1-12-2001

NEWS AND NOTES 2001, VOL. 12, NO.13

The Rockefeller University

JANUARY 12, 2001 VOLUME 12, NUMBER 13

news & notes

THE NEWSLETTER OF THE ROCKEFELLER UNIVERSITY

FRIDAY LECTURE

Steitz to discuss atomic-level insights into the structure and function of the ribosome

Thomas A. Steitz, chairman of the Department of Molecular Biophysics and Biochemistry at Yale University and an investigator at the Howard Hughes Medical Institute, will present the Friday lecture today (Jan. 12). His topic will be "Structural Principles and Functional Insights From the Atomic Structure of the Large Ribosomal Subunit."

During the past three decades, Steitz has used X-ray crystallography to determine the structures of proteins and nucleic acids, particularly those involved in gene expression and recombination, with a consistent focus on their biological function. His studies on yeast hexokinase with and without bound glucose demonstrated that substrate binding induced a large conformational change, closing the deep cleft in the enzyme.

Virtually all aspects of nucleic acid metabolism have come under his scrutiny: replication, transcription, recombination and protein synthesis. The structures of *lac* repressor core and the catabolite gene activator protein plus its complex with DNA have led to molecular insights into gene activation and repression.

More recently, the structures of T7 RNA polymerase bound

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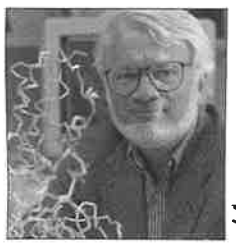

Hard copy only

Thomas Steitz, an HHMI investigator, is the Eugene Higgins Professor of Molecular Biophysics and Biochemistry and a professor of chemistry at Yale University.

Campus toasts Nobel laureates Greengard and Kandel

On Tues., Jan. 9, the Rockefeller community gathered in the Welch Hall Reading Room for a champagne reception to honor Nobel laureates Paul Greengard and Eric Kandel. Greengard, the university's Vincent Astor Professor, shared the 2000 Nobel Prize in Medicine or Physiology with Rockefeller University Trustee Eric Kandel and Arvid Carlsson. President Arnold J. Levine introduced the laureates and praised their contributions to science. "The entire campus shares in the excitement of your Nobel Prize," he said.

#00-061

Above: Paul Greengard, President Levine and Eric Kandel pose by a facsimile of the Nobel citation. Top right: Greengard and his wife, Ursula von Rydingsvard, enjoy the festivities. Right: President Levine proposes a toast.

"Successful Aging" is topic of next Cohn Forum

Hard copy only

John W. Rowe will discuss the physiology of the aging process.

John W. Rowe, president and CEO of Aetna, Inc., will present the next Zanvil Cohn Forum, entitled "Successful Aging," on Mon., Jan. 22.

The last 10 years have seen a revolution in the field of gerontology: Aging is being approached not in terms of expected disease and decline, but through an exploration of factors that might contribute to ongoing health and vitality. Rowe will explain that successful aging is largely determined not by genetic inheritance but by individual lifestyle choices in diet, exercise, the pursuit of mental challenges, self-efficacy and involvement with other people.

Rowe joined Aetna in September 2000, after serving as president and CEO of Mount Sinai NYU Health, a position he assumed after overseeing the 1998 merger of the Mount Sinai and NYU Medical Centers.

Prior to the Mount Sinai NYU Health merger, Rowe was president of the Mount Sinai Hospital and the Mount Sinai School of Medicine in New York City. He is a professor of medicine and geriatrics at Mount Sinai School of Medicine.

Before joining Mount Sinai in 1988, Rowe was a professor of medicine and the founding director of the Division on Aging at Harvard Medical School, and he served as chief of gerontology at Boston's Beth Israel Hospital.

He has authored more than 200 scientific publications, primarily in physiology of the aging process, and recently co-authored *Successful Aging* (Pantheon, 1998) with Robert Kahn. He has received many honors and awards for his research and health policy efforts regarding care of the elderly.

Rowe was a director of the MacArthur Foundation Research Network on Successful Aging, and he served on the Board of Governors of the American Board of Internal Medicine and as president of the Gerontological Society of America. He is a member of the Institute of Medicine of the National Academy of Sciences and the Medicare Payment Advisory Commission.

Rowe's talk takes place in the Abby Aldrich Dining Room at 5:30 p.m. and is preceded by a reception at 5 p.m. All are welcome.

The Cohn Forum is a series of colloquia on issues in health and biomedicine. The Cohn Forum's Web site is www.rockefeller.edu/pubinfo/cohn.html.

Trusts and Estates Committee hosts winter dinner

Right: Titia de Lange, Leon Hess Professor and head of the Laboratory of Cell Biology and Genetics, was the featured speaker at the dinner program sponsored by the Committee on Trust and Estate Gift Plans on Tues., Dec. 12. Attending the presentation, entitled "The Problem with Immortality: Chromosomes, Cancer and Aging," was the late Leon Hess's daughter, Marlene Hess, pictured (left) with her husband, James Zirin, and de Lange.

#00-057

#00-057

Left: The Trusts and Estates Committee is a volunteer group of prominent attorneys and bankers. At the event were new members Susan M. Bennett (left) and Roberta Grossman.

Below: Committee Chairman and Trustee Frederick A. Terry Jr. (right) greeted Judge Robert W. Sweet and Adele Hall Sweet, president of the Dorothy Schiff Foundation.

#00-057

AROUND CAMPUS

Superstring theory physicist meets with students at President's House event

#00-056

Physicist Brian Greene (top, right) met with Rockefeller graduate students at the President's House on Wed., Dec. 6. President Levine and his wife, Linda Hirst Levine, host a number of evenings for graduate students to meet with authors, artists and scientists in an informal setting.

Greene's area of research is superstring theory, a theory that purports to give the first sensible theory of quantum gravity as well as a unified theory of all forces and all matter. As such, superstring theory has the potential of realizing Einstein's long sought for dream of a single, all encompassing, theory of the universe.

Peggy Rockefeller Concert

Austrian lyric baritone Wolfgang Holzmair will perform with pianist Russell Ryan at the next Peggy Rockefeller Concert on Wed., Jan. 24, in Caspary Auditorium. Holzmair, a Grammy Award winner, is acclaimed for both his operatic roles and his song recitals. For information, contact Jennifer Goldschlag, x8437.

Centennial corner: Jacobs to give lecture on TB

William R. Jacobs Jr., a professor at Albert Einstein College of Medicine and an investigator at the Howard Hughes Medical Institute, will present a special Infectious Disease Centennial Lecture on Fri., Jan. 19. His topic will be "Mycolic Acids of *Mycobacterium tuberculosis*: An Achilles Heel or a Neutralizing Weapon?"

Mycobacterium tuberculosis, the tubercule bacillus, was originally described by Robert Koch and, characterized by its unusual staining properties, was proven to be the causative agent of tuberculosis (TB). These acid-fast staining properties have been found to result from the unique lipid surface that is predominantly composed of long-chain fatty acids called mycolic acids. These mycolic acids are common to the entire genus of *Mycobacterium*, thus providing a unique signature for the species. The TB-specific drugs isoniazid and ethionamide have been shown to target the synthesis of these mycolic acids. Using a combination of genetic, biochemical and X-ray crystallographic analyses, the target, InhA, has been identified and characterized. Specific inhibition of InhA induces the lysis of mycobacterial cells, thus defining a key Achilles heel for the mycobacterial species that has led to novel drug development.

Both *M. tuberculosis* and *M. leprae*, the causative agent of leprosy, have been shown to decorate their mycolic acids with unique cyclopropyl groups. Mutations that affect cyclopropanations of mycolic acids have been shown to render *M. tuberculosis* both unable to cord and to cause a persistent infection in mice. The cyclopropanated lipids appear to represent a unique virulence factor that protects pathogenic mycobacteria against an effective immune response. Thus, mycolic acids represent a unique two-edged sword for *M. tuberculosis* pathogenesis.

Jacobs began studying *M. tuberculosis* while a postdoctoral fellow with Barry Bloom (a Rockefeller University alumnus) at Albert Einstein College of Medicine, where he sought to develop BCG as a recombinant vector for eliciting immune responses against cloned foreign antigens. Jacobs and Bloom were the first to introduce foreign DNA into slow-growing mycobacteria using a novel recombinant DNA vector called a shuttle plasmid. This system further allowed Jacobs to achieve the first transformation of BCG and *M. tuberculosis.*

Jacobs and Bloom went on to develop the first recombinant BCG vaccines and demonstrated that they could elicit protective immune responses to a variety of cloned foreign antigens. Jacobs has used phage systems to develop a variety of tools for genetically manipulating mycobacteria including transposon delivery phages, luciferase reporter phages and specialized transducing phages.

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HHMI Investigator William R. Jacobs Jr., a professor at Albert Einstein College of Medicine, will discuss the role of mycolic acids in tuberculosis.

The talk will take place in Caspary Auditorium at 3:45 and will be preceded by a tea at 3:15 p.m. All are welcome.

Lederberg to give Sackler centennial lecture

Raymond and Beverly Sackler Foundation Scholar Joshua Lederberg, president emeritus of The Rockefeller University, will give the Raymond and Beverly Sackler Centennial Lecture on Fri., Jan. 26. His talk is entitled "Crowded at the Summit: The Future of Infectious Disease."

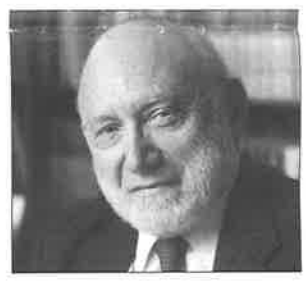
The last 20 years have seen the emergence of new infectious diseases, such as AIDS and hepatitis C, and the resurgence of diseases, like tuberculosis, once considered vanquished. Scientists have discovered that the pace of microbial evolution vastly outstrips that of their multicellular hosts. As a result, most encounters are dominated by parasite adaptations, taking account of ancient innovations like our immune system. Lederberg, a Nobel laureate, will discuss the danger of attempts to eradicate microbes without considering backup strategies.

Lederberg discovered a mechanism of genetic recombination in bacteria while a doctoral student at Yale University, demonstrating that a form of sexual reproduction occurs in these microorganisms. This work earned him the Nobel Prize in Physiology or Medicine in 1958 at the age of 33.

In 1978, Lederberg came to The Rockefeller University as its fifth president, serving until June 1990. Since retiring as president, he has returned to research as head of the Laboratory of Molecular Genetics and Informatics.

A member of the National Academy of Sciences and charter member of its Institute of Medicine, Lederberg was elected a foreign member of the Royal Society of London and an honorary fellow of the New York Academy of Medicine.

Throughout his career, Lederberg has taken important advisory roles in government, serving as scientific counselor to world leaders and heading a number of influential committees and policy studies. In 1989 he was awarded the U.S. National Medal of Science.



On File

President Emeritus and Sackler Foundation Scholar Joshua Lederberg will discuss the future of infectious disease.

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Steitz continued from page 1

either to T7 lysozyme, a transcription inhibitor, or a promoter being transcribed have shown the differences between DNA and RNA polymerases and their regulation. Clues concerning the mechanism and fidelity of DNA copying have come from the structures of DNA polymerase and the reverse transcriptase from HIV complexed with an anti-AIDS drug. The crystal structures of Gln-tRNA synthetase bound to $tRNA^{Gln}$ as well as Ile-tRNA synthetase bound to $tRNA^{Ile}$ have answered many questions concerning the mechanisms by which the genetic code is accurately translated.

The laboratory has also provided insights into the details of genetic recombination through studying the structures of *E. coli recA* and a site-specific recombination protein, resolvase, bound to DNA. Most recently, the first atomic-level insights into the structure and function of the ribosome have come from crystal structure analysis of the 50S ribosomal unit.

Steitz received his B.A. in chemistry from Lawrence College in Appleton in 1962. He then pursued his Ph.D. studies at Harvard University in the laboratory of William Lipscomb, receiving his degree in biochemistry and molecular biology in 1966. Steitz's doctoral studies on the crystal structure of carboxypeptidase A initiated his career in structural biochemistry, in which he has used X-ray crystallography as his primary tool.

He subsequently pursued studies of alpha chymotrypsin with David Blow at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England. In 1970, Steitz was appointed an assistant professor of molecular biophysics and biochemistry at Yale University, where he is currently the Eugene Higgins Professor of Molecular Biophysics and Biochemistry, professor of chemistry and investigator in the Howard Hughes Medical Institute.

Steitz is a member of the National Academy of Sciences and the American Academy of Arts and Sciences and is the recipient of the 1980 Pfizer Award in Enzyme Chemistry of the American Chemical Society and the 2001 Rosenstiel Award.

His talk begins at 3:45 p.m. in Caspary Auditorium and is preceded by a tea at 3:15 p.m. All are welcome.

News & Notes is published every other Friday throughout the academic year by **The Rockefeller University,**
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Joseph Bonner, Director of Communications

Lisa Stillman, Assistant Director of Communications

Jim Stallard, Science Writer

Ideas and submissions can be sent interoffice (Box 68), by electronic mail (newsno) or by fax (212.327.7876).

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calendar

JANUARY 12 THROUGH JANUARY 28

EVENTS

Friday Lectures

THIS EVENT IS HELD IN CASPARY AUDITORIUM AT 3:45 P.M. AND PRECEDED BY TEA AT 3:15 P.M. IN ABBY ALDRICH ROCKEFELLER LOUNGE. ALL ARE WELCOME.

FRIDAY, JANUARY 12

Structural Principles and Functional Insights from the Atomic Structure of the Large Ribosomal Subunit. Thomas Steitz, Eugene Higgins Professor, Department of Molecular Biophysics and Biochemistry, Yale University, and Investigator, Howard Hughes Medical Institute.

FRIDAY, JANUARY 19

Centennial Infectious Disease Lecture: Mycolic Acids of Mycobacterium tuberculosis: An Achilles Heel or a Neutralizing Weapon? William R. Jacobs Jr., Investigator, HHMI, and Professor, Departments of Microbiology and Immunology and Molecular Genetics, Albert Einstein College of Medicine.

FRIDAY, JANUARY 26

Centennial Sackler Lecture: Crowded at the Summit: The Future of Infectious Disease. Joshua Lederberg, Professor and President Emeritus and Sackler Foundation Scholar, RU.

FRIDAY, JANUARY 12

2:00 P.M. **Identification of Xkid, a Chromokinesin That Binds Chromosomes in Metaphase and Is Degraded in Anaphase.** Hironori Funabiki, Department of Molecular and Cellular Biology, Harvard University. Cell Biology Seminar. 116 ROCKEFELLER RESEARCH LABORATORIES, MSKCC, 430 EAST 67TH ST.

MONDAY, JANUARY 15

12:00 P.M. **Pharmacological Mechanisms of Resistance: A Role for Efflux Transporters?** Dave Back, University of Liverpool. CFAR Seminar. SIXTH FLOOR CONFERENCE ROOM, ADARC, 455 FIRST AVE. CONTACT GARY GAILOR, 212-448-5163.

TUESDAY, JANUARY 16

11:00 A.M. **Regulation of Mitosis and Replication by Cell-Cycle Checkpoints.** Nicholas Rhind, The Scripps Research Institute. Chromosome Biology/Gene Expression Seminar. 301 WEISS. CONTACT BOBBIE LARRAGA, 327-7240. OPEN TO RU COMMUNITY AND GUESTS.

WEDNESDAY, JANUARY 17

12:00 P.M. **DNA Dependent Protein Kinase (DNA-PK), Innate Immunity and Vaccines: The Case of Immunostimulatory DNA.** Eyal Raz, Associate Professor of Medicine, University of California, San Diego. Seminars in Clinical Research. 110B NURSES RESIDENCE. CONTACT DALE MILLER, 327-8411.

4:00 P.M. **Mycobacterium: Existence in the External Endosome.** David Russell, Professor and Chairman, Microbiology and Immunology, College of Veterinary Medicine, Cornell University. Microbiology and Immunology Seminar. B-307 WMCCU, 1300 YORK AVE. CONTACT DENISE CRUZ, 746-6505.

4:30 P.M. Gene **Regulation during Lineage Specification in the Thymus.** Dan Littman, Investigator, Howard Hughes Medical Institute, Skirball Institute for Biomolecular Medicine, NYU Medical Center. MSKCC President's Research Seminar Series. AUDITORIUM, ROCKEFELLER RESEARCH LABORATORIES, MSKCC, 430 EAST 67TH ST. TEA AT 4:00 P.M.

THURSDAY, JANUARY 18

3:00 P.M. The Influence of Efficient Processing of Brief Auditory Temporal-spectral Cues in Infancy on Later Language Development. April Benasich, Assistant Professor, Center for Molecular and Behavioral Neuroscience, Rutgers University. Systems Neuroscience Seminar. 305 WEISS. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

4:00 P.M. **Lineage Tracing of Hematopoietic Cells.** Thomas Graf, Department of Developmental and Molecular Biology, Albert Einstein College of Medicine. LFKRI Research Seminar. LOWER LEVEL CONFERENCE ROOM, NEW YORK BLOOD CENTER, 310 EAST 67TH ST. TEA AT 3:45 P.M. CONTACT ROSANNA MARTINEZ, 570-3357.

4:00 P.M. **Reverse Remodeling during LVAD Support in Patients with End-stage Heart Failure.** Daniel Burkhoff, Associate Professor of Medicine, Columbia University College of Physicians and Surgeons. Anesthesiology Research Seminar. ANESTHESIOLOGY LIBRARY, M-309, WMCCU, 1300 YORK AVE. CONTACT LISA FERRER, 746-2744.

4:15 P.M. **Compartmentation of G Protein-Coupled Receptor Signaling: Adenylyl Cyclases as Paradigm.** Rennolds Ostrom, Postdoctoral Fellow, Department of Pharmacology, UC San Diego School of Medicine. Pharmacology Special Seminar. WEILL AUDITORIUM, WMCCU, 1300 YORK AVE. COFFEE AT 4:00 P.M. CONTACT LISSETT CHECO, 746-6250.

8:00 P.M. **Ubiquitin, The N-End Rule, and The Functions of Protein Degradation.** Alexander Varshavsky, Smith Professor of Cell Biology, Division of Biology, California Institute of Technology. Harvey Society Lecture. CASPARY AUDITORIUM.

FRIDAY, JANUARY 19

9:00 A.M. **Using HIV-1 Viral Dynamics to Document the Greater Potency of a Novel Four-Drug Regimen Relative to Standard HAART.** Michael Louie, Clinical Scholar, Aaron Diamond AIDS Research Center, RU. Clinical Scholar's Grand Rounds. 110B NURSES RESIDENCE. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

12:00 P.M. **Checkpoint Responses and Repair of a Broken Chromosome.** James Haber, Professor, Department of Biology, Brandeis University. Cell Biology Seminar. 116 ROCKEFELLER RESEARCH LABORATORIES, MSKCC, 430 EAST 67TH ST.

MONDAY, JANUARY 22

1:30 P.M. **Post Transcriptional Control of TNF α Production.** Paul Anderson, Associate Professor of Medicine, Brigham and Women's Hospital. Immunology Seminar. 2ND FLOOR CONFERENCE CENTER, ROOM C, HSS, 525 EAST 68TH ST.

4:30 P.M. **Cadherins and Catenins in Development and Cancer.** Barry M. Gumbiner, Member, Cellular Biochemistry and Biophysics Program, MSKCC. Cell Biology and Genetics Seminar. PAPANICOLAOU LIBRARY, A-106, WMCCU, 1300 YORK AVE. COFFEE WILL BE SERVED. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

5:30 P.M. **Successful Aging.** Jack Rowe, President and Chief Executive Officer, Aetna Inc. Zanvil A. Cohn Forum on Health Affairs. ABBY DINING ROOM. SHERRY AND WINE AT 5:00 P.M. IN THE ABBY LOUNGE.

TUESDAY, JANUARY 23

4:00 P.M. **The Molecular Physiology of Na^+-Coupled Bicarbonate Transporters.** Walter Boron, Professor of Cellular and Molecular Physiology, Yale University School of Medicine. Pharmacology Seminar. WEILL AUDITORIUM, WMCCU, 1300 YORK AVE. COFFEE AT 3:45 P.M. CONTACT LISSETT CHECO, 746-6250.

WEDNESDAY, JANUARY 24

10:30 A.M. **Biostatistics Course.** Knut Wittkowski, Biometrician and Senior Research Associate, RU Hospital. 128 HOSPITAL. CONTACT KNUT WITTKOWSKI, 327-7175. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

12:00 P.M. **Hyperhomocysteinemia: Mediator of Marker or Vascular Disease?** Steven R. Lentz, Associate Professor of Internal Medicine, University of Iowa College of Medicine. Seminars in Clinical Research. 110B NURSES RESIDENCE. CONTACT DALE MILLER, 327-8411.

4:30 P.M. **Genetic Control of Apoptosis in C. elegans.** Robert Horvitz, Professor, Howard Hughes Medical Institute, Massachusetts Institute of Technology. MSKCC President's Research Seminar Series. AUDITORIUM, ROCKEFELLER RESEARCH LABORATORIES, MSKCC, 430 EAST 67TH ST. TEA AT 4:00 P.M.

THURSDAY, JANUARY 25

4:00 P.M. **In vivo TH0, TH1 or TH2 Cells May Not Exist: The CD4 Cells That Mediate Type 1 and Type 2 Immunity Show Segregated Expression of the Individual Cytokines.** Paul V. Lehmann, Associate Professor of Pathology, Case Western Reserve University. Alexey Y. Karulin, Senior Postdoctoral Research Fellow, Case Western Reserve University. LFKRI Research Seminar. LOWER LEVEL CONFERENCE ROOM, NEW YORK BLOOD CENTER, 310 EAST 67TH ST. TEA AT 3:45 P.M. CONTACT ROSANNA MARTINEZ, 570-3357.

FRIDAY, JANUARY 26

12:00 P.M. **Unnatural Ligands for Engineered Receptors: New Tools for Chemical Biology.** Kevan Shokat, Associate Professor, Department of Cellular and Molecular Biology, UCSF. Molecular Biology Seminar. 116 ROCKEFELLER RESEARCH LABORATORIES, MSKCC, 430 EAST 67TH ST. TEA AT 11:45 A.M. CONTACT LINDA SMITH, 639-7655. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

The Arts and Other Events

FRIDAY, JANUARY 12

12:00 P.M. **Tri-institutional Noon Recitals.** The Raphael Trio. Performing piano trios of Dvorák and Beethoven. CASPARY AUDITORIUM. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

FRIDAY, JANUARY 19

12:00 P.M. **Tri-institutional Noon Recitals.** David Walker, countertenor; Timothy Hoekman, piano. CASPARY AUDITORIUM. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

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8:00 P.M. **Peggy Rockefeller Concerts.** Wolfgang Holzmair, baritone. Caspary Auditorium. Contact Jennifer Goldschlag, 327-8437.

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MONDAY, JANUARY 29

12:00 P.M. **New Approaches to HIV Therapy.** Martin Hirsch, Massachusetts General Hospital. CFAR Seminar. SIXTH FLOOR CONFERENCE ROOM, ADARC, 455 FIRST AVE. CONTACT GARY GAILOR, 448-5163.

1:30 P.M. **Modulation of Immunity.** Nina Bhardwaj, Associate Professor for Clinical Investigation, RU. Immunology Seminar. WEILL AUDITORIUM, WMCCU, 1300 YORK AVE.

4:30 P.M. **Biophysical and Molecular Dissection of Vesicle Traffic in Synaptic Terminals.** Timothy A. Ryan, Assistant Professor, Department of Biochemistry and Structural Biology, WMCCU. A-106 WMCCU, 1300 YORK AVE. COFFEE WILL BE SERVED. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

TUESDAY, JANUARY 30

4:00 P.M. **Generation of Target Sites for cAMP via AKP-PKA Complexes.** Charles Rubin, Professor and Chairman, Department of Molecular Pharmacology, Albert Einstein College of Medicine. Pharmacology Seminar. WEILL AUDITORIUM, WMCCU, 1300 YORK AVE. COFFEE AT 3:45 P.M. CONTACT LISSETT CHECO, 746-6250.

WEDNESDAY, JANUARY 31

10:00 A.M. **Dissecting Gene Regulatory Networks — Lessons from Yeast.** Bing Ren, Department of Molecular and Cellular Biology, Harvard University. Cancer Biology Seminar. 301 WEISS. OPEN TO RU COMMUNITY AND GUESTS.

12:00 P.M. **A Protein Engineering Approach to Controlling Protein Secretion.** Tim Clackson, Vice President, Gene Therapy, ARIAD Pharmaceuticals, Inc. Student-sponsored Seminar. 301 WEISS. PIZZA LUNCHEON AT 1:00 P.M. ON THE 17TH FLOOR OF WEISS. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

12:00 P.M. **Hematopoietic Stem Cell Therapies for Chronic Granulomatous Disease: Allogeneic Transplantation or Autologous Gene Therapy.** Harry L. Malech, Deputy Chief, Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, NIH. Seminars in Clinical Research. 110B NURSES RESIDENCE. CONTACT DALE MILLER, 327-8411.

4:30 P.M. **Cell Signaling by Tyrosine Phosphorylation.** Joseph Schlessinger, Chair and Professor of Pharmacology, and Director, Skirball Institute of Biomolecular Medicine, NYU School of Medicine. MSKCC President's Research Seminar Series. AUDITORIUM, ROCKEFELLER RESEARCH LABORATORIES, MSKCC, 430 EAST 67TH ST. TEA AT 4:00 P.M.

7:30 P.M. **Psoriasis Support Group.** Meeting. 110B NURSES RESIDENCE. CONTACT PATRICIA GILLEAUDEAU, 327-8333.

THURSDAY, FEBRUARY 1

4:00 P.M. **Making a Difference: The Asymmetric Division of Stem Cells in the Germline.** Haifan Lin, Assistant Professor, Department of Cell Biology, and Head, Laboratory of Stem Cells and Germline Development, Duke University Medical School, Comprehensive Cancer Center, Durham, N.C. Endocrinology and Reproductive Biology Seminar. 301 WEISS.

The Arts and Other Events

FRIDAY, JANUARY 19

12:00 P.M. **Tri-institutional Noon Recitals.** David Walker, countertenor; Timothy Hoekman, piano. CASPARY AUDITORIUM. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

WEDNESDAY, JANUARY 24

8:00 P.M. **Peggy Rockefeller Concerts.** Wolfgang Holzmair, baritone. Caspary Auditorium. Contact Jennifer Goldschlag, 327-8437.

SUNDAY, FEBRUARY 4

1:00 P.M. **Chamber Music Recital.** Möbius String Quartet. Performing works by Schubert, Scott Johnson and Hindemith. CASPARY AUDITORIUM. ADMISSION IS FREE. OPEN TO RU/WMCCU/NYPH/MSKCC COMMUNITY AND GUESTS.

Simon lab stalks proteins in natural habitat

When a rough draft of the human genome was announced last summer, many researchers noted that the next step was to tackle the human "proteome"—the huge number of proteins for which our genes encode. Scientists have already begun the daunting task of identifying and isolating single proteins so they can be sequenced, crystallized and catalogued.

But studying proteins in static form is somewhat like looking at butterflies only when they are mounted—it does not reveal the details of their behavior. To gain a true understanding of proteins, researchers also need to know how they interact with other molecules. An essential component of proteome research will require putting proteins back into the cell and tracking their movement and expression.

Professor Sanford Simon and colleagues in the Laboratory of Cellular Biophysics are taking advantage of the latest technology to study protein activity in innovative ways. In three papers over the last nine months, the lab has reported landmarks in the study of protein transit and expression in the living cell.

"Researchers have learned how to break cells open and separate out the components," says Simon. "Now, the question is: Can we study how those components work, once they're put back in the living cell? When you study proteins in isolation, they might behave very differently from how they do back in their normal environment."

In the past, studying protein activity in cells has been neither precise nor efficient. Studying the activity of a particular protein—call it "Protein X"—involves characterizing the changes that result from expressing Protein X in a cell where it normally is not found.

Unfortunately, the techniques to express proteins in cells produce a mixed population that is difficult to analyze. Most cells—often 90 percent of them—fail to express the protein in the first place. Among the small number of cells that do, the levels of Protein X vary dramatically, with differences up to 1,000 fold. Scientists usually deal with this problem by selecting a subpopulation to be grown.

In a process taking months, a population of cells is raised, all of whom are expressing the same amount of Protein X. However, this leads to two problems. First, if these cloned cells differ from the original parent, are the differences the result of expressing the new protein or merely an artifact of the cell selection and cloning process? Second, if you want to characterize a protein, how could you study its behavior in the living cell over a wide range of concentrations – not just at the single fixed concentration found in the cloned cell line?

"Yu Chen, a biomedical fellow in the lab, solved this by turning the problem on its head," says Simon. "He decided that the short term expression that gave the very mixed population could be quite advantageous.

> "When you study proteins in isolation, they might behave very differently from how they do back in their normal environment."

The cells that do not express the protein (the majority of cells) serve as your control: how a cell should behave if it was not altered.

"The cells that express the protein will each express the protein at very different levels. By measuring the concentration of our protein in each individual cell and, at the same time, the activity of the protein in the same cells, we could study the relationship between the levels of expression of a protein and its activity."

All that was needed was to be able to simultaneously measure the levels of the protein *and* the activity of the protein in single cells. This was accomplished in two steps. First, they took the coding region for a green fluorescent protein found in jelly fish and spliced into it the coding region for the protein they wanted to study.

Thus, the amount of protein in each living cell can be quantified by green fluorescence of the cell. Next, the activity of each cell is measured by red fluorescence. The activity and the expression of Protein X could be measured in each individual cell. Rapid analysis of thousands of cells can be performed, which gives a detailed biochemical profile of Protein X in living cells.

In a paper published last March in the *Journal of Cell Biology*, Chen and Simon reported using this approach to study the mechanism of action of P-glycoprotein (Pgp), a protein involved in resistance to anticancer drugs. To measure the activity of Pgp they used chemotherapeutic drugs that were themselves fluorescent, but red rather than green. If Pgp was active, then they should be able to measure, in each individual cell, how the amount of chemotherapeutic drugs (the red fluorescence) was affected by the amount of Pgp (the green fluorescence).

"This gave us a very nice relationship between amount of an enzyme (in this case Pgp) and its activity. That information can be critical to understanding a protein's role," says Simon.

Another technological breakthrough, reported last April in the *Journal of Cell Biology*, involves studying how cells secrete materials into their environment through the use of membrane-bound compartments called vesicles. This process of fusion is an essential step in cell growth, secretion and transmission of signals between nerve cells.

> "In some cases what you really want to learn is: Where is the protein, and more specifically, where is it active?"

Simon and fellow lab members Jan Schmoranzer and Mark Goulian (now of the University of Pennsylvania), along with Dan Axelrod of the University of Michigan, used a special microscope that allows them to detect material only moving within 50 nm of the surface of the cell (less than 1/10th the wavelength of light). Vesicles tagged with fluorescent proteins in their own membranes could be studied as they approached and then fused with the cell surface.

Simon says the technique could help them piece together how this happens. "If we believe that certain molecules are involved with the fusion, we can mark them with different colored probes and ask: When do these things interact with each other? By studying the dynamics of when the different proteins interact with each other and with the vesicles, we could test various models for how these proteins work to cause membrane fusion."

Measuring protein expression at different locations in the cell is a logical next step in tracking the flow of genetic information, known as the "Central Dogma," from DNA to RNA to proteins. Scientists already know a great deal about how a DNA sequence produces a protein sequence, which results in a specific structure. From that structure they also have been able to predict some protein functions. Now, by putting the proteins into cells, they are starting to explore where that function comes into play.

"In some cases what you really want to learn is not only what is the amount of DNA you have for a certain protein, not how much messenger RNA it is making, and not even how much protein there is but rather: Where is the protein, and more specifically, where is it active?" says Simon.

The ability to study proteins in living cells has been limited, in part, by the sensitivity of the microscopes. Usually when scientists study the fluorescent signal from a protein in a living cell they require 5,000 to 50,000 molecules rather than one. In the fall, Simon and Mark Goulian made another landmark breakthrough when they tracked the motion of single proteins within living cells. Using a highly specialized imaging technique, the scientists followed a fluorescent protein called R-phycoerythrin (RPE)

ON FILE

Professor Sanford Simon's Laboratory of Cellular Biophysics is applying innovative techniques to study protein activity.

as it moved about the nucleus and cytoplasm of mammalian cells. Simon and Goulian reported this work in the October issue of *Biophysical Journal*.

"When you follow individual proteins, you learn things that are quite different from what you get when you study the general population," Simon says. "Certain assumptions made from studying the population don't necessarily hold up for single proteins."

One conjecture already proven wrong is that a protein has a single "diffusion constant"—the term characterizing the way a particle moves in a cell. By following individual proteins across different regions, they found that a single protein has a wide range of diffusion constants. Again, cellular environment must be factored into any meaningful protein definition.

"Albert Claude started breaking open cells and separating components 50 years ago," says Simon. "In the interim, we became adept at characterizing these components, determining their structure, and even setting up artificial systems outside the cell to study their behavior. Now we're coming back to see how they actually function in the living cell. The research has come full circle."

This research was supported in part by the National Institutes of Health, the American Cancer Society, the Keck Foundation, the Wolfenshon Foundation and the Molecular Biophotonics Laboratory in Japan.

ANNOUNCEMENTS

New *News&Notes* schedule

News&Notes will now be published every two weeks. The next issue will be on Fri., Jan. 26. The Calendar of Events will be published weekly as usual.

Choral society seeks singers

The Choral Symphony Society, Inc. will begin rehearsing on Tues., Jan. 23, 2001. All rehearsals start at 7:20 p.m. (Tuesdays) at The Rockefeller University Music Room in Caspary Hall. Their program will consist of two major works. On Sun., May 20, they will perform Haydn's *Missa Cellensis*; on Sun., June 3, they will perform one of Handel's greatest oratorios, *Athalia*. Anyone interested in becoming a member should call David Labovitz, music director, at 864-7541 for an audition appointment.

Papers and talks

If you are about to publish a paper or give a scientific talk, *News&Notes* would like to know about it. Please send your information by campus mail to Box 68, by E-mail to newsno or by fax to x7876.

Scenes from the 2000 campus holiday party

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