news&notes

APRIL 7, 2000 VOLUME 10, NUMBER 23 THE ROCKEFELLER UNIVERSITY

Celebration of university centennial commences

When The Rockefeller Institute for Medical Research was incorporated on June 14, 1901, it was the first institution in the United States devoted solely to finding the underlying causes of disease through scientific research. Medicine at the time had few cures for disease, and the idea of supporting science through philanthropy was completely new.

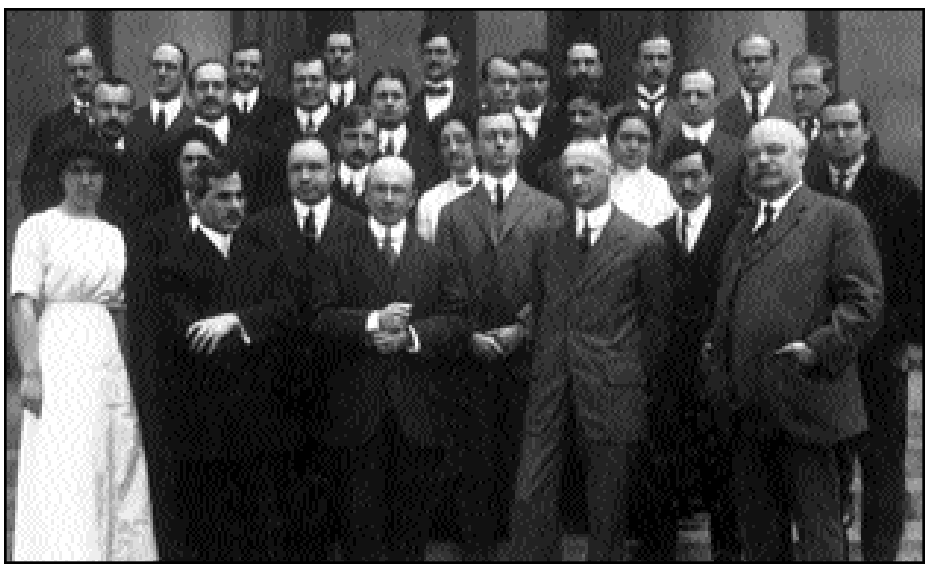
Today, nearly 100 years later, science has transformed the practice of medicine and enjoys broad public support. "When every day brings headlines of advances in science and medicine coming out of university research, it is hard to imagine the sense of daring exhibited by the founders in launching the first institution devoted exclusively to medical research in this country," says Arnold J. Levine, president of The Rockefeller University. "But their trust in science contributed to the many essential discoveries made here that have brought us to the genomic era."

In celebration of the university's centennial and the vision of its founders, scientific symposia, public events and publications have been planned, culminating with next year's convocation, which will coincide with our 100th birthday on Thurs., June 14, 2001. The goal of the centennial celebration is to capture the founding spirit of adventure and confidence in research and to demonstrate how this spirit continues to advance medicine today.

About 18 months ago, the Torsten Wiesel and Arnold Levine administrations challenged faculty, staff and students to develop a celebration that would honor the past and accentuate today's science; support the new academic plan; and reinvigorate current friends and introduce new audiences of scientists, opinion makers and members of the public to the university.

Plans evolved in discussions with trustees, faculty and alumni, and in the University Centennial Planning Committee, which has met monthly for the past year. While planning is still under way, many events already have been scheduled.

Faculty committees, organized by Professor Stephen Burley, deputy for academic affairs and an HHMI investigator, have scheduled scientific symposia that will activate discussion on topics such as medical genetics, the interface of chemistry and biology, and infectious diseases. Additional programs covering addiction research, tropical diseases, cell biology and physics are also under discussion.



The scientists and staff of the Founder's Hall laboratories. First row (from left to right): P.A.T. Levene, Alexis Carrel, Simon Flexner, Samuel J. Meltzer. Second row:Unknown, Angelia M. Courtney, Walter A. Jacobs, Peyton Rous, Hideyo Noguchi, Donald Van Slyke (1912). *Photo courtesy of the Rockefeller Archive Center.*

The Centennial Committee, which comprises faculty and staff, has scheduled public lectures designed to share the exciting world of science with a lay audience. Many coincide with the scientific symposia. The committee also has planned special centennial publications, exhibits and media and Web outreach programs, including an illustrated history of the university (see story, below) and a new version of the institution's seal, designed especially for use during the centennial celebration. In addition, fundraising opportunities have been identified.

Art and music programs also have been expanded in celebration of the centennial. To offer a wider breadth of programs, the university will collaborate with other institutions, including the Van Cliburn Foundation, WNET with Charlie Rose, the 92nd Street Y, the Fred Friendly Seminars, the American Museum of Natural History, the American Chemical Society and the National Academy of Sciences.

Among the scientific symposia scheduled for the centennial year is a program on infectious disease, on Thurs., Nov. 9, 2000. During this day-long event Rockefeller scientists will explore molecular, computational, genetic, structural and chemical approaches to pathogenesis. The talks will highlight the university's historic and current strengths in infectious disease research. The evening before the symposium, Wed., Nov. 8, Ruth Berkelman of the Centers for Disease Control will give a public lecture about emerging diseases.

To provide historic perspective to the centennial, the Rockefeller Archive Center will sponsor a two-day symposium on Mon., Nov. 13, 2000, and Tues., Nov. 14, 2000. Historians, members of the tri-institutional community and the public will be invited to explore the history of the university and its role in 20th century biomedicine. In addition, on Tues., Nov. 14, at the university, Levine will host the Rockefeller Family's annual meeting.

The centennial is much more than an excuse to celebrate—it is an opportunity to inform and excite many audiences about the university. All of these projects support the goals of the university's academic plan and therefore the associated centennial campaign, seek to introduce new audiences to the university and show how this institution is looking to the future with confidence and optimism based on its accomplished past.

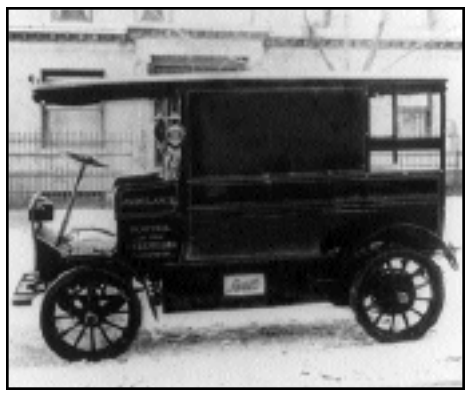
Centennial exhibit celebrates history in pictures in the Abby Lounge

The centerpiece of the centennial publications is a 140-page illustrated history of the university by historian of science and public affairs writer Elizabeth Hanson, which will be published in September 2000. A preview of some of the photographs appearing in the book can be viewed in "Breaking New Ground," an exhibit that will open Wed., April 12, in the Abby Aldrich Rockefeller Lounge.

"With the help of the Rockefeller Archive Center and other sources, Betsy has unearthed marvelous images that often tell the story of a different world," says Mariellen Gallagher, vice president for communications and public affairs. "The next year and a half will be exciting, as the academic plan unfolds amid the centennial celebration."

The exhibit features 11 photographs from the university's first decades, organized around the institution's founders, the Hospital and laboratory research. Included are photographs of John D. Rockefeller and his son, John D. Rockefeller Jr., who pioneered the idea of philanthropic support of science; Nobel laureates Peyton Rouse and Alexis Carrel; and various investigators at work in the institute's labs.

The exhibit will be open to the public every Friday from 11 a.m. to 2 p.m. The campus community is encouraged to stop by during regular business hours.

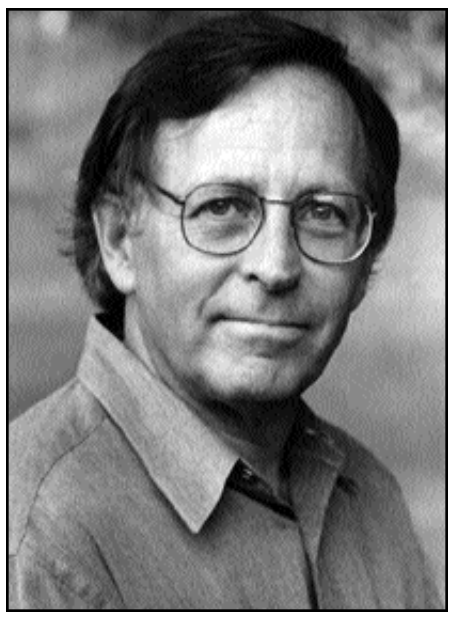


An ambulance used by the Hospital of The Rockefeller Institute (c. 1917), the nation's first center for clinical research.
Photo courtesy of the Rockefeller Archive Center.

Friday lecture: Mark Ptashne to discuss evolvability of regulatory systems

At today's Friday lecture (April 7) Mark Ptashne, professor and principal investigator at the Sloan-Kettering Institute, will present a talk entitled "On the Evolvability of Gene (and Other) Regulatory Systems."

The award of the 1997 Albert and Mary Lasker prize to Ptashne includes the following citation: "Ptashne is an acknowledged founder of molecular studies of gene regulation. For three decades he has kept his scientific eye on this single target and, in so doing, laid the conceptual framework on which many other investigators have built their research. His major accomplishment has been to figure out how 'regulatory molecules' control the function of genes."



Mark Ptashne will present today's Friday lecture.
Photo courtesy of Mark Ptashne.

In today's talk Ptashne will focus on the "evolvability" of gene regulatory mechanisms. He will argue that these systems, from bacteria to humans, are assembled from a few simple, even crude, elements. Reiterations and modifications can then be seen as stepwise additions that improve the workings of individual cases. The general description that emerges characterizes in a general way the nature of the complexities we observe. Moreover, the system, as so analyzed, readily generates useful variants and thereby gives new and expanded meanings to physiological signals. A more elegant solution to the regulatory problem can be imagined ("designed"), but that system is inherently much less

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Howdy neighbor

Harold Varmus (left), former head of the NIH and now president of Memorial Sloan-Kettering Cancer Center, received a warm welcome to the neighborhood by Rockefeller faculty at a campus reception in his honor last week in the Abby Dining Room. RU President Arnold J. Levine (center), a longtime friend, and Professor Titia de Lange (right), who worked in Varmus' lab at UCSF, hosted the reception. Varmus pledged to work closely with the university in bringing more biotechnology business to New York City and, along with New York-Presbyterian Weill Medical College, create a collaborative scientific research hub at 68th St. and York Ave. *Photo by Arnold Adler.*

Potpourri

Campus tree spraying
Trees and shrubs throughout the campus grounds will be sprayed on Sat., April 8, from 4 a.m. to 10 a.m. During this time it is recommended that you:

- close all windows;
- shut off any air conditioners;
- stay out of direct contact of the drift;
- keep pets indoors.

In the case of inclement weather, the tree spraying will be on Sun., April 9.

92nd Street Y lectur e
The 92nd Street Y will present a panel discussion on the legacy of Marilyn Monroe on Tues., April 11, in Caspary Auditorium. Panelists include authors Joyce Carol Oates and Dominick Dunne, columnist Liz Smith and film critic Molly Haskell. Tickets are $20 and can be purchased at the 92nd Street Y's box office or by calling 996-1100. A number of free tickets will be available for RU students. Call x8072 for details.

Take Your Child to Work Day
Human Resources will host the annual Take Your Child to Work Day on Thurs., April 27, from 9 a.m. to 3 p.m. Children must be between the ages of 7 and 14 and be accompanied by an adult in order to attend. To register your child, please contact Mary O'Donnell, x8300, or e-mail her at odonnem by Mon., April 17. Registration is limited, so please sign up early.

Library news
In celebration of National Library Week (April 9 to 15), the library will host an open house on Thurs., April 13, from noon to 2 p.m. The event will include vendor demonstrations of ISI's Current Content Direct and Web of Science, CAS's SciFinder Scholar and Elsevier's Science Direct. Attendees will also be eligible to win door prizes, such as a photocopy card good for 100 copies, lunch for two at the Abby Dinning Room, an RU book bag from the Children's School and books by RU's own Donald Pfaff.

The library is pleased to announce that through Wed., May 31, both the Oxford English Dictionary and American National Biography are available online to the RU community. To use these reference materials visit the appropriate Web site: http://dictionary.oed.com (dictionary) or http://www.anb.org (biography). Comments regarding either service may be e-mailed to Patricia E. Mackey, university librarian, at mackey, or to Beverly Gordon, reference librarian, at gordonb.

Online calendar training session
Need to know how to reserve a room for a campus event or post events in the Calendar of Events or on the RU online calendar? Individual training sessions will be held next Thurs., April 13, in A21 Smith Hall between 2 p.m. and 4 p.m. To schedule an appointment call Jennifer Goldschlag, x8073.

1999 FSA deadline
Sat., April 15 is the 1999 Flexible Spending Account (FSA) reimbursement request deadline for dependent care and health care expenses. Please submit all 1999 FSA eligible expenses to 21st Century for reimbursement by this date. Any unclaimed balance after this date will be forfeited. FSA Reimbursement claim forms are located in Human Resources. If you have questions, call x8300.

AfternoonTea

The Rockefeller University renews a tradition of informal scientific exchange with the introduction of afternoon tea every Monday through Thursday from 3:30 p.m. to 4:30 p.m. in the Welch Hall Reading Room. Come join your colleagues for stimulating scientific discussion. *Photo courtesy of the Rockefeller Archive Center.*

Blobel to speak in lecture series discussing impact of research on the future of medicine

The American Museum of Natural History is hosting a lecture series entitled "Revolutionizing Medicine," which will focus on current scientific research and its impact on the future of medicine and the treatment of genetic diseases. One of the featured speakers is Günter Blobel, RU professor and HHMI investigator. Blobel will discuss "The Empowered Cell" on Tues., April 18, focusing on the therapeutic potential of the latest developments in cell biology.

Blobel's talk is one in a series of six lectures in two parts. In the first part, along with Blobel's lecture, the impact of the Human Genome Project and the legal and ethical issues of genetic medicine will be discussed. The second set of lectures will examine specific medical topics, including new directions in cancer, advances in gene therapy and the promise of stem cell research. Other speakers include Harold Varmus, new president of Memorial Sloan-Kettering Cancer Center; Bartha Knoppers, bioethics and law expert at the University of Montreal; Nancy Wexler of Columbia University; Michael Waldholz of the *Wall Street Journal;*Karn Antman, director of Columbia's Herbert Irving Comprehensive Cancer Care Center and chief of the Division of Medical Oncology; Ronald Crystal, gene therapy researcher at the Weill Medical College of Cornell University; Samuel Waksal, president and CEO of ImClone Systems Inc.; Eric Hecht of Merrill Lynch and Matthew Murray of Alliance Capital.

The series begins Tues., April 11 at 7 p.m. in the Main Auditorium of the American Museum of Natural History, Central Park West and 79th St. Subsequent lectures will take place each Tuesday through May 23. The cost for all six lectures is $50 ($45 for museum members, students and senior citizens), or $12 for a single lecture ($10 for members, students and senior citizens). To register call 439-4300 or fax reservation requests to 769-5272. You can also reserve tickets at tickets@amnh.org. Reserved tickets can be paid for at the door on the night of the lecture. The series is sponsored by New York-Presbyterian Hospital, Columbia University College of Physicians & Surgeons, Weill Medical College of Cornell University and NYC & Co.

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evolvable. And, he will argue, these principles apply to many biological "information processing" systems.

Ptashne began his studies of the molecular mechanisms of gene regulation by working on bacterial systems, in particular the bacteriophage lambda. Among his lab's findings were how proteins recognize specific sites on DNA and how interactions between such proteins help determine DNA binding specificity, gene activation, integration of multiple physiological signals and the formation of sensitive "on-off" switches.

Further studies showed that the principles identified in the bacteriophage studies also applied to higher organisms such as yeast, *Drosophila*and even mammals. The realization by Ptashne's lab that activating regions can be separated from DNA-binding domains, taken with the idea that DNA-bound activating regions work by recruiting the transcriptional machinery to DNA, provided the conceptual basis for the yeast "two-hybrid" system widely used for detecting protein-protein interactions.

Ptashne received a bachelor of arts degree in chemistry from Reed College in Oregon and, in 1968, a Ph.D. in molecular biology from Harvard University. Four years later he became a professor of biochemistry and molecular biology at Harvard. While at Harvard, Ptashne served as chairman for the biochemistry and molecular biology department from 1980 to 1983, was scientific co-founder of the Genetics Institute with Tom Maniatis and, in 1993, was appointed Herchel Smith Professor of Molecular Biology. In 1997, Ptashne became the Ludwig Chair of Molecular Biology at Sloan-Kettering Institute.

Many visitors to RU worked either as students or postdoctoral fellows in Ptashne's lab. A sampling includes: Barbara Meyer from Berkeley, who was a recent Harvey Society lecturer; Tom Maniatis from Harvard University, who is speaking at Sloan-Kettering Institute today at noon; Lenny Guarante from the Massachusetts Institute of Technology (MIT), who will soon give a seminar at RU and Robert Sauer, also from MIT, who is scheduled to speak at RU later this year.

Among the many honors and awards Ptashne has received, in addition to the 1997 Lasker Prize, is the General Motors Cancer Research Foundation's Sloan Prize in 1990. He is a member of the National Academy of Sciences and is the author of *A Genetic Switch*a widely read book that describes the ideas he developed in his studies of gene regulation.

In addition to his scientific accomplishments, Ptashne is also an accomplished violinist. Last year he was a featured performer at the Tri-institutional Noon Recital, where he played a duo violin recital with Romanian violinist Irina Muresanu. Ptashne will return this year to Caspary Auditorium for a second engagement on Fri., April 28, where he will accompany the prominent Russian violinist Mela Tenenbaum.

The lecture will take place today at 3:45 p.m. in Caspary Auditorium and is preceded by a tea at 3:15 p.m. in Abby Aldrich Lounge. All are welcome.

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Rockefeller researchers identify novel penicillin resistance gene in pneumonia bacteria

Findings promise new target for development of drugs to combat antibiotic resistance

by Joseph Bonner

Penicillin resistance of the bacterium that causes pneumonia, the pneumococcus, is a growing global health problem. Although *S. pneumoniae* was once considered to be routinely susceptible to penicillin, since the mid-1980s the incidence of resistance of this organism to penicillin and other antimicrobial agents has been increasing in the United States and throughout the world.

S. pneumoniae (along with *M. tuberculosis,* the bacterium that causes tuberculosis) represents the most important microbial pathogen, causing a number of frequent community-acquired infections, some life threatening. In the United States alone, *S. pneumoniae* is estimated to cause at least 6,000 cases of meningitis, 50,000 cases of blood infections, a half million cases of pneumonia and several million cases of childhood ear infections annually. The global annual rate of mortality from pneumococcal disease is estimated at one million. A powerful threat to the elderly, young children and people with underlying medical conditions, including HIV infection, drug-resistant strains of pneumococcus are spreading from day-care centers to hospital rooms, raising the concern of public health officials and physicians about the possible failure of antibiotic therapy against the resistant bacteria.

S. pneumoniae is a familiar microbe to Rockefeller scientists. It was in studies with this bacterium that DNA was discovered as the genetic material by Oswald Avery, Colin MacLeod and Maclyn McCarty in the early 1940s. It was also in the early 1940s that the antibiotic era began with the introduction of penicillin into therapeutic practice, and between that time and now, strains of bacterial pathogens resistant to penicillin and other antimicrobial agents have emerged and spread globally. For the last 20 years, researchers from the Laboratory of Microbiology, led by Professor Alexander Tomasz, have been studying the biochemical and genetic basis of penicillin resistance in the pneumococcus. This week, Sergio Filipe, a young researcher in the Tomasz lab from Portugal, and Tomasz presented new work that may have major impact on future treatment of this deadly bug. In the April 25 issue of the *Proceedings of the National Academy of Sciences,* they show that resistance can be stopped by inactivating a pair of genes responsible for producing molecules, called branched muropeptides, the availability of which appears to be essential for the bacterium to survive in the presence of penicillin. The finding suggests that the branched peptides may be a new drug target for fighting penicillin-resistant bacteria.

The finding opens the door to the development of new drugs that would block the production of branched peptides, restoring penicillin's potency.

"We have known for some time about the connection between the branched muropeptides—structural elements of the pneumococcal cell wall—and penicillin resistance in pneumococcus," says Tomasz. "Sergio has now identified two genes that are responsible for making these branched muropeptides, and we have shown for the first time that by inactivating these genes we can restore penicillin's potency. This opens the door to the development of new drugs that would act synergistically with penicillin by blocking the production of the branched peptides."

A new bacterial ploy

The mechanism of penicillin resistance in clinical isolates of pneumococci was first identified in the Tomasz lab in 1980. He and former graduate student Sonia Zighelboim studied South African strains of pneumococci that were a thousand times more resistant to penicillin than any other previous strains and discovered a new bacterial ploy. Instead of producing an enzyme that destroyed penicillin—a tactic seen in resistant strains of another bacterial pathogen, *Staphylococcus aureus*—the South African pneumococci rebuilt the target proteins of the antibiotic, enzymes called penicillin-binding proteins (PBPs).

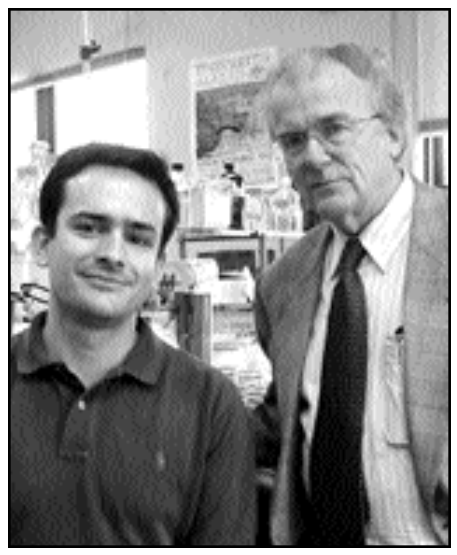
Working in assembly-line fashion, PBPs play an important role in building the cell wall, an uninterrupted protective network of molecules that maintains the integrity of the cell. Composed of sugar molecules crosslinked to one another through short chains of amino acids called peptides, the cell wall maintains the integrity of the cell, regulates the orderly traffic of thousands of nutrient molecules in and out of the cell every second and serves as the cell's communications center, receiving and transmitting signals from and to the outside world.

Penicillin produces its devastating effect on bacteria by inactivating PBPs and thus inhibiting synthesis of the cell wall. A thorough study by the researchers revealed the PBPs in the penicillin-resistant pneumococci had undergone subtle alterations in their DNA blueprints. As a result, the PBPs had a reduced ability to bind penicillin, thus providing penicillin resistance to the bacteria.

By 1990, Tomasz and former Rockefeller postdoctoral fellow Jose Garcia-Bustos discovered that the resistant pneumococci not only had altered low-affinity PBPs, but the altered PBPs appeared to build a chemically unusual cell wall enriched with branched muropeptides. In penicillin-susceptible pneumococcal strains, most of the muropeptides are linear in shape. But in penicillin-resistant strains, "branched" muropeptides—so-called because of the presence of two additional amino acids, either a serine and an alanine or two alanines, that branch off from the main peptide—are abundant in the cell wall.

In the new work, Filipe and Tomasz identified two genes, called *murM* and *murN,* that work in concert and are involved in the synthesis of branched cell wall muropeptides. The two genes work in tandem in a genetic system called an operon. The researchers showed that inactivation of the *murMN* operon in penicillin-resistant strains causes the disappearance of the branched muropeptides from the cell wall and also a complete loss of penicillin resistance.

"These studies show that penicillin resistance in the pnemococcus requires not only the alterations in the PBPs but intact *murMN* genes as well," says Filipe.



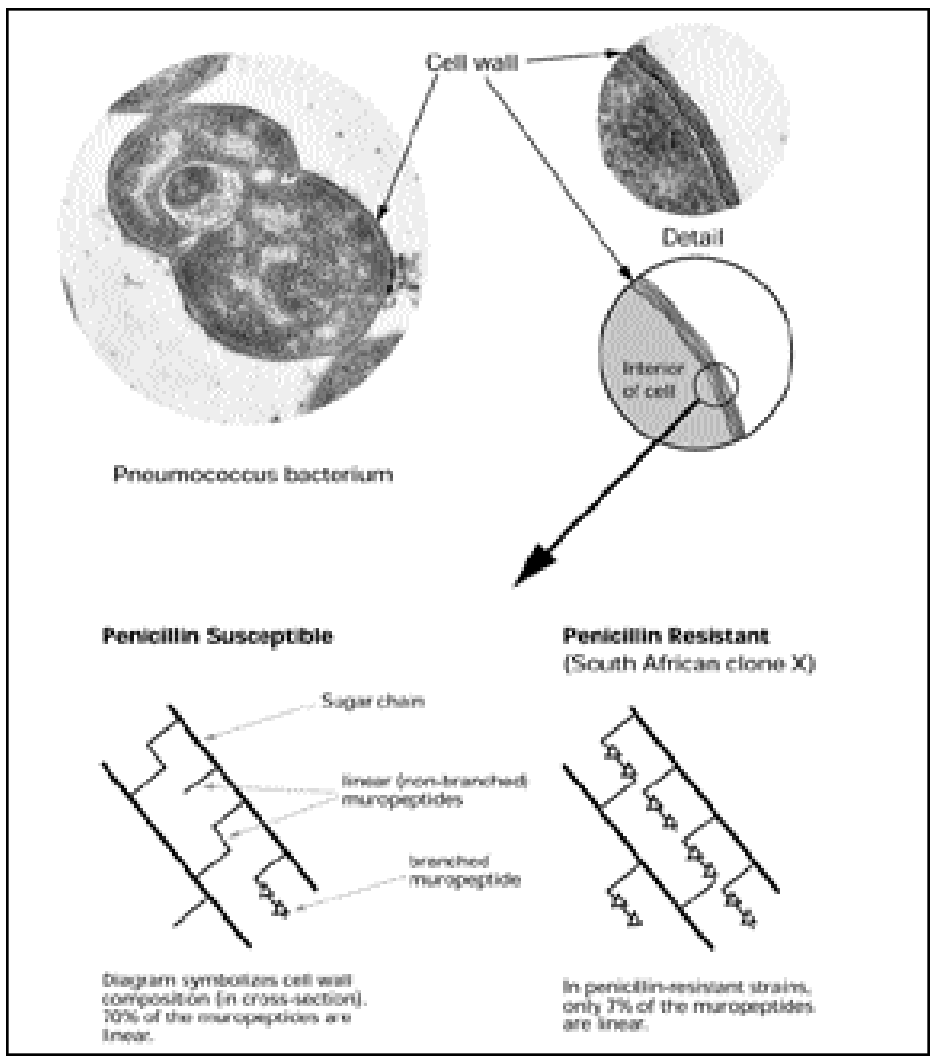
Sergio Filipe, guest investigator, and Alexander Tomasz, RU professor, have recently found that penicillin resistance in the bacteria that causes pneumonia can be stopped by inactivating branched muropeptides. *Photo by Linne Ha.*

A new weapon

How exactly the *murMN* genes contribute to the expression of penicillin is not clear yet. Branched muropeptides may compete with penicillin for a site on the resistant PBPs, or they may perform some yet-to-be-identified signaling function in cell wall synthesis or occupy strategic sites within the cell wall that are important for the continued growth of bacteria in the presence of penicillin.

Tomasz and Filipe think that the synthesis of branched muropeptides is a good target for the design of new antibacterial drugs that would work synergistically with penicillin to treat resistant pneumococcal disease. Inhibitors of the synthesis of branched muropeptides may also reduce virulence of pneumococcal infections. The principle of using a combination of two drugs is already in use in such successful and widely marketed antimicrobial drugs as Augmentin, a combination of the antibiotic amoxicillin and clavulanate, which inhibits β-lactamase, an enzyme that inactivates penicillin.

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, and by the Irene Diamond Foundation.



A slender band measuring about a thousandth of a millimeter and visible only through the electron microscope, the pneumococcal cell wall is an enormous molecular envelope, conforming to the size and shape of the cell and surrounding the entire cell with an uninterrupted protective network of molecules. Enzymes called penicillin-binding proteins (PBPs) play an important role in building the cell wall. Penicillin produces its devastating effect on bacteria by inactivating PBPs and thus inhibiting synthesis of the cell wall.

Research by the Tomasz lab showed that the cell wall of penicillin-resistant pneumococcus contains genetically altered PBPs and molecules called branched muropeptides. In the April 25 issue of the *Proceedings of the National Academy of Sciences,* Filipe and Tomasz show that resistance can be stopped by inactivating a pair of genes responsible for producing branched muropeptides, the availability of which appears to be essential for the bacterium to survive in the presence of penicillin. The finding suggests the branched peptides may be a new drug target for fighting penicillin-resistant bacteria.
Diagram by Ravi Rajakumar.