



news & notes

THE NEWSLETTER FROM THE ROCKEFELLER UNIVERSITY'S OFFICE OF COMMUNICATIONS AND PUBLIC AFFAIRS

TODAY'S EVENTS

Centennial symposium highlights clinical research

Today (Dec. 14), the university hosts a Centennial symposium. "From the Bench to the Bedside: Celebration of Excellence in Clinical Research" takes place from 1 to 5 p.m. in Caspary Auditorium.

David Rockefeller Professor Barry Collier, physician-in-chief of The Rockefeller University Hospital, will give an overview of clinical research at Rockefeller. Then, four of the world's leading clinical scientists will present talks about their research: Brian Druker of Oregon Health Sciences University will discuss STI-571/Glivec; Martin Cetron of the Centers for Disease Control and Prevention, global migration and emerging infections; David Nathan of the Dana-Farber Cancer Institute, the history and future of clinical research; and Irving L. Weissman of Stanford University, the biology of stem cells.

Founded in 1910, The Rockefeller University Hospital was the first medical institution in the U.S. devoted solely to the purpose of patient-oriented clinical research.

The hospital links laboratory investigations with bedside observations to provide a scientific basis for disease detection, prevention and treatment. This special hospital environment served as the model for the Warren G. Magnuson Clinical Center, opened at the National Institutes of Health in 1953, and similar facilities supported by federal funding at more than 75 medical schools in the United States.

Further information is available at: www.rockefeller.edu/lectures/clinre121401.html.

Today at 2 p.m. on NPR

Vincent Fischetti talks with Ira Flatow of National Public Radio's "Science Friday" about using phage enzymes to destroy bacteria. "Science Friday" can be heard on the Internet at www.sciencefriday.com.

Bacteria's natural foe may prove valuable human friend Novel Method to Fight Drug-resistant Infections Emerges from Lab — and Nature

Scientists have turned to nature once again for help in fighting deadly infections. Reporting in the Dec. 7 issue of *Science*, Rockefeller University researchers show that a natural enzyme derived from tiny viruses that live inside bacteria can successfully target and kill disease bacteria, including those that are resistant to drugs.

This novel approach may be used to prevent infections and, in combination with antibiotics, may provide a more efficient strategy for attacking bacterial invaders.

"A nasal spray containing this enzyme would prevent infections before they start," says Vincent A. Fischetti, first author of the paper and co-head of the Laboratory of Bacterial Pathogenesis at Rockefeller University. "We would no longer have to wait for an infection to arise in order to treat it.

"Resistance to antibiotics is rapidly becoming a serious public health concern. These enzymes offer an alternative method for combating resistant pathogens," he adds.

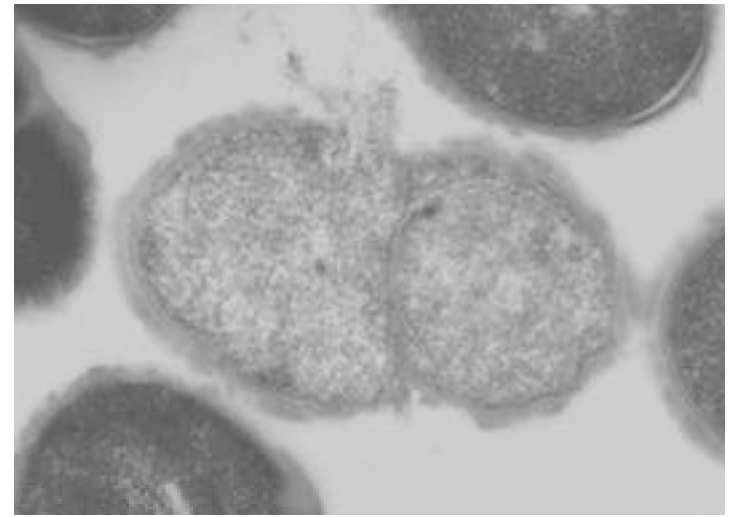
Traditional antibiotics primarily attack bacteria that reside inside cells, while the recently discovered "bacteriophage" enzymes kill only disease bacteria that

lie on the surface of cells. In this study, Fischetti and his colleagues used these enzymes to eliminate *Streptococcus pneumoniae* present in the nasopharynx, an area between the back of the nose and throat, of mice. In addition, the researchers demonstrated that these enzymes can kill penicillin-resistant strains of this bacterium in a test tube.

S. pneumoniae normally lives on mucous membranes in the nose and throat of humans. It is from here that it strikes out and causes infections, including ear infections, pneumonia and bacterial meningitis. According to the Centers for Disease Control and Prevention (CDC), this pathogen is among the leading causes worldwide of illness and death in young children, persons with underlying medical conditions and the elderly. It is a special concern in nursing homes and daycare centers, where drug-resistant strains thrive.

Until now, there has been no strategy to remove the reservoir of *S. pneumoniae* from the noses and throats of humans. Yet, this "home base" provides an excellent target for controlling infections.

"This enzyme will kill pneumococci on mucous membranes within seconds," says Jutta Loeffler, first author of the paper and a postdoctoral fellow



Phage enzyme is shown rupturing the cell wall of an *S. pneumoniae* bacterium. Without this outer layer of protection, the bacteria cannot hold themselves together, and they explode.

at Rockefeller. "By treating individuals carrying this bacterium with the enzyme, you could significantly reduce the reservoir of these bugs in the population and consequently reduce infection rates."

Such a decline in the number of worldwide infections would lessen the need for traditional antibiotics and subsequently ease the mounting drug-resistance problem.

Bacteriophage, or phage, can be found just about anywhere: in sewage, and soil and any other locations where bacteria are found. As part of their normal lifecycle, these tiny viruses

infect, replicate, then burst out of bacteria before infecting their next host.

Special phage enzymes, which punch holes in the bacterial cell wall, ensure the phage a rapid exit; without this outer layer of protection the bacteria essentially cannot hold themselves together, and they explode.

Fischetti discovered that the phage enzymes also work when applied to the outside of the bacterial cells: by adding a few drops of phage enzyme to a test tube of millions of bacteria, he

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Hundreds of High School Students Spend Holiday Break at Rockefeller

While their classmates descend on area shopping malls in droves, upwards of 400 high school students and their teachers from more than 40 high schools in and around New York City will spend a day of their winter holiday in Caspary Auditorium,

attending a scientific lecture by Rockefeller University professor Thomas P. Sakmar, Thursday, Dec. 27.

Few would disagree that the completion of the Human Genome Project — the deciphering of the

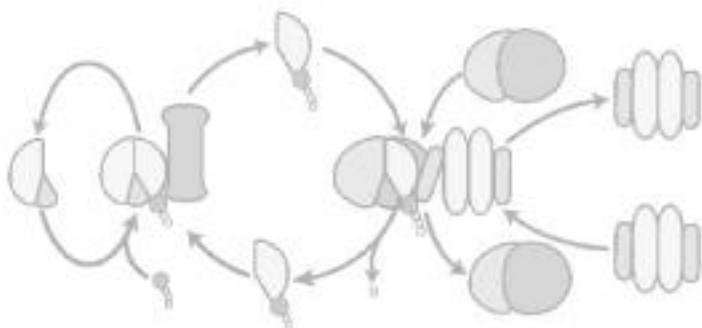
three billion bases, or chemical letters, of the human DNA code — is revolutionizing the study of biology. Technologies and methods that researchers could only dream about a few years ago have become reality, opening up entirely new realms of possibility for the diagnosis, prevention and treatment of human disease. Almost daily, the news media report that a gene or cluster of genes for a specific disease or biological function have been pinpointed. What do these discoveries truly mean to our lives and health? And how are high school science students taking it all in?

Sakmar, head of the Laboratory of Molecular Biology and

Biochemistry, will address these and other questions, and offer students a solid basis for understanding current research on genomics, when he presents "Turn On, Tune In: The Human Genome, Molecular Switches and Signaling," the 42nd Annual Alfred E. Mirsky Holiday Lectures on Science.

"It's clear that the new world ushered in by the Human Genome Project requires today's students to jump into the study of biology at a level far more complex than the Mendelian genetics many of us remember from our high school biology

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Signal transduction pathway that underlies vision

Centennial 2001

A Year in Pictures



Just back from Stockholm, Rockefeller University's 21st Nobel laureate, Paul Greengard, enjoyed a second round of celebrations as President Arnold Levine proposed a toast.

Docent for a day: At Spring Neighborhood Day in May, Lynn Kolibaba of the Office of Communications and Public Affairs, led visitors on tours of the sculptures loaned to Rockefeller by the Museum of Modern Art.



"Discomania": The campus rocked at the employees' Centennial picnic as President Levine performed his rendition of *Wild Thing*.



In Reflection: Professor Seth Darst performed at an event that offered the campus community a time to come together and reflect after the September 11 tragedy.

Associate Professor Tom Muir and his son James enjoy the Centennial picnic festivities.



At the Employee Recognition Program, Elizabeth Phillips receives thanks from Executive Vice President Alice Lustig and a gift for her 20 years of service.



At Centennial Convocation, Professor Emeritus Maclyn McCarty receives last-minute help with his academic regalia from Diane DeMann of the Office of Communications and Public Affairs.



President Levine with research colleague Michael Elowitz after the press conference announcing that Levine had received the first Albany Medical Center Prize in Medicine and Biomedical Research.



Professor Ali H. Brivanlou (right) poses with warm-blooded and cold-blooded members of his lab. Brivanlou and postdoctoral fellow Chenbei Chang (left) discovered that a protein known to be involved in the early development of embryos indirectly leads to the formation of nerve tissue in frogs. The findings, reported in the March 22 issue of *Nature*, may have applications in such neurodegenerative diseases as Alzheimer's and Parkinson's.

Professorship Honors Woman Scientist

A new professorship for a senior woman scientist to be recruited to the university has been established and will be supported by funds initiated by a \$1 million challenge grant from Patricia Cloherty, a former university trustee and a current RU Council member.

The new Rebecca C. Lancefield Professorship is named in honor of the Rockefeller scientist who was a pioneer in microbiology and major contributor to the field of infectious disease research.

Lancefield, a member of the National Academy of Sciences, was a member of the Rockefeller faculty from 1918 until 1965.

"The creation of this professorship highlights Rockefeller's commitment to increasing the women faculty in number and in influence at the university," says President Arnold J. Levine.

Participants in the university's *Women & Science* initiative are raising the \$3 million needed to establish the chair through the Partners in Discovery program. All gifts from new donors will be matched *one-for-one*. For past donors, any increase over the most recent gift will be matched *two-for-one*.

Contributions to the Lancefield Professorship will advance one of the primary objectives of *W&S*: enhancing opportunities and securing support for gifted women working at the frontiers of biomedical science.

Novel Method to Fight Drug-resistant Infections *continued*

found that he could kill nearly all of them within a few seconds.

Because phage enzymes are specific for the species or strain of bacterium from which they were produced, it may be possible to cultivate a tailor-made killer for any bacterium of interest. Last February, for example, Fischetti and colleagues reported the isolation of a phage enzyme specific for Group A streptococci, an infectious pathogen that causes strep throat and flesh-eating disease. Human clinical trials testing the ability of a throat spray containing this enzyme to prevent strep throat are in the planning stages.

Another benefit of this approach, says Fischetti, is that it should not easily lead to enzyme resistance in the targeted organisms, as antibiotics tend to do. Phage and bacteria evolved together over millions of years, and, as a result of this ongoing battle, the phage have ensured that their host bacterium will not find ways to thwart or resist their lifecycle; the enzymes they employ to get out of the bacteria target essential components of the bacterial cell wall that will be difficult to change.

To verify this theory that resistance will be a rare event, the researchers repeatedly exposed bacteria to increasing concentrations of the enzymes. Not once did resistance organisms develop, the scientists report in *Science*.

Moreover, these enzymes are unlikely to produce side effects. Antibiotics indiscriminately kill

many different bacteria in a person's system, leading to such common side effects as intestinal problems. Because the phage

are unlikely to cure full-blown infections. Antibiotics can get at the bacteria inside of our body's cells, but the phage enzymes



Professor Vincent A. Fischetti (left), with postdoctoral fellows Jutta M. Loeffler (center) and Daniel Nelson, has shown that a natural enzyme derived from tiny viruses that live inside bacteria can successfully target and kill disease bacteria, including those that are resistant to drugs.

enzymes target only the disease organism, they do not harm useful bacteria.

"We have always accepted the bad side effects of antibiotics as a consequence of killing the virulent bacteria," says Fischetti. "The unique thing about these enzymes is that they are targeted killers and therefore should result in minimal side effects."

However, it is important to note that these enzymes, which seem to excel at preventing infections,

cannot: they are too big to enter cells. On the other hand, these enzymes are better at killing infectious bacteria that lie on the surface of the cells, or mucous membranes, where antibiotics are less effective. Consequently, a combination of these two strategies might prove to be a powerful weapon against infectious bacteria and, additionally, may reduce the amount of traditional antibiotics a person is required to take.

Fischetti and colleagues say that hospitals, daycare centers and nursing homes would greatly benefit from a treatment based on their latest phage enzyme against *S. pneumoniae*. These environments tend to foster infections, and because large amounts of antibiotics are used, the number of people infected with resistant strains of *S. pneumoniae* continues to rise. A pneumococcal vaccine is available for children and adults, but this technique is not perfect.

"Even with vaccination, children can still be colonized by other pneumococcal strains," says Loeffler. "But if you use this enzyme in addition to the vaccine, doctors might be able to reduce the reservoir of pneumococci in the population."

The idea of using bacteria's number one natural enemy to treat infections has been around for decades, but past attempts involved using the whole phage. It wasn't until Fischetti thought of using solely the enzymes of these tiny viruses that promising results arose.

"People probably didn't think of this strategy, perhaps because these enzymes help the phage get out of the bacteria — they work from the inside," says Fischetti. "It seems like such a simple idea now, to use these enzymes from the outside to kill bacteria."

Clinical trials with the new phage enzyme are currently in the planning stages.

— Whitney Clavin

Holiday Break at Rockefeller *continued*

classes," says Sakmar. "Textbooks really can't be written fast enough to keep up with our rapidly evolving understanding of human biology.

"Ideally," he adds, "these lectures will enrich students' knowledge base and send them back to school feeling less swept-away by the tidal waves of new information coming at them almost continuously."

In the morning lecture, Sakmar will discuss "Genomes and Sequences." Why are humans so much more complex than flies, when we have only twice as many genes as they do? What is evolution, and what does it mean at the molecular level? As organisms evolve to become

more complex, they devote more and more DNA to encoding the protein building blocks of signal transduction networks — biochemical pathways that link detection of an external event to a cellular response. In the human genome, the largest category of genes builds up and regulates signal transduction networks.

Sakmar will build on the information from the morning lecture to discuss "Molecular Switches and Signaling" in the afternoon. In his own lab, Sakmar uses rhodopsin — the receptor for dim light in the retina — as a model system to study the dynamics of receptor activation. How does light stimulate the retina to initiate vision? How

does a hormone trigger a response? How does HIV hijack cell-surface receptors to enter a cell and cause infection?

The common theme tying these processes together is signal transduction. Molecular switches interact with receptors to turn enzyme cascades on or off. Many human diseases are caused by defects in signal transduction, and many drugs target signal transduction proteins.

Using the visual system as a model, Sakmar will explain how signal transduction in the nervous system works, and how receptors receive signals involved in many of the body's processes to turn on specific signaling cascades within cells.

Using rhodopsin, Sakmar has continued to study the dynamics of receptor activation — the conformational changes that occur rapidly when rhodopsin absorbs a photon of light or a receptor binds to a hormone. He also has made major contributions to understanding the chemical basis for color vision.

The Mirsky Lectures were established in 1959. Mirsky, a biochemist and Rockefeller University librarian, modeled the lectures on a popular series of children's science lectures pioneered in London by Michael Faraday — known as the greatest experimenter in the history of science.

— Holly Teichholtz



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