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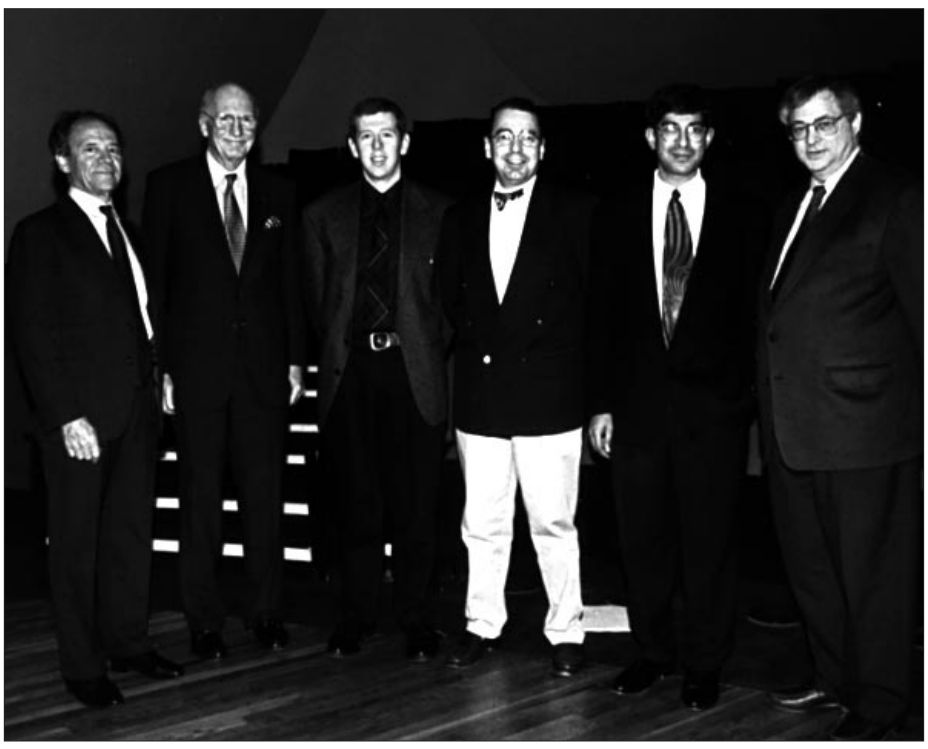
The Rockefeller University 1901

news&notes

OCTOBER 9, 1998 VOLUME 9, NUMBER 4 THE ROCKEFELLER UNIVERSITY

RU Council holds its fall meeting



President Torsten Wiesel, RU Council Chairman Richard Furlaud, Assistant Professor Tom Muir, Professors Stephen Burley and John Kuriyan, and President-elect Arnold Levine gathered in Caspary Auditorium after the program portion of The Rockefeller University Council's fall meeting, which was held on Wednesday, October 7, 1998. The event featured Burley, Kuriyan and Muir. More than 100 Council members and guests were in attendance.

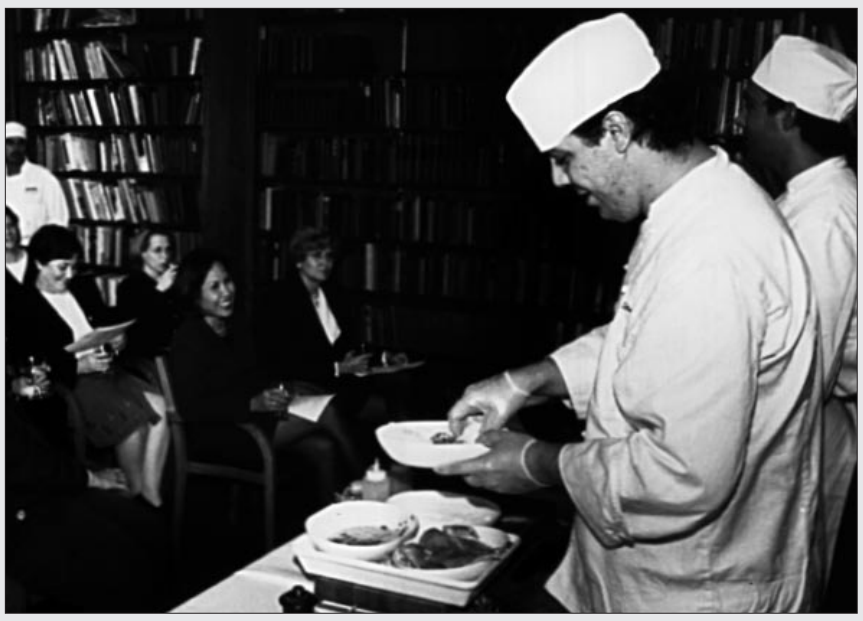
City of Medicine honors Darnell

Vincent Astor Professor James Darnell will receive a City of Medicine award for his 40 years of research in molecular biology.

Vincent Astor Professor James Darnell will receive the 1998 City of Medicine Award on October 14 for his 40 years of achievement in molecular biology. Over the years, Darnell's work has been devoted to better understanding how gene expression is regulated in mammals. His early research supplied much of the original evidence for how messenger RNA (mRNA) is formed in animal cells. More recently, his lab has discovered a direct signaling pathway from the cell surface to genes in the nucleus; this finding has important implications for the design of rational drugs.

The City of Medicine program was established as a nonprofit organization in Durham, North Carolina, in 1981. RU's President-designate Arnold Levine was a City of Medicine Award recipient last year.

Restaurant Associates shows what's cooking



Restaurant Associates introduced its 1998-99 conference dining and catering menu to the RU community on Oct. 6. The evening included demonstrations and complimentary food and wine.

Friday lectures

Sakmar to discuss signal transduction by G protein-coupled receptors

RU Associate Professor Thomas Sakmar will give the Friday lecture today (Oct. 9).

Thomas Sakmar, an associate professor and head of the Laboratory of Molecular Biology and Biochemistry at RU, will discuss "Signal Transduction by GPCRs: Lessons from Rhodopsin" at the Friday lecture today (Oct. 9).

G protein-coupled receptors (GPCRs) allow certain types of extracellular signals to move across a cell's membrane and into its interior to produce a particular cellular effect. They are part of a key molecular mechanism to help cells respond to signals from within the body and from the outside world. Some reactors specifically respond to the presence of hormones (the most famous of these is the adrenaline receptor). Sakmar's lab has concentrated on visual pigments, which sense the presence of light. When light is absorbed by one of these receptors, a series of events is triggered within the cell. Sakmar's lab is trying to find out how light is converted to a chemical signal, how this pathway is regulated and which proteins are involved.

Part of the Friday lecture will focus on the molecular basis of color vision and how visual pigments tune to certain wavelengths. (Color blindness, for example, is caused by genetic changes in this class of receptors in the cone cells of the retina.) Sakmar's lab determined that the primary mechanism of spectral tuning in visual pigments involves interaction of the vitamin A chromophore with dipolar amino acids.

Sakmar will also discuss what his studies of visual pigments can tell us about GPCRs in general. His work over the past few years showed that the different GPCRs probably function analogously. They look very similar, and the G-proteins that they couple to on the inside of the cell are related to one another. The specificity for signaling depends upon the segregation of the molecules within the cell.

The GPCRs Sakmar studies are useful prototypes for understanding the whole family of receptors. Visual pigments have certain practical advantages in the laboratory: they are available in sufficient quantities, and they have chromophores—which means that they can be examined using biophysical and spectroscopic techniques. Sakmar's lab is using these techniques to determine as

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President-elect Levine to discuss p53 next week

RU President-elect Arnold J. Levine will discuss "Deregulation of the p53 tumor suppressor protein" at the Friday lecture on Oct. 16.

Levine is one of the world's leading authorities on the molecular basis of cancer. In 1979, he discovered the p53 tumor suppressor gene, a molecule that inhibits tumor development. Because disruption of this protein's normal function is associated with an estimated 60 percent of human cancers, p53 has become a focus of research in laboratories around the world and is helping fuel the design of a new generation of anticancer therapies.

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Levine received his B.A. from Harpur College, SUNY, in 1961 and his Ph.D. from the University of Pennsylvania in 1966, and then worked as a postdoctoral fellow at the California Institute of Technology. He went to Princeton in 1968 as an assistant professor and in 1976 became a full professor of biochemistry. In 1979, Levine left Princeton to chair the department of microbiology at SUNY Stony Brook School of Medicine. He returned to Princeton in 1984 as the Harry C. Weiss Professor and chair of the department of molecular biology. This past summer, he was selected as the eighth president of Rockefeller University.

President-designate Arnold Levine will discuss p53 proteins at the Friday lecture on Oct. 16.

Levine is currently a member of both the scientific and medical advisory boards of the Howard Hughes Medical Institute and a trustee of the Cold Spring Harbor Laboratory and the University of Pennsylvania, where he is on the executive committee. He also serves on scientific advisory boards at the Memorial Sloan-Kettering Cancer Center, the Basel Biozentrum in Switzerland, the Mount Sinai Research Institute in Toronto, the Huntsman Cancer Center at the University of Utah and the Institute for Cancer Research at Lausanne.

He was elected to membership in the U.S. National Academy of Sciences in 1991 and to its Institute of Medicine in 1995. Among his numerous awards are the Katharine Berkan Judd Award from Memorial-Sloan Kettering Cancer Center and the Brinker International Award from the Susan G. Komen Breast Cancer Foundation, both in 1993; the 1994 Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research; and the First Annual Strang Award from the Strang Cancer Prevention Center, also in 1994. In 1998 he has received the Paul Ehrlich and Ludwig Darmstaeder Prize from the Paul Ehrlich Foundation, the Bertner Award from the University of Texas M.D. Anderson Center and Eli Lilly's Clowes Award from the American Association for Cancer Research.

The lecture will begin at 3:45 p.m. in Caspary Auditorium. Tea will be served prior to the lecture in Abby Aldrich Rockefeller lounge at 3:15 p.m. All are welcome.

Tri-Institutional Noon Recitals

A Little Day Music

Pianists take center stage in the next two Tri-Institutional noon recitals.

On Fri., Oct. 9, Valery Kuleshov will perform a program featuring Bach, Listz and Listz-Busoni.

On Tues., Oct. 13, Fabio Bidini will perform Beethoven, Chopin and Schubert. (Please note that this concert is not in the usual Friday time slot.)

Both concerts take place in Caspary Auditorium at noon and are free for Tri-Institutional affiliates and their guests.

Pianist Fabio Bidini will perform Tues., Oct. 13.

Pianist Valery Kuleshov will perform this Friday (Oct. 9) at noon in Caspary Auditorium.

Potpourri

Cancer screening

The Employee Health Office is offering all men in the RU community a free screening for prostate cancer, the most common type of cancer in American men and one that rarely has any symptoms in the early stages. The screening program, which runs until Tues., Nov. 17, consists of a blood test to determine levels of prostate specific antigen (PSA); a follow-up physical examination will also be offered on Wed., Nov. 18.

Who is at risk? The American Cancer Society recommends annual PSA screening for all men over age 50; in addition, African American men and men with two or more first-degree relatives (father, brother or son) with prostate cancer should be tested annually after age 45. Please call the Employee Health Office at x8414 for more information.

Influenza vaccines

The Employee Health Office is offering free influenza vaccinations to all RU students and employees. Those wishing to be vaccinated should go to Hospital Room 118 between 10:00 a.m. and 4:00 p.m. Monday through Friday. No appointment is necessary. Call the Health Office at x8414 for more information

The National Coalition of 100 Black Women held their Economic Development Colloquy on the RU campus on Oct. 1 and 2. Among the speakers at the event were Jewell Jackson McCabe, president of the coalition, and former New York City Mayor David Dinkins. Above: Conference participants enjoy lunch in Caspary.

Attention shoppers

The RU Sweatshirt Shop has reopened for the school year. It is located in the tunnel between RRB and Bronk. Normal operating hours are Tuesday from noon to 2:00 p.m. Next week, however, the shop will be open every day from Tuesday through Friday (noon to 2:00 p.m.) for back-to-school shopping. The shop is run by the Parents' Association of the Child and Family Center to benefit ongoing programs for children at CFC.

On Oct. 22, an African violet sale to benefit the Children's School will take place in the lobby of the Weiss Building between 8:00 a.m. and 3:30 p.m.

New RU events hotline

Trying to find information about an upcoming event at RU? The university has a new phone number with information about RU events, including the Peggy Rockefeller Concerts, Tri-institutional Noon Recitals, public lectures and symposia, along with directions to the campus. Call x7007.

A music room of one's own

The music room on the first floor of Caspary Hall is available for use. The room, equipped with a Steinway grand piano, music stands and chairs, may be reserved for time slots of one hour during the day or evening. A sign-up sheet is available on the door outside the music room.

Visa lottery

The Department of State will award immigrant visas to 50,000 winners of a visa lottery. The filing period runs from noon Thurs., Oct. 1 through noon Sat., Oct. 31. For detailed information about the lottery, please visit the Office of Human Resources, Founder's Hall 103.

Author, author

If you have recently published a book, *News&Notes* would like to know about it. Please send your publication particulars, along with a brief summary of the book, to Lisa Stillman at Box 68 or fax x7876.

News&Notes Schedule

News&Notes will not be published next week because of the Columbus Day holiday. The calendar will be published as usual.

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).

NSHL study

RU geneticist searches for hearing-loss genes

BY PAUL C. FOCAZIO


Assistant Professor Suzanne Leal is trying to understand the genetic basis of hearing loss.

Hearing impairment, which ranges in severity from modest difficulty with speech comprehension to profound hearing loss, affects 28 million Americans. It is a common birth defect that can modify communication, language acquisition, speech, cognitive skills and psychosocial development.

Approximately one in every 1,000 children is born with a significant hearing impairment; a similar number of children also become severely hearing impaired before adulthood. More than 60 percent of the cases of profound early-onset deafness are caused by genetic factors, which in most cases are due to single gene mutations.

Suzanne Leal, an assistant professor in RU's Laboratory of Statistical Genetics, studies the genetics of non-syndromic hearing loss (NSHL), which is characterized by hearing impairment without any other clinical symptoms.

"By studying families with a history of hearing loss, we are attempting to find genes that are involved in the process of hearing," says Leal, principal investigator of the study. "The isolation of NSHL genes will aid in understanding the function of genes controlling the mechanism of hearing, which should facilitate the development of intervention strategies to prevent and treat hearing loss. Identification of NSHL genes will also allow for the diagnosis of NSHL subtypes."

The genetics of hearing loss

About 75 percent of individuals with genetically determined deafness have NSHL; the other 25 percent have identifiable syndromes. Inheritance of NSHL can be in either of two primary forms: autosomal dominant (NSDHL), in which only one copy of the hearing loss gene is necessary, or autosomal recessive (NSRHL), in which two copies of the gene is needed.

Among school-aged children, an estimated 75 percent of the genetic cases display autosomal recessive inheritance and 15 percent are autosomal dominant. The majority of hearing impaired people with the autosomal dominant form of NSHL have post-lingual progressive hearing loss, while those with autosomal recessive forms suffer hearing impairment that is usually prelingual (before language acquisition) and profound. (Only two to three percent of cases have hearing impairment due to X-linked inheritance, in which genes are carried on the X chromosome. NSHL can also be due to mitochondrial inheritance.)

NSHL is one of the most heterogeneous genetic Mendelian diseases. Thus far, more than 30 NSHL loci have been mapped (4 X-linked loci, 14 autosomal dominant loci and 15 autosomal recessive loci), but only seven genes have been identified. These genes are starting to give insight into what causes the phenotype of mild hearing loss to deafness. For example, three of the genes discovered (Myosin VIIa, HDIA1 and alpha-tectorin) are thought to maintain the cytoskeletal integrity.

Since many specialized cells of the cochlea (part of the inner ear) are likely to serve essential functions in the process of hearing, any disturbance of a particular cell type may impair the ability to hear. An estimated 100 genes may be involved in NSHL, which supports the hypothesis that mutations can disrupt the ability to hear via many different processes.

All in the family

Leal became interested in the genetics of hearing loss as a postdoctoral fellow in the Department of Otolaryngology at the University of Tuebingen, Germany. There she developed a study of the genetics of NSHL. "What particularly interested me about non-syndromic hearing loss is its extreme genetic heterogeneity," she says. After finishing her postdoctoral studies Leal came to RU, were she continues to study the genetics of NSHL.

Currently, Leal is studying families with a history of NSHL from the United States, Switzerland, Turkey and Jordan. Her long-term goals are to localize one or more novel NSHL genes, refine the genetic region for known NSHL loci and isolate NSHL genes. The study, which began in February 1997, is part of the research program of the University's Starr Center for Human Genetics. Since the inception of the study, more than 500 DNA samples have been obtained from 49 families. Fourteen of these families can independently establish linkage.

Leal says, "Although we are able to ascertain large autosomal dominant pedigrees within the United States and Western Europe, it has not been possible to find autosomal recessive pedigrees of sufficient size to independently establish linkage." She adds, however, that in countries such as Jordan and Turkey, where it is common to marry a close relative, she and her colleagues have been successful in ascertaining a number of autosomal recessive pedigrees of sufficient size to independently establish linkage.

Location, location, location

To map NSHL loci, a genome scan is being carried out by covering the entire genome with 387 genetic markers spaced approximately 10cM apart. Leal explains that linkage analysis methods can then be used to estimate the recombination fraction between the genetic marker and the disease locus. "When the estimate of the recombination fraction is 0.5, the marker and disease locus are unlinked," Leal says. "The disease locus may be on a different chromosome or very far apart on the same chromosome. Therefore, the smaller the estimate of the recombination fraction, the closer the marker locus is to the disease locus. Once there is evidence of linkage in a region, additional makers are genotyped to establish and fine-map the disease locus."

Because of NSHL's extreme genetic heterogeneity, Leal says, "mapping novel loci using small, unrelated families is impossible, even if the hearing impairment has a similar etiology. "We can test for linkage in the presence of heterogeneity," she says, "but if almost every family is segregating a different NSHL locus, we won't be able to detect linkage."

To overcome this problem, Leal says, "We have to study large families, which can independently establish linkage. Although such families can elucidate the position of novel NSHL loci, because of the limited number of informative meioses in one family, the disease locus can map to a large region, in some case regions greater than 10cM."

Since most of the NSHL genes are rare, Leal cautions that there may be only a handful of families—or in some cases only one family—known to segregate a particular locus. In cases where NSHL loci map to a large genetic region without suitable candidate genes within the genetic region, gene isolation can be difficult.

Smaller NSHL kindreds, which cannot independently establish linkage, have also been ascertained in Leal's study. She says, "These smaller kindreds are useful for refining the genetic region for known NSHL loci and for gene isolation."

Statistics for geneticists

In addition to studying the genetics of NSHL, Leal collaborates with other researchers studying a variety of Mendelian and complex disease traits, including Fanconi anemia and drug addiction. "It is stimulating to collaborate with other investigators on the analysis of data for various genetic traits," she says. "Each data set is unique, and the analysis must be adapted to fit a particular data set. In addition, the analysis of genetic disease data often gives insight into a particular methodological problem that needs to be solved."

Her work on methodological issues in statistical genetics includes the development of a likelihood method to calculate the upper and lower bounds for a particular risk. Leal says, "Usually genetic risks are computed under the assumption that genetic parameters, such as the recombination fraction, penetrances and allele frequencies are known without error. However, uncertainty in parameter estimates can lead to an inaccurate genetic risk. Using a maximum-likelihood framework, the upper and lower bounds for the risk can be calculated." She adds that this "risk support interval" can be used in genetic counseling situations to evaluate the accuracy of risk point estimate.

Understanding statistics is often a problem for researchers working in the field of genetics. To increase their understanding, Leal, in collaboration with Jürg Ott, professor and head of the Laboratory of Statistical Genetics, organizes and teaches basic and advanced courses on linkage analysis. At these courses, investigators can learn about various statistical methods as well how to use them to analyze their data. These courses are held both at The Rockefeller University and in Europe.

For more information, consult Leal's World Wide Web site, http://linkage.rockefeller.edu/suzanne.

This work is supported by the American Hearing Research Foundation, The National Institute on Deafness and other Communication Disorders and the National Human Genome Research Institute at the National Institutes of Health and the Starr Center for Human Genetics.

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much structural information as possible about visual pigments; the lab then hopes to develop models that can be tested on other receptors, which cannot be studied using the biophysical or spectroscopic methods.

The G protein-coupled receptors have an important role in the pharmaceutical industry; more than two-thirds of non-antibiotic drugs target GPCRs. Sakmar's training as an M.D. makes him particularly aware of the medical possibilities of GPCR research

Sakmar received his A.B. degree in chemistry and his M.D. degree from the University of Chicago. He completed a medical residency at the Massachusetts General Hospital and conducted research in the laboratory of H. Gobind Khorana at the Massachusetts Institute of Technology. In addition to heading up his lab at RU, Sakmar is an associate investigator in the neuroscience program at the Howard Hughes Medical Institute and a physician at the RU Hospital. Since 1997 he has also served as Associate Dean for Graduate Studies in the Tri-Institutional MD-PhD Program.

The lecture begins at 3:35 p.m.in Caspary Auditorium and is preceded by a tea at 3:15 p.m. in Abby Aldrich Rockefeller lounge. All are welcome.