the living cell as our biochemical chamber to study overall cell organization in three dimensions." Just as, 50 years ago, what Albert Claude termed "the accident of technical progress" opened up vast new vistas with electron microscopy, today a new wave of technological advances may soon bring undreamed of worlds into focus.

Potpourri

Christian Steiner



Nokuthula Ngwenyama, viola, will perform at the noon recital today (Mar. 17), accompanied by Reiko Uchida, piano.

Tri-Institutional Noon Recital

Nokuthula Ngwenyama, viola, and Reiko Uchida, piano, will perform works by Kreisler, Brahms, Bartók, and Paganini at the Tri-Institutional Noon Recital today (Mar. 17). The concert, to be held at noon in Caspary Auditorium, is in celebration of Women's History Month. Admission is free; all are welcome.

International dinner

The annual RU Faculty Housing Tenants' Association international dinner will be held Sun., Mar. 19 at 6:00 P.M. in the 38th floor solarium of Scholars Residence. Attendees are asked to bring an entree, salad, or dessert and a beverage to share. The dinner is open to all members of the Rockefeller community.

Computer course

The Electronics Shop, a unit of Information and Computing Services, is offering an eight-week course entitled "Computers in the Laboratory (Part II)" Tuesdays at 3:00 P.M. in Caspary 1A beginning March 21. For further information contact Gordon Silverman, x7899, or box 186.

Clinical Research Seminar

Associate Professor Elaine Tuomanen will discuss "Pathogenesis of Pneumococcal Disease" at the Clinical Research Seminar Wed., Mar. 22 at noon in Nurses Residence 110B.

Cottage lottery

Reservations for the MacInnes and

Hostage Cottages will be made by random drawing. Reservation request forms can be obtained outside the guest pantry on the third floor of Abby Aldrich Rockefeller Hall. Requests must be returned by Fri., Mar. 24 at noon. Confirmations will be made after Apr. 1.

Workshops

Computing Services is offering the following workshops:
UNIX for Sequencers, I & II: Mon., Mar. 27 and Mon., Apr. 3, 10:00 A.M. to noon;
E-mail: Tues., Mar. 28, 2:00 to 4:00 P.M.;
WordPerfect for Windows, I & II: Thurs., Mar. 30 and Thurs., Apr. 6, 10:00 A.M. to noon.
 Workshops are free, but registration is required. Contact Joan Falciano, x8925, or leave voice mail at x7768.

Support group

The Employee Assistance Program Consortium is offering a four-week support group on "Caring for Elderly Loved Ones" Mondays beginning Apr. 3 at 1:00 P.M. The group, which is open to employees of the tri-institutions facing the responsibilities of eldercare, will be held at 411 East 69th St., Room 229. Call 746-5890 if interested in attending.

Flexible spending reminder

All 1994 Flexible Spending Account claims must be submitted to MassMutual by Sat., Apr. 15. Contact Ginny Hansen, x8299, or Kristin Gross, x8297, if you have any questions.

Call for mentors

The Science Outreach program needs volunteers to mentor teachers and students this summer, and to visit schools, give workshops, and host lab tours. Contact Bonnie Kaiser, x7431, or e-mail, bonnie.

Book award

The Hostage Brain by Rockefeller Professor Bruce McEwen and Harold M. Schmeck, Jr., received honorable mention for "Excellence in Book Design and Production" from the Professional/Scholarly Publishing Division of the Association of American Publishers at its annual meeting last week. Published by the RU Press, the book may be ordered by calling x8572; it is also on sale at the Sweat Shirt Shop, open Tuesdays from 11:30 A.M. to 1:30 P.M. and located in RRB 133.

Honor

Professor David Gadsby has accepted an invitation to serve as a member of the National Institutes of Health Physiology Study Section, Division of Research Grants. His term runs from October 27, 1994 to June 30, 1998.

AAAS goes to Congress

President Torsten Wiesel has been appointed to serve on the advisory board of the American Association

Friday lecture

(continued from page 1)

Goldstein and Brown were named Paul J. Thomas Professors in Molecular Genetics in 1975, and Regental Professors of the University of Texas in 1985. In addition to the Nobel Prize, both men shared the 1985 Albert Lasker Basic Medical Research Award and the National Medal of Science for their work on the LDL receptor.

Brown, a member of the scientific advisory boards of the Salk Institute and the Scripps Clinic, serves on the scientific advisory board of Memorial Sloan-Kettering Cancer Center with Goldstein. Goldstein is a member of the medical advisory board of the Howard Hughes Medical Institute and the board of trustees of The Rockefeller University.

The first lecture, to be given by Brown, begins at 3:45 P.M. in Caspary Auditorium, followed by Goldstein at 4:30 P.M. The lectures will be preceded by tea at 3:00 P.M. in Abby Aldrich Rockefeller Lounge. All are welcome.

for the Advancement of Science Center for Science, Technology, and Congress. The center is intended as a nonpartisan source of information on scientific and technological issues before Congress.

ROCKEFOLLIES '95 comes to Caspary next Tuesday



The ROCKEFOLLIES company has gotten its act together—10 acts, that is—for their performance, to take place Tues., Mar. 21 at 7:00 P.M. in Caspary Auditorium. More than two dozen members of the Rockefeller community and their friends will perform, and door prizes will be awarded. Tickets (\$5) may be purchased at the door or by calling Peggy Hempstead, x7794. The ROCKEFOLLIES poster features Pan, the Greek god of shepherds, playing his syrinx.