FEBRUARY 23, 2001

news & notes

THE NEWSLETTER OF THE ROCKEFELLER UNIVERSITY

FRIDAY LECTURE

Tsien to discuss single synapses today

Richard Tsien, the George D. Smith Professor at Stanford University Medical Center, will present the Friday lecture today (Feb. 23). Tsien's topic will be "Modulating the Song of Single Synapses."

Tsien's laboratory studies signaling mechanisms that link electrical activity to cytoplasmic events and to intracellular and intercellular communication. Tsien was the founder of the Department of Molecular and Cellular Biophysiology at Stanford University and was chairman of the department from 1988 to 1994. In addition, he has been the director of Silvio Conte-National Institutes of Mental Health Center for Neuroscience Research since 1991.

Tsien received his S.B. and S.M. degrees from the Massachussetts Institute of Technology and his Ph.D. in biophysics from Oxford University, where he was a Rhodes Scholar.

He has won a number of awards for his work and is a member of the Institute of Medicine of the National Academy of Sciences, the National Academy of Sciences and the American Academy of Arts and Sciences.

Tsien's talk will take place in Caspary Auditorium at 3:45 p.m. and is preceded by a tea at 3:15 p.m. All are welcome.

Richard Tsien is the George D. Smith Professor at Stanford University Medical Center.

Rockefeller hosts open house for prospective students

On the first two weekends in March, prospective students will attend an Open House at The Rockefeller University. This is an important step in the admissions process, giving admitted students a chance to learn more about the university, both its research and ambiance.

The students who will be visiting were selected from an applicant pool of more than 500 candidates. "We had many outstanding candidates this year," says Dean Sidney Strickland. After an initial screen of applications, the most competitive were sent to two members of the admissions committee with expertise in the applicants' fields of interest. The members of the admissions committee are Fred Cross, David Gadsby, Magda Konarska, Michel Nussenzweig, Michael Rout, Andrej Šali and Leslie Vosshall, with Strickland and Jean Devlin, director of educational affairs, also participating.

The committee looks for several factors: students should have a high academic performance in their coursework, some laboratory experience showing commitment to scientific study and strong letters from their advisors. The admissions committee also looks at an applicant's personal statement. "We are always interested in students with unconventional backgrounds who show a commitment to research," says Strickland.

"We're also able to take a number of top international students," he says. "At many other schools, government funding limits support to U.S. citizens or green card holders. But because of Rockefeller's central funding, we can admit the best scientists without concern for citizenship."

Strickland is pleased that many of the admitted students express an interest in interdisciplinary studies. The university has increased its interdisciplinary programs in the past few years. Among the new initiatives is a tri-institutional program in chemical biology with Cornell University and Sloan-Kettering Institute, and a collaboration in mathematical biology with the Courant Institute of New York University.

The visiting students will attend poster sessions on Fri., March 2, and Fri., March 9, to learn more about research at the university. This year, about 70 faculty, postdocs and students will present posters about their current laboratory projects. These sessions will take place on the 17th floor of Weiss from 1 p.m. to 3:30 p.m. All members of the campus are encouraged to attend to experience the vitality of research at the university and to meet the prospective students.

Dean Sidney Strickland is pleased that Rockefeller had so many outstanding candidates for admission this year.

Blobel to give Friday lecture on March 2

Cell biologist Günter Blobel will give the Friday lecture on March 2. Blobel, the John D. Rockefeller Jr. Professor at The Rockefeller University and a Howard Hughes Medical Institute investigator, studies the process by which newly made proteins are transported across the membranes of cell structures called organelles.

Because the accurate distribution of proteins to their proper places in the cell is necessary for a cell to function, these findings have an immediate bearing on many diseases, including cystic fibrosis, Alzheimer's disease and AIDS. Blobel was awarded the 1999 Nobel Prize in Physiology or Medicine for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell.

An average cell possesses about a billion protein molecules that exist in thousands of types and constantly need replacement. Making proteins and shipping them to appropriate destinations, such as the cell's internal organelles, is a vital activity in cells. Proteins are manufactured by cellular structures called ribosomes. Pioneering research by Blobel and his associates revealed how proteins are transported from ribosomes and integrated into other organelles or transported out of the cell.

Work in Blobel's laboratory revealed the existence of a ZIP code system in the cell. Each

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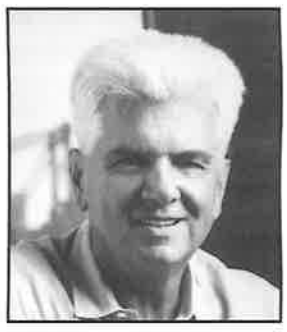

Nobel laureate Günter Blobel is the John D. Rockefeller Jr. Professor at The Rockefeller University. He is also an HHMI investigator.

An alumna sets up lab

When Rockefeller alumna Leslie Vosshall came back to campus in October, she wasn't just going to be working in a lab but running it. Vosshall, head of the university's new Laboratory of Neurogenetics and Behavior, is trying to understand the molecular basis of olfaction (the sense of smell) in the fruit fly. Scientists know a lot about fruit fly behavior, but little is known about how the flies recognize food sources.

As a graduate student, Vosshall worked in Michael Young's Laboratory of Genetics. "Mike Young made enormous strides in understanding how genes impact behavior," says Vosshall. "In the last 15 years, he's identified many of the important molecular components that regulate the circadian clock. Remarkably, these same components are now also showing up in the analysis of the vertebrate clock." What she wants to do is apply the same sort of analysis to olfactory behavior.

The sense of smell is very distinct from other sensory systems. Olfactory systems are designed to detect stimulus quality and concentration in the environment, a complex task considering that there are thousands of different odors. Olfactory systems also appear not to be evolutionarily related. "There's a dividing line at vertebrates," she said. Nematodes and flies, for example, use different gene families for olfaction. "The proteins have a similar structure but the amino acid sequences are completely different. Nature found many ways to solve the same problem."

The fruit fly *Drosophila* has very specific olfactory behavior strategies. Like other insects, it is a specialist and has narrow food interests. The fly has a repertoire of 61 odorant receptors, which are distributed among different olfactory neurons in the antenna. "That's probably how you get specificity," she says. Fruit flies love ethyl acetate, for example.

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Rockefeller alumna Leslie Vosshall is head of the Laboratory of Neurogenetics and Behavior.

ETCETERA

Woodstock Inn & Resort discount

Laurence S. Rockefeller is offering a special discount rate at the Woodstock Inn for 2001 to employees of The Rockefeller University. The discount room rate is $99 (plus Vermont state tax and a housekeeping surcharge) per room. For reservations, please fax or mail a request to:

Reservations
The Woodstock Inn & Resort
Fourteen the Green
Woodstock, Vt. 05091-1298

Fax: (802) 457-6699

Support group for "Improving Communications"

The Employee Assistance Program Consortium is sponsoring a six-part psychoeducational lunchtime support group on Improving Communication Skills, starting on Mon., March 19, and running through Mon., April 23. The group will meet from noon to 1 p.m. in the Whitney Conference Room 118 at New York-Presbyterian Hospital. Feel free to bring your lunch. Call Josephine at 746-5890 to register. Group size is limited.

Employee Assistance Program has new Web site

The Employee Assistance Program Consortium is a free, confidential counseling service available to all employees of the five consortium members (Hospital for Special Surgery, New York-Presbyterian Hospital, Rockefeller University and Weill Medical College of Cornell University). The program now has a new Web site (eapc5.com) where you can learn more about this service.

Alumna continued

Vosshall is looking to associate particular receptors with their corresponding odorants, and to understand how functional olfactory wiring patterns are established in development.

One of Vosshall's goals is to understand why some odorants lead to attraction and some to repulsion. She is also interested in how odorants interact with olfactory neurons and how this interaction is encoded in the brain to lead to stereotyped behaviors.

"A classic question in neurobiology is whether synaptic activity is required for the development of functional synapses or whether animals are genetically wired," says Vosshall. Using what she calls "genetic trickery," her lab is silencing neurons and allowing the flies to develop, then reactivating the neurons. This allows the researchers to see whether a functional olfactory system can form in the absence of activity.

Behavior is hard to study, she says, because it involves the interaction of complex neural circuits. Her lab is now conducting studies with larvae ("They live to eat") to try to determine the range of odorants they respond to. The researchers hope to be able to identify reproducible larval behaviors that can be the basis of further genetic studies.

The fruit fly is an appealing study subject because it is relatively simple, has robust olfactory behaviors, and can be genetically manipulated. She notes that Assistant Professor Peter Mombaerts, head of the Laboratory of Developmental Biology and Neurogenetics, is looking at some of the same questions in mice. "Hopefully there can be some cross-pollination," she says.

Vosshall is glad to be back on campus. "One great change," she says, "is a real commitment to junior faculty. President Levine is actively recruiting and expanding."

Vosshall also appreciates how helpful the university's administration was in helping her set up her first lab. "The Rockefeller infrastructure is a well-oiled machine," she says. Starting a new lab involves dealing with Purchasing, Maintenance, Sponsored Programs and other offices. "Everyone was incredibly helpful," she says. "At other places, I think it can sometimes be more of a struggle. Rockefeller is a real paradise for junior faculty."

Muir continued

ficity groups of *Staphylococcus aureus* defined by which type of peptide they produce. A group 1 strain of Staph responds to an extracellular group 1 peptide, and group 2 strain normally is activated by a group 2 peptide. Lyon took the group 1 receptor, AgrC, and the minimal components required for signal transduction in Staph, and put them into a group 1 strain from which he had deleted all of these components, in effect replacing all the components in that strain with group 1 specificity. This strain now responded to group 1 peptide and was inhibited by group 2 peptide.

Manipulating the group 2 strain in the same way—reconstituting with the group 2 components—Lyon showed that it is activated by group 2 peptide and inhibited by group 1 peptide.

The genetic trick, says Lyon, was to swap the receptors. He took a group 2 strain, which would have all those other potential receptors, in that group 2 cell, and reconstituted the cell with group 1 circuitry. The questions were then which peptide does it respond to, group 1 or group 2, and is it inhibited by group 1 or group 2 peptide?

Lyon found that the "group 1 swap" is activated by group 1 peptide and inhibited by group 2 peptide, convincing evidence that group 2 peptide must be inhibiting virulence at the level of the receptor AgrC.

"By logical induction, it had to be the receptor AgrC, and therefore no other co-receptor or anything else in the cells conferring group specificity for inhibition and activation," says Lyon.

"The fascinating part is that a related molecule, but not identical, can bind the same receptor, but instead of switching it on, switches it off," says Muir. "That was the key bit of information we needed in designing a molecular inhibitor, because it would be much more difficult to design an inhibitor if activation and inhibition were occurring at different receptors."

Lyon and Muir reasoned that it might be possible to design a molecule that would be an inhibitor of virulence by modifying the structure of the peptides in the right way.

The peptides are composed of a ring-shaped arrangement of five amino acids, called a cyclic pentapeptide, and a tail composed of three to four amino acids. Previous analysis by Muir's group showed that the tail component is necessary for activation of virulence. Remove the tail, and the peptide is no longer able to activate virulence. But the ring part seems to be important for both activation and inhibition.

"It appears that the ring is important in directing the peptide to the receptor, but the tail, once the peptide gets to the receptor, tells it to activate," says Muir. "We thought if we could just remove the tail, the ring should still be able to get to the receptor—but once it gets there, it doesn't have the information to tell the receptor to activate virulence. So it will sit there, kind of like a cork in a bottle, and prevent the natural peptide from coming in and binding."

Lyon and Muir synthesized a chemical analog of the peptide, removing the tail part and replacing it with a chemical capping group. What they found was that not only does this molecule inhibit all the other groups, but it also inhibits its own group, which is a fundamental requirement for a potential therapeutic. "We've been able to change this from an agonist of virulence to an antagonist," says Muir.

The researchers showed that this molecule inhibits all of the four known specificity groups in *Staphylococcus aureus*, and thus appears to be a global inhibitor of virulence in this pathogen.

Lyon has already performed preliminary experiments on certain other species of Staph and has obtained encouraging results as well.

"This suggests to us that molecules of that general type will be inhibitors of Staph virulence—period," says Muir. "Whether or not it's exactly this molecule, we don't know, but this will be the template from which we can go off and find it."

Muir is head of the Selma and Lawrence Ruben Laboratory of Synthetic Protein Chemistry. This research was supported in part by the National Institute of Allergy and Infectious Diseases, part of the federal government's National Institutes of Health (NIH), and the Burroughs-Wellcome Fund. Lyon is supported by the Medical Scientist Training Program of the NIH.

Nussenzweig continued

in the B cells after the animals had developed.

They found that 25 percent of the light chains on the surface of the B cells' antibody molecules are produced by receptor editing. Further, that editing was shown to occur in the B cells during a two-hour delay in development, at a stage in which they are normally recombining their light-chain genes.

"The body senses that the B cell is self-reactive, so it halts the cell to be modified during that early stage in development," Casellas says.

In some ways it makes biological sense for the body to rely on receptor editing to such a large degree. Modifying potentially harmful immune cells rather than destroying them conserves energy while maintaining an immune system that is both strong and safe.

"It is quite striking that what is being targeted so often is not the B cell per se, but a specific part of the antibody—the receptor—that the cell produces," Casellas says. "It is a much finer distinction, one that the body makes more often than most of us suspected."

This type of experiment became possible only through the development of innovative genetic manipulations that allow researchers to target precise DNA locations to ask specific questions.

"The technology is allowing us to develop sophisticated systems aimed at answering very specific questions about immunity and tolerance," says Michel Nussenzweig. "Use of these 'knock-in' genes should lead us to a much clearer understanding of how the body codes for its antibodies."

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