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- State-of-the-Art Technologies
- Cracking Cancer's Secret Code

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Viewpoint

A New Phase of Development

The opening of the John D. Rockefeller, Jr. and David Rockefeller Research Building marks a new phase in the development of this university and campus. The 100,000 square feet of new laboratory space inside this $90 million dollar, state-of-the-art building will enable us to recruit new junior and senior faculty, and free up facilities for scientists working on other parts of the campus who for years have needed additional research space.

To celebrate the opening of this marvelous new facility, we invited representatives from many worlds—government, business, science, and culture. For this day of dedication and the three festive days that followed it, we tried to take as much of the ivory out of our tower as possible. We organized exhibits, tours, and lectures for friends of The Rockefeller University, for the surrounding community, and for individuals in all parts of this university, to demonstrate our desire to be linked more closely with the diverse worlds of this great city.

For all the astounding intellectual and technical advances of recent years, the scientists of this campus's past would find much that is familiar in the laboratories this building will house—labs devoted to cell biology and immunology, to molecular and structural biology—all fields that the university helped pioneer. And I am certain that they also would find familiar the continuing commitment of the Rockefeller family to this university. But they might be surprised by another name that helped make this building possible—that of Howard Hughes. The Howard Hughes Medical Institute has quite literally provided the foundation for our new facility, and will continue to support the Howard Hughes senior and junior investigators working on four of its floors.

The similarity between the Howard Hughes Medical Institute and The Rockefeller University transcends the parallel use of private fortunes for the public good. Both share a philosophy that strikes at the heart of the whole scientific enterprise: Find the most talented researchers possible, and then give them the facilities and the freedom to pursue their studies wherever they might lead. For like novelists being surprised when one of their characters takes on a life of its own—performing actions that were not planned, not part of the plot—we scientists are constantly being overtaken by surprises as we work in our laboratories. We try to make a cell do one thing, and instead it keeps doing another, until we are forced to ask: Why is it doing that? And then, this new question asked, we are off performing a series of experiments we could hardly have anticipated a week ago.

The current debate in Washington on how best to balance support for basic and applied research is in some ways misleading: the two interpenetrate. The history of science at Rockefeller and other research institutions powerfully attests that it is the asking of basic questions about the operations of nature, pursued by investigators working alone or in small groups, that largely provides the foundations for novel clinical and industrial applications. Science is a creative activity rooted in the independence of the individual researcher, and respect for this intellectual freedom must continue to be at the core of government support for science.

Yet in times of scarce resources, we in the scientific community recognize that more must be done to enable the fruits of our discoveries to blossom into economically and medically useful technologies and treatments. Whether our towers are made of ivory, or of glass, steel, and stone, they must have doors that lead out as well as in. Let us hope they lead out to more open-air symposia like the one that occurred at the opening of our new research facility, when the worlds of government, business, science and culture came together and freely discussed how our common interests may best be served.

Torsten Wiesel
President, The Rockefeller University

The Shape of Nature

X-ray crystallography and nuclear magnetic resonance spectroscopy reveal the 3-D structure of molecules

by Susan Blum

In the course of its lifetime, a cell receives countless messages to grow, divide, and differentiate. Properly communicated, these messages promote the normal development and healthy functioning of the organism to which the cell belongs. But if the communication goes awry, disaster can ensue.

Among biology's most compelling (and competitive) efforts is the search to unravel the intricacies of the cellular signaling network. Recently, two Rockefeller research groups advanced this endeavor significantly by providing important new information about a crucial element in the signaling matrix.

Among biology's most compelling (and competitive) efforts is the search to unravel the intricacies of the cellular signaling network. Recently, two Rockefeller research groups advanced this endeavor significantly by providing important new information about a crucial element in the signaling matrix. Each group started work independently, using their own specialized research techniques. But their efforts were facilitated by Rockefeller's historic areas of scientific inquiry, and by the unique opportunities for communication that the university's structure provides.

In a hotly contested field, the Rockefeller researchers provided the first views of the three-dimensional structure of protein regions called SH2 domains. A protein "domain" is a protein segment that performs a particular function. An individual protein may contain many different domains with different functions. The role of SH2 domains, found in a large number of proteins, is to serve as "readers" for messages sent through the cell in response to signals that reach its surface.

Susan Blum is a science writer in The Rockefeller University Public Affairs Office.

"To send a signal, you need something that acts as a switch, like a green or red light," explains John Kuriyan, who led one of the multi-lab groups involved in the research. There are several kinds of molecular switches, one of the most important of which is a phenomenon known as tyrosine phosphorylation. This is a process that puts a highly charged substance called phosphate on tyrosine, one of the twenty amino acids used as the building blocks for all proteins. The specific pattern of tyrosine phosphorylation varies for each different protein that can serve as a molecular switch.

TRIPPING THE MOLECULAR SWITCH

SH2 domains bind to phosphorylated tyrosines, thereby registering that the molecular switch has been tripped. The protein in which the SH2 domain is embedded then helps pass the cellular signal along. "SH2 domains are vitally important in regulating cell differentiation, growth, and division," says David Cowburn, the leader of the other multi-lab team. "The aberrant cell differentiation that leads to birth defects and the uncontrolled cell growth that is a hallmark of cancer frequently result from the breakdown of switching mechanisms directly involved with these domains." Indeed, many oncogenes, or cancer genes, are genes whose normal function is to code for proteins containing SH2 domains. When these genes are mutated, the messages they transmit are scrambled in ways that can contribute to cancer.

Before the work of the two Rockefeller groups was published simultaneously last summer, scientists had already determined the order in which the amino acids of SH2 domains are linked together like beads on a chain. But this knowledge, though useful, gave no hint about how the domains actually accomplish their cellular tasks. To know how any protein functions, researchers must also know its 3-D structure—the characteristic conformation of twists, pockets, and projections that endows it with exactly the right combination of chemical, mechanical, and electrostatic forces to get the job done. Thus, by providing the first 3-D views of two different SH2 domains, the Rockefeller researchers inaugurated a new phase in the understanding of the cellular signaling network. (A third group, from Oxford and London Universities, reported the structure of another SH2 domain at the same time.)

The team headed by Cowburn revealed the structure of the SH2 domain of a protein called abl (pronounced "able.") The gene that codes for this protein—a gene that is involved in leukemia—is under intensive study in the laboratory of Rockefeller Professor David Baltimore. Researchers in the Baltimore lab collaborated with the Cowburn group by supplying ample quantities of the abl protein's SH2 domain.

The domain was the right size for investigation by the nuclear magnetic resonance (NMR) spectroscopy techniques employed by members of the Cowburn lab. This method, which studies molecules as they float in solution, exploits the magnetic properties of atomic nuclei, revealing the distances between atoms and the "cross talk" they engage in (see "How does

nuclear magnetic resonance spectroscopy work?", page 14).

The group led by Kuriyan derived the structure of the SH2 domain of a protein called src (pronounced "sark"). The gene that codes for this protein has a long tradition of study at Rockefeller dating back to 1911, when Peyton Rous isolated a virus that transmitted cancer among chickens. The virus' cancer-causing gene was later identified and named *src*. As one of the first cancer genes ever investigated, *src* is in many ways a reference point for researchers; in fact, the "SH" in the name SH2 stands for "src homology region."

Today, the *src* gene is under intensive study in the laboratory of Rockefeller professor Hidesaburo Hanafusa, as well as in the laboratory of Marilyn Resh, a cancer researcher at Sloan-Kettering Institute for Cancer Research (see "Cracking Cancer's Secret Code," page 16). Together, these two scientists provided the guidance and insights that enabled researchers in the Kuriyan lab to use the techniques of molecular biology to produce the large quantities of the src SH2 domain they needed for their studies.

The Kuriyan lab used the techniques of x-ray crystallography to derive their 3-D structure. This method bombards crystallized proteins with x-ray beams. The beams bounce off electrons whirling around individual atoms within the crystal, and then scatter ("diffract") in all directions. The pattern of this diffraction can be interpreted to reveal the 3-D structure (see "What is x-ray crystallography?", page 12).

The Kuriyan and Cowburn labs embarked on their projects independently, but they soon learned about one another's research. "Rockefeller has a very high concentration of labs working on biological problems without departmental barriers. You tend to talk to a lot of people," Kuriyan says.

Scientists in the Cowburn lab had synthesized small tyrosine-phosphorylated protein segments (called peptides) as part of a series of studies; but, for technical reasons, NMR could not visualize these peptides bound to the abl SH2 domain. The Cowburn lab provided the peptides to the Kuriyan lab. When they were mixed with the src SH2 domains, crystals resulted that were close to ideal for the x-ray crystallographic studies. The Cowburn group also provided the Kuriyan lab with some data on the abl SH2 domain derived from their NMR studies.

REVEALING THE FORCES THAT BIND

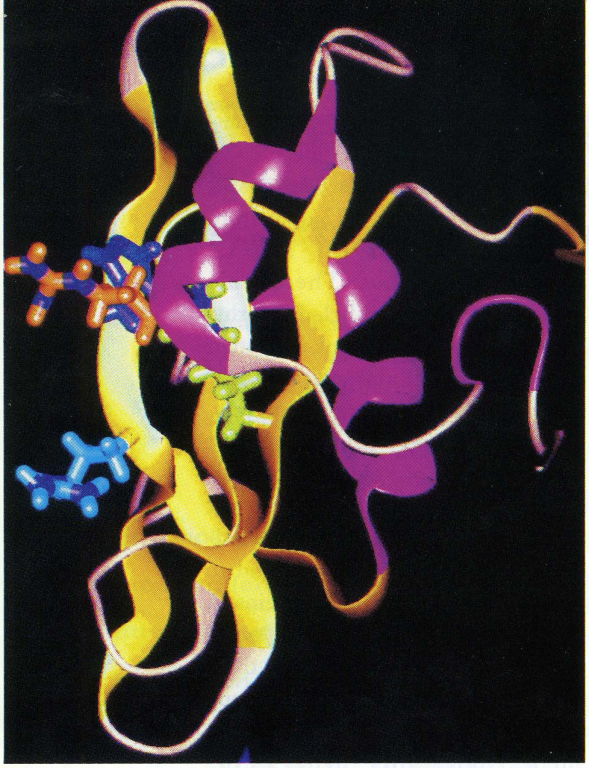
The structures revealed by the research groups show that the SH2 domains have a novel socket-like area that binds the region of the switch protein containing phosphorylated tyrosine. By revealing this area of the SH2 domain on an atom-by-atom basis, the structures give powerful insights into the various forces that contribute to the binding. The structures also show that, as a whole, the SH2 domain has a modular aspect, thus explaining how SH2 domains can be a part of so many different kinds of proteins (see illustrations, page 6).

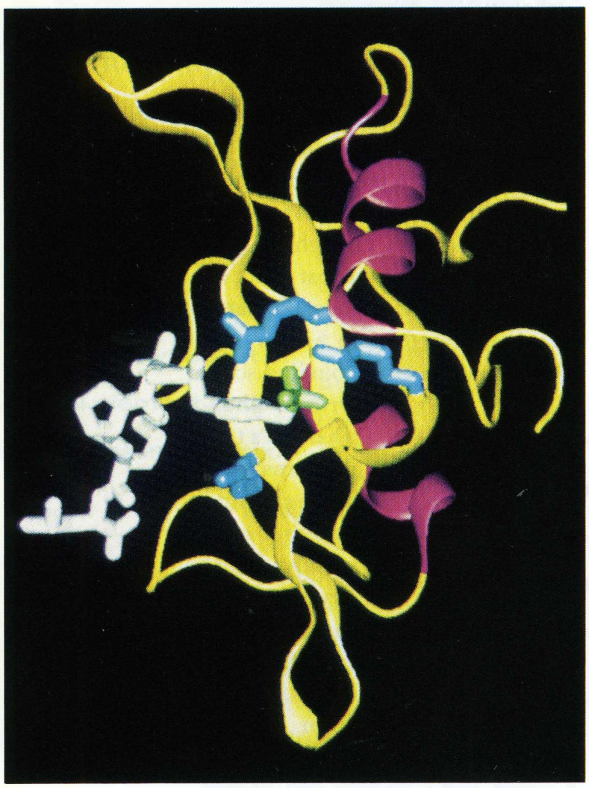
In a hotly contested field, the Rockefeller researchers provided the first views of the three-dimensional structure of protein regions called SH2 domains.

Though the work of both research groups resulted in views of the 3-D structures of SH2 domains, their investigations differed in one important way. The NMR studies presented a view of the domain in its unbound state, while the x-ray crystallography studies visualized it bound to a tyrosine-phosphorylated peptide. (Not only was this a first for studies of SH2 domains, but it also provided the first-ever view of any bound tyrosine-phosphorylated peptide.)

"Comparing these two structures allows us to see the SH2 domain in both its 'on' and 'off' states," Kuriyan points out. The double view presents unparalleled insights into how this crucial linker protein may bind to cellular switches and pass the signal along. Ultimately, such insights may lead to a better understanding of how cancer develops, and to therapies that might halt its progress. With a detailed knowledge of how SH2 domains bind to tyrosine-phosphorylated proteins, it might be possible to build small molecular inhibitors that block these interactions. Such "rational drug design" is still years away, but is a distinct possibility thanks to the kind of structural information provided by NMR and x-ray crystallographic techniques.

The structures of the src and abl SH2 domain are so similar that the Rockefeller researchers believe all SH2 domains will prove to resemble each other overall. But now a new question beckons. Though all SH2 domains probably bind just about all proteins containing phosphorylated tyrosine, each domain has its own characteristic pattern, binding some tyrosine-phosphorylated proteins very strongly, and others only weakly. What structural features make each SH2 domain different from all the others? Once researchers such as Kuriyan and Cowburn can answer these questions, they will be closer still to a fundamental understanding of how cellular messages are communicated, and of how they might be intercepted when they threaten to go awry.





◀ TWO DIFFERENT SH2 DOMAINS HAVE REMARKABLY SIMILAR STRUCTURES

Research at Rockefeller using nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography revealed remarkably similar three-dimensional structures for the SH2 domains of two different proteins. They show that the domains of both proteins have a novel socket-like area that can bind small protein regions (peptides) containing phosphorylated tyrosines—substances that serve as an important "switch" to pass along cellular messages. The NMR studies provided a view of an SH2 domain in its unbound state (*top*), while the x-ray crystallography studies visualized a domain bound to a tyrosine-phosphorylated peptide, shown in white (*bottom*). Comparing these two structures allows the researchers to see SH2 domains in both their "on" and "off" state—an important advance in understanding the details of cellular communication. The structures also show that, as a whole, an SH2 domain has a modular aspect. The two ends of the domain are close to one another and form simple strands that can easily insert into any number of proteins, while the bulk of the protein takes the characteristic twists, turns, and loops that are essential to its function. This modularity explains how SH2 domains can be a part of many different kinds of proteins essential for cellular communication.

DAVID COWBURN

Since the start of his research career, Rockefeller faculty member David Cowburn has been fascinated by the relationship between the structure and function of biological molecules. Cowburn and his colleagues were among the first to realize the potential of nuclear magnetic resonance (NMR) spectroscopy to reveal a molecule's three-dimensional structure. He has been utilizing this method for over a decade, all the while making important contributions to its improved sensitivity and versatility.

David Cowburn joined The Rockefeller University in 1973. He received his Ph.D. from King's College at The University of London in 1970. After a postdoctoral fellowship at the European Molecular Biology Organization, he conducted interdisciplinary research in neurobiology and psychiatry at Columbia University's College of Physicians and Surgeons before coming to Rockefeller.

In addition to his work on the SH2 domain of the abl protein, Cowburn and his colleagues are cooperating with researchers at Rockefeller and elsewhere to explore the structure of other SH2 domains and the tyrosine-phosphorylated proteins to which they bind. Another of his projects is an investigation of the 3-D structure of adenylate kinase, an enzyme that catalyzes an essential step in the conversion of food to energy. Still other projects using NMR seek to discover the structure of growth factors and hormones, substances that set the cellular communication process in motion by binding to receptors located at the cell surface.

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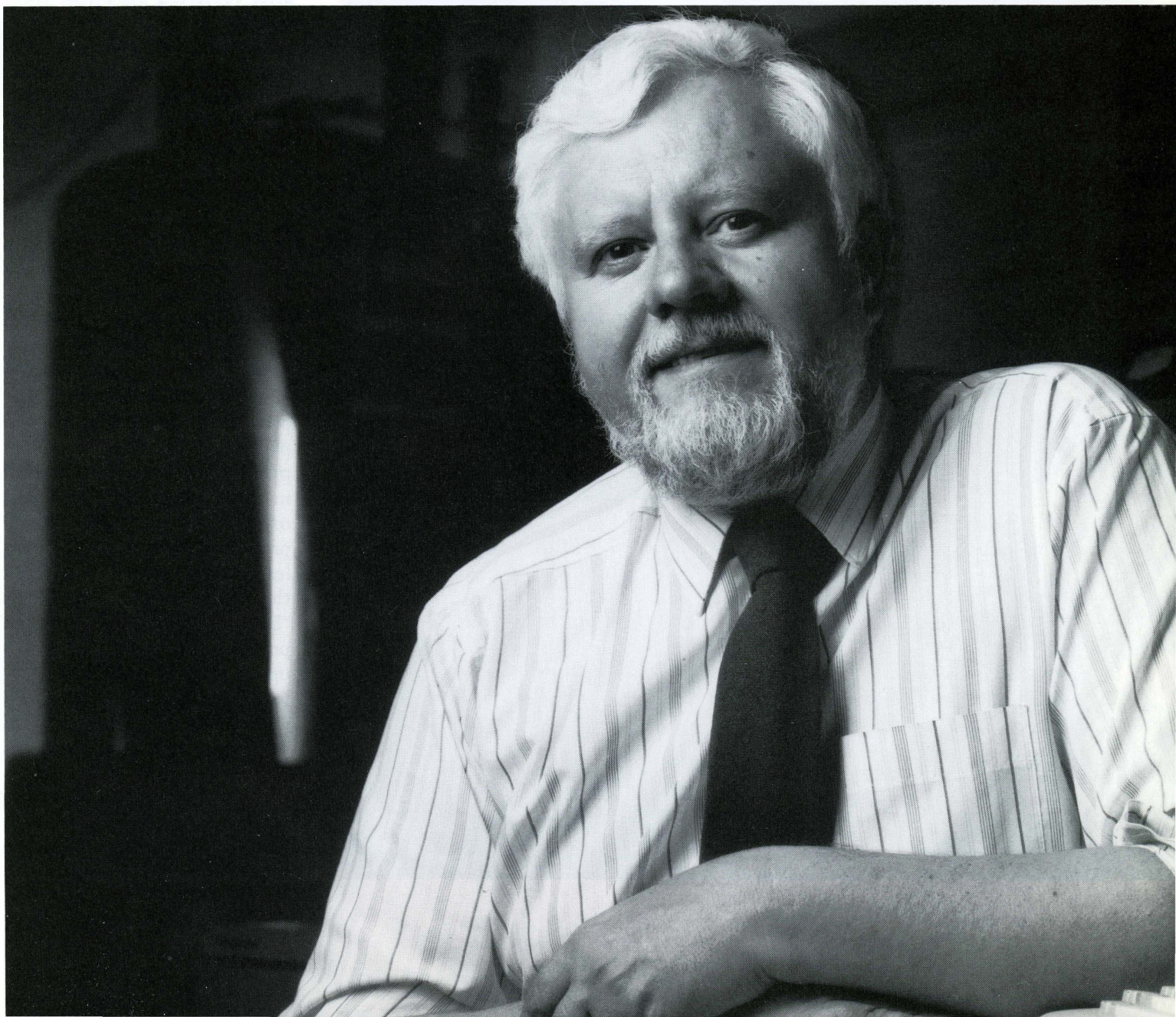

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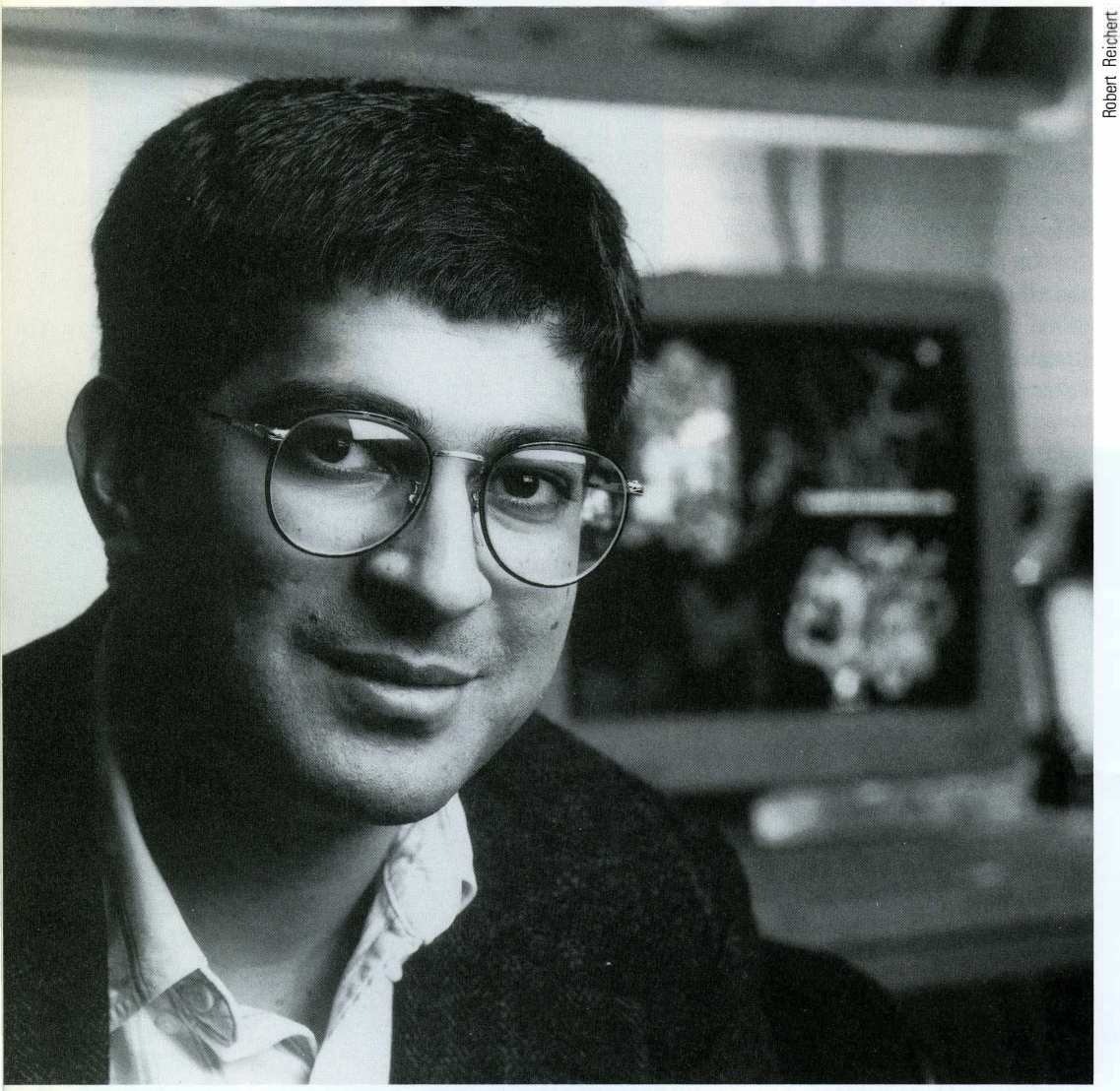


Robert Reichert

◀ JOHN KURIYAN

The x-ray crystallographic studies of Rockefeller faculty member John Kuriyan draw on a combination of experimental and theoretical approaches to derive a molecule's 3-D structure. They aim to understand, at the level of atomic detail, how proteins function as part of the cellular machinery.

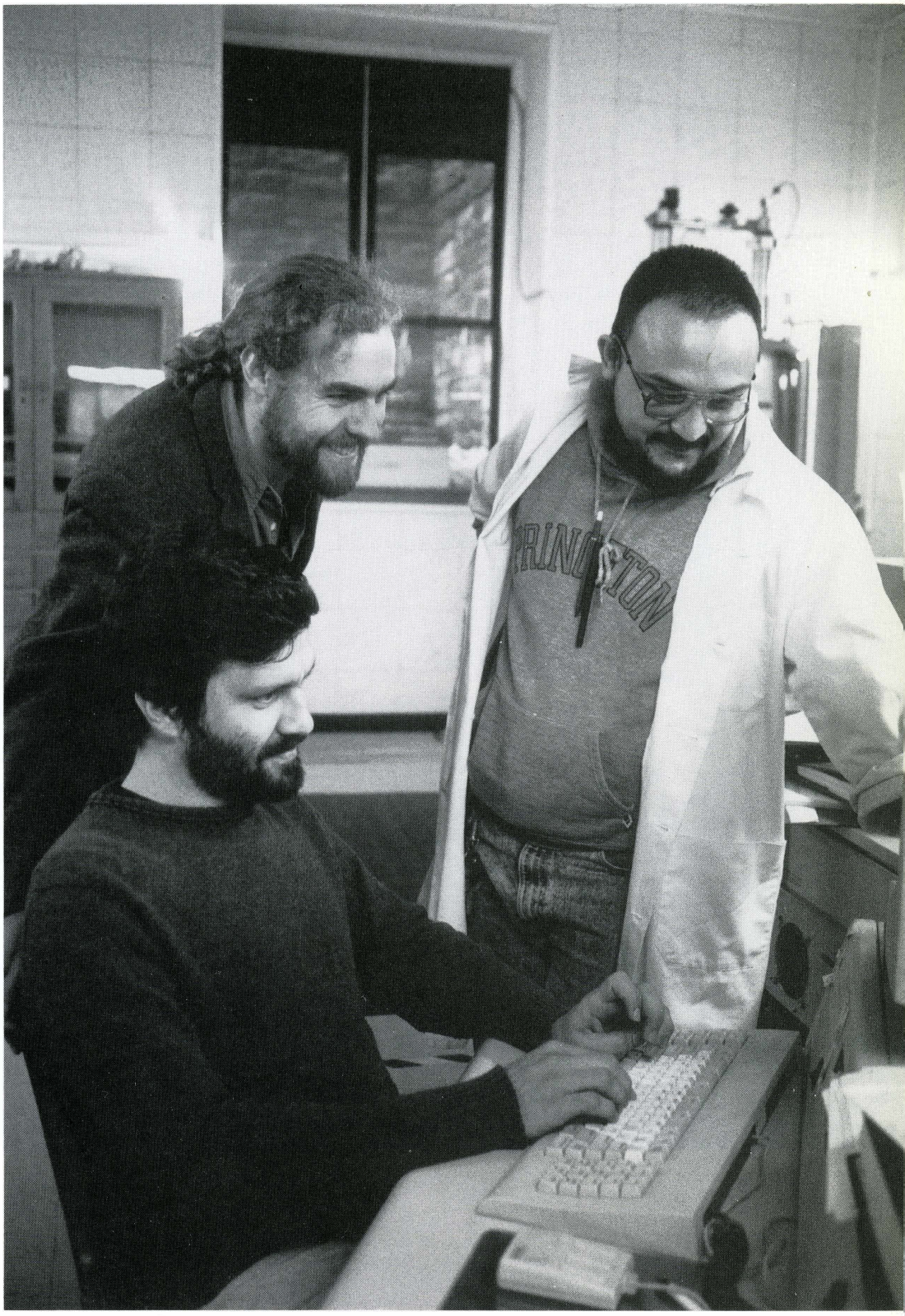
John Kuriyan joined The Rockefeller University in 1987, after receiving his Ph.D. from the Massachusetts Institute of Technology in 1986 and completing a postdoctoral fellowship at Harvard University. He was named Assistant Investigator of the Howard Hughes Medical Institute in 1990.

In addition to the src SH2 domain and the protein region to which it binds, a number of other cellular "machines" are currently under investigation in his laboratory. One such protein is a bacterial enzyme that is required for the proper folding of many proteins. Yet another protein under study is DNA polymerase III (Pol III), a complex bacterial enzyme involved in chromosome replication, one of life's most fundamental processes. Kuriyan and his colleagues have already discovered the 3-D structure of Pol III's "beta-subunit"—one of the ten protein components that makes up the bacterial enzyme. A long-term goal of the laboratory members is to depict the structures and explain the functions of Pol III's nine other components. They are also pursuing the structures of proteins that perform similar functions in the cells of plants and animals.

THE PROCESS OF DISCOVERY: RUNNING EXPERIMENTS AND INTERPRETING RESULTS

Many scientists contributed to the discovery of the 3-D structure of the abl SH2 domain. (*Clockwise from right*) Postdoc Nalin Pant, postdoc Carlos Rios, and graduate student Michael Overduin are members of the Cowburn lab. Overduin and Rios were key players in running the NMR experiments and interpreting their results. Overduin determined the domain's final 3-D structure. Pant synthesized short protein fragments (peptides) for ongoing studies in the Cowburn lab, and also provided them to researchers in the Kuriyan lab for use in their studies of the src SH2 domain. Rockefeller postdoc Bruce Mayer (not shown) provided the Cowburn team with ample quantities of the abl SH2 domain for their NMR studies. Mayer is a member of the laboratory of Rockefeller faculty member David Baltimore, where the cancer-causing gene that codes for the abl protein is under intensive study. ▶

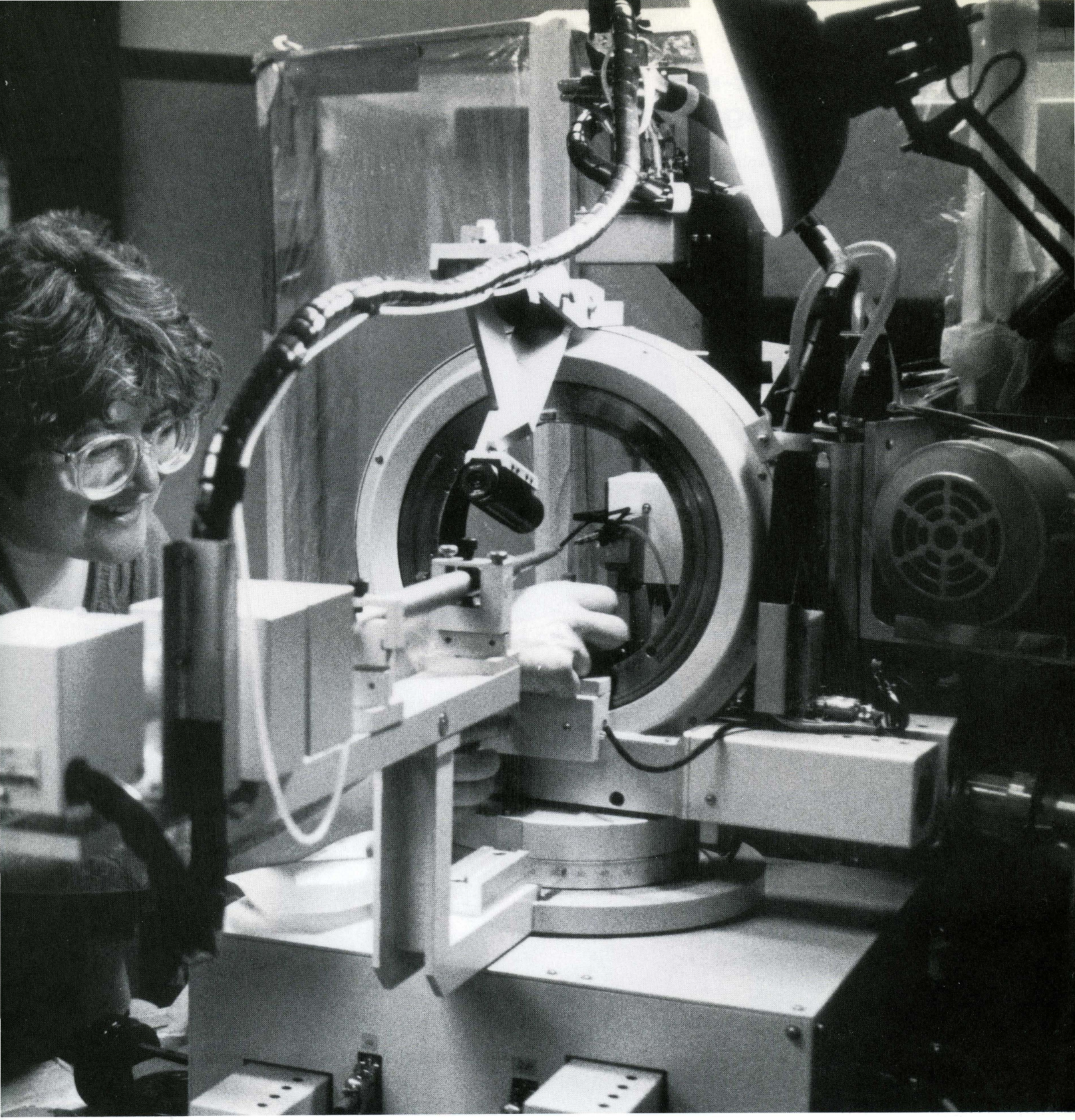
Robert Reichert



FINDING THE STRUCTURE: MANY STEPS, MANY SCIENTISTS INVOLVED

Numerous steps, and numerous scientists, were involved in finding the 3-D structure of the src SH2 domain bound to tyrosine-phosphorylated peptide. Rockefeller scientist Hidesaburo Hanafusa, a pioneer in studies of the *src* gene, was among those who provided guidance and insight to postdoc Dorothea Kominos (*right*) and research associate Gabriel Waksman (*left*) in the Kuriyan lab. These researchers, along with research asssitant Scott Robertson (not shown), used the techniques of molecular biology to genetically engineer as much of the src SH2 domain as they needed to grow crystals of the protein. Waksman conducted the x-ray crystallographic studies, interpreted their results, and derived the final 3-D structure. ▶

Robert Reichert



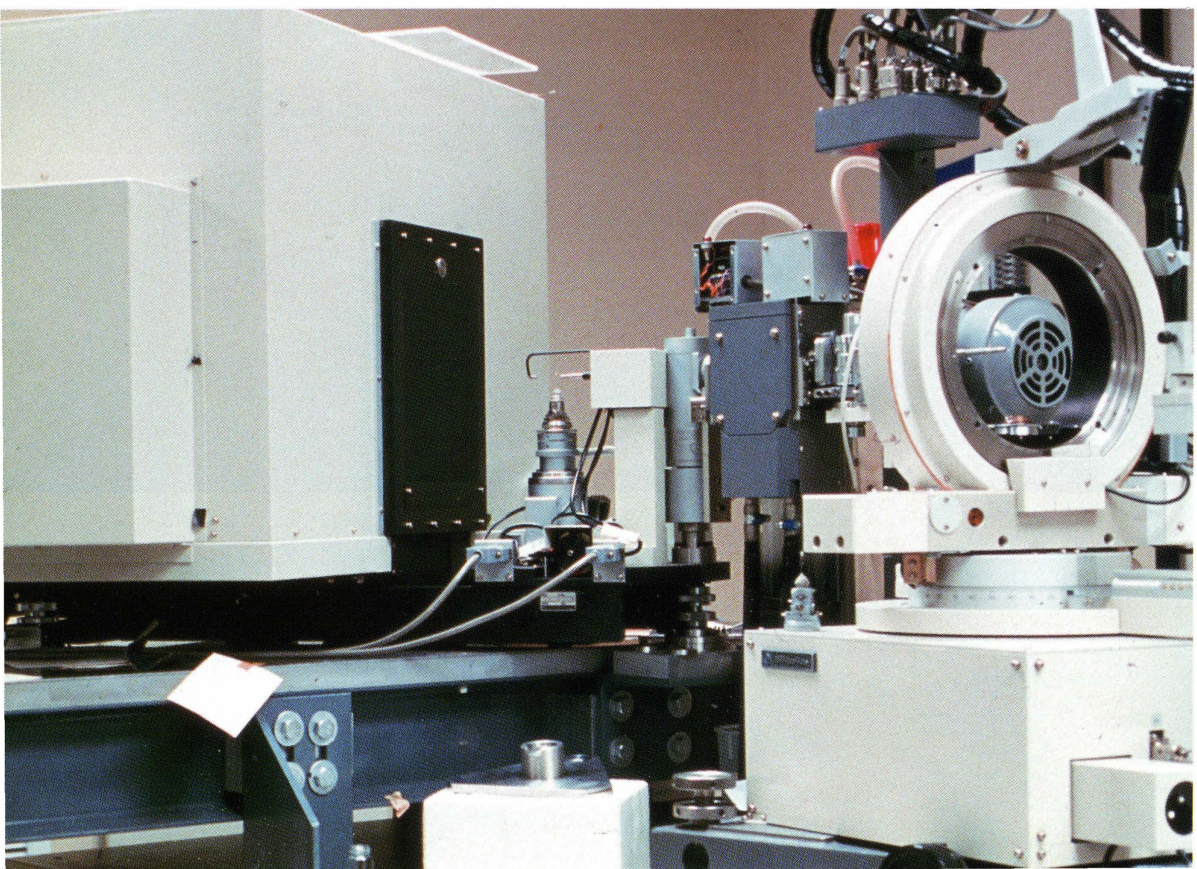
What is x-ray crystallography?

X-ray crystallography reveals the three-dimensional position of every atom in a molecule. The technique has been used for simple molecules since 1912, but the first protein structure was not achieved until 1959 after decades of effort. Recently, the pace of discovery has accelerated remarkably thanks to powerful new computing and recording equipment that speeds up the process of data collection and analysis, and to genetic engineering techniques that vastly increase the number of proteins available for study.

In principle, x-ray crystallography is similar to natural vision or light microscopy: Electromagnetic waves diffract off an object—in this case, the electrons whirling around atoms—and are then refocused into an image. But crystallography uses x-rays rather than visible light, because only x-rays have wavelengths small enough to resolve the interatomic distances within molecules. Moreover, since x-rays cannot be focused by any physical lens, crystallographers use mathematics to "focus" the diffracted rays back into an image.

▲ The electrons in a single protein molecule would never diffract x-rays well enough to produce an image, but a crystal of protein provides tens of trillions of molecules arrayed in a lattice that diffracts x-rays strongly. For reasons that remain mysterious, growing crystals is a chancy business. Researchers can coax some proteins to crystallize in less than a day, but must labor over others for months or years. Occasionally, despite their best efforts, a satisfactory crystal can never be grown.

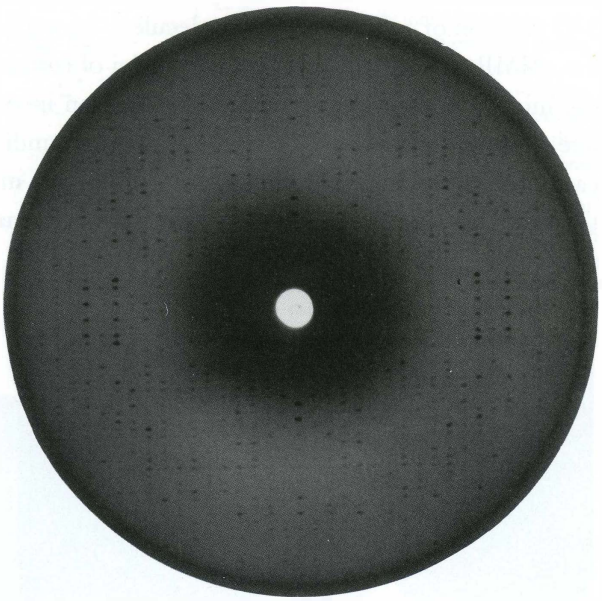
Until recently, obtaining sufficient supplies of protein was also a problem for crystallographers, since many of the proteins they are most eager to study are scarce in a cell. Today, however, Rockefeller crystallographers use recombinant DNA technology to engineer and mass-produce virtually any protein they wish to study.



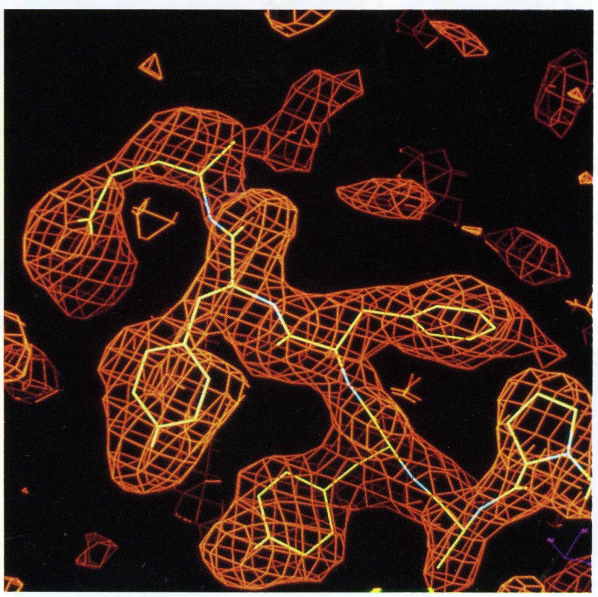
◀ With the crystallized protein obtained, researchers can begin the process of data collection. An x-ray source shoots a beam of waves through the crystal. To obtain all the necessary data, experiments are conducted so that the x-ray beam hits the crystal at many different angles. Most of the waves go straight through the crystallized protein, but some hit the electrons whirling around the atoms and scatter, or diffract, in all directions. Interference cancels out some of the diffracted x-rays, but reinforces others, which are recorded on a detecting device.

At Rockefeller, many experiments are conducted using a state-of-the-art "area detector," which registers many diffracted x-ray beams at once and sends the information directly to a powerful mini-

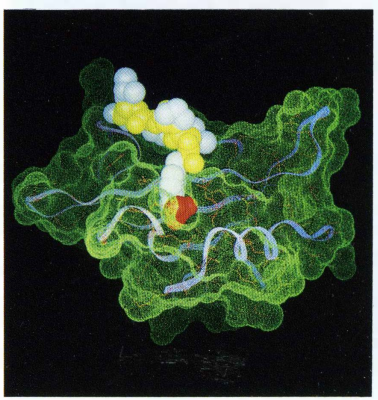
▶ The ensemble of diffracted beams produces an array of spots called a diffraction pattern. To learn more about the individual atoms that generated this pattern, three aspects of the diffracted x-ray waves must be known: their amplitude, their wavelength, and their phase. The intensity of the spots on the diffraction pattern gives information about the waves' amplitude, and the wavelengths are known to the scientists from the start. But to solve the so-called "phase problem," crystallographers must compare the diffraction patterns made by the original crystal with those made by crystals of proteins to which "marker" atoms have been added. Such comparisons entail growing new crystals, running scores of additional diffraction experiments, and performing many complex mathematical calculations.

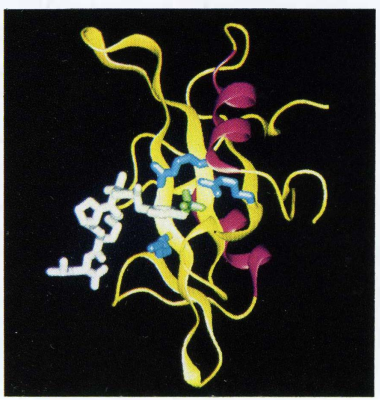


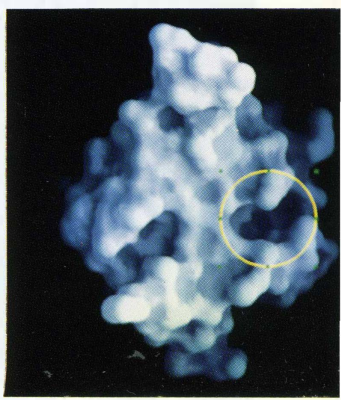
Once crystallographers have solved the phase problem, they can prompt computers to produce a preliminary "electron density map." The initial map, which highlights regions of electron density around each atom, is not without errors. Nor does it unequivocally tag each atom's identity, since a number of atoms resemble one another at the level of detail the map can provide. The task of refining and interpreting the map is up to the crystallographers. Drawing on their knowledge of chemistry, physics, and mathematics, and referring to the known amino-acid sequence of the protein, atom by atom they build up the structure of the protein as a whole. ▶



When each atom in the electron density map has been assigned its identity, sophisticated computer graphics can present the 3-D structure in any number of formats. The protein's secondary structure (its helices and strands), the peaks and valleys of its surface, the chemical forces that shape its internal dynamics, its individual atoms—all can be displayed in virtually any combination. These beautiful images, which can be moved and rotated in all directions with the simple click of a computer "mouse," help crystallographers decipher the innermost details of a protein's structure, and thereby provide insights into how the protein





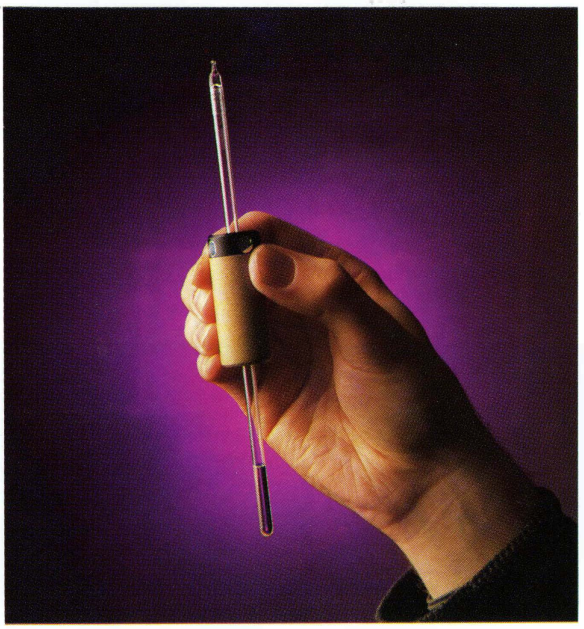


How does nuclear magnetic resonance spectroscopy work?

Scientists have long used nuclear magnetic resonance (NMR) spectroscopy to determine a molecule's chemical composition. But only in the past decade have conceptual and technical advances made it possible to use NMR to determine the 3-D position of every atom in a molecule.

NMR exploits the fact that the nuclei of certain atoms—including hydrogen, the most abundant atom in proteins—have an intrinsic spin that makes them act like small bar magnets. Differences in the surrounding chemical "environment" of each atom affect the behavior of these minuscule magnets in ways that give clues to their position within the molecule. This information can then be used to develop a 3-D picture of the protein as a whole.

Robert Reichert

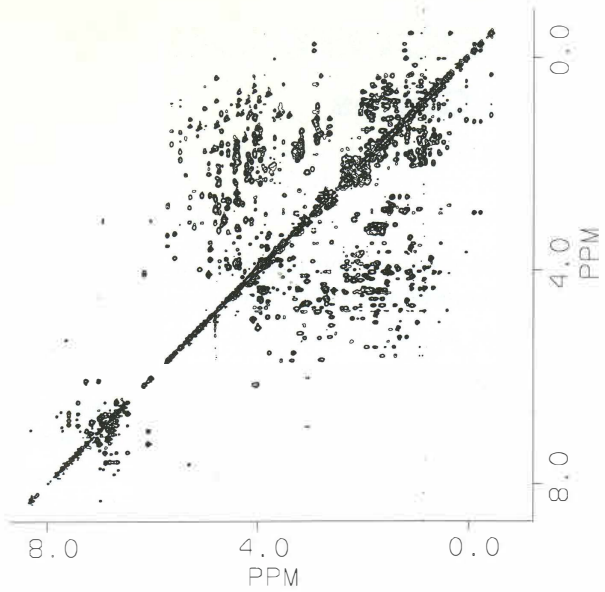


◀ NMR studies protein molecules as they float in solution, so researchers who use this method are freed from the challenges x-ray crystallographers must surmount each time they attempt to crystallize a protein. But NMR poses its own constraints. The proteins investigated with this method must be highly soluble, available in copious quantities, and relatively small.

The NMR spectroscopists at Rockefeller conduct the protein chemistry necessary to obtain the proteins and peptides they study. They synthesize certain protein segments (peptides) from scratch and purify other proteins they have "grown" themselves in the appropriate culture medium. These proteins and peptides are dissolved, the solution is poured into a glass vial, and the vial is put into a ceramic holder before being inserted into the NMR magnet.

Robert Reichert

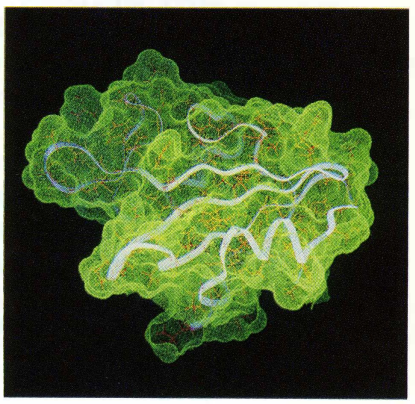
◀ The dissolved protein molecules are subjected to intense magnetic fields produced by a supermagnet housed in the apparatus. The greater the strength of the field, the greater the sensitivity of the measurements, and the magnet at Rockefeller generates fields up to 200,000 times stronger than that of the earth. The strong magnetic field causes the nuclear "bar magnets" of certain atoms such as hydrogen to line up in one of two orientations. Generally, the nuclei take the orientation that requires the least energy. But a boost of extra energy in the form of radio frequency waves flips some of the nuclear magnets into a higher-energy orientation. When these excited nuclei revert to their former, lower-energy state they emit the absorbed radio energy, which can be measured, recorded, and analyzed by powerful computers.

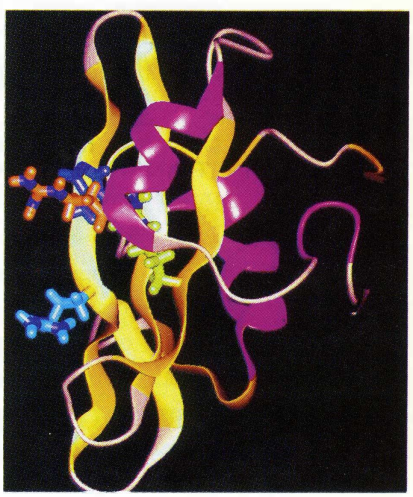


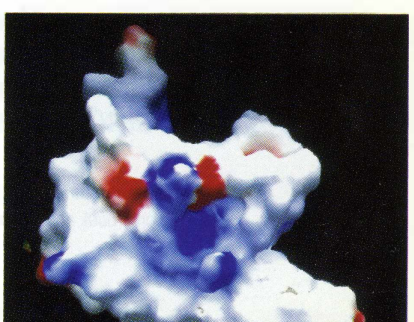
◀ The characteristic energy absorption profile, or spectrum, of each atom's nucleus depends on many different factors in its chemical environment, including its own surrounding electrons and the nuclei and electrons of neighboring atoms. Typically, NMR experiments are designed to produce spectra that not only identify individual atoms, but give information about nearby atoms, as well. Depending on the experiment, these two-dimensional spectra may indicate which atoms belong together in the same amino acid or which ones, though "unrelated," are close together in space. Many NMR runs are conducted to obtain the massive amounts of data required to characterize all the atoms in a protein. As one of the first steps in analyzing this data, scientists draw on their knowledge of chemistry, physics, and mathematics, combined with their knowledge of the protein's amino acid sequence, to develop a picture of the protein's "secondary structure"—the twisted helices and crimped, pleated sheets that help give a protein its shape.

◀ With knowledge of the secondary structure in hand, NMR spectroscopists use interactive computer programs to help them derive a set of "conformers"—a number of 3-D structures any one of which might be correct. Unlike x-ray crystallography, NMR does not directly visualize the atoms in a protein molecule, but rather provides information about the atoms' positions relative to one another. The constraints that determine these positions lie within strictly defined limits. The computer program assesses the enormous number of permutations that are possible within these constraints, and generates potential 3-D structures. Many of these proposed structures violate the original NMR data in some way, and the spectroscopists must analyze and refine the models. For instance, more than 100 structures were originally generated for the abl SH2 domain; in the end, the Rockefeller researchers identified twenty that best fit the NMR data.

One or more of these structures can be chosen for imaging with powerful computer graphics programs. Like x-ray crystallographers, NMR spectroscopists use programs that allow the images to be moved and rotated in all directions. These programs portray the protein's three-dimensional structure—the characteristic conformation of twists, pockets, and projections that endows it with exactly the right combination of chemical, mechanical, and electrostatic forces to perform its function. Researchers can select any combination of the protein's features—its sheets, loops, and helices, its individual atoms, its surface area, and its electric charges—to focus in on particular functional aspects they wish to study. ▼







Cracking Cancer's Secret Code

Hidesaburo Hanafusa and the Onc Genes

by John Langone

"All things are hidden, obscure, and debatable if the cause of the phenomena be unknown," Louis Pasteur once observed. "But everything is clear if this cause be known."

The words of the great French chemist readily apply to cancer. For years, scientists and clinicians knew it only as an insidious disease that ravaged the body, but its central mechanism, the trigger that propelled it along its fatal course, was a mystery—until about a dozen or so years ago, when cancer was determined to be a disease of the genes, and, more specifically, a disease spawned by a certain group of genes. Known as oncogenes (from the Greek, onkos, meaning "mass"), the first cancer-causing genes researchers discovered were a class that started out as harmless as those that code for our eye and hair color. The normal function of these genes, now referred to as protooncogenes, is to promote cell growth and division. Occasionally, something—perhaps chemicals, radiation, or some other physical carcinogen—damages their genetic structure, and transforms them into the potentially deadly oncogenes that promote the uncontrolled cell growth that is cancer. Another class of cancer-causing genes—known as anti-oncogenes, or tumor suppressor genes—has as its normal task the halting of cellular growth; changes in these genes can also result in the development of cancer.

DELVING INTO CELLULAR TRANSFORMATION

But while the discovery of the cancer-causing genes makes it possible to understand how cancer originates, it does not in itself explain what jams a normal gene's regulatory signals and converts it into a hostile oncogene, nor how a turned-on oncogene wreaks havoc in the cells. At The Rockefeller University, a tumor virologist with a penchant for protein chemistry, Hidesaburo Hanafusa, has been unraveling the complex mechanism of cellular transformation. Delving deeply into the molecular basis of cancer, Hanafusa is, in a sense, an engineer trying to determine the cause of a communications breakdown: he searches for flaws in a cell's "wiring," for a malfunction in the equipment that sends, relays, and receives the chemical messages a cell needs to function smoothly, for errors in the signals themselves as they beam from within a cell, and between cells. "There are," he says, "a lot of combinations, a lot of possibilities for some mistake. But I think the progress we've all made in oncogenesis is phenomenal. Gradually, too, we've learned more and more about the key elements in all of this, the proteins that can disrupt the cell's regulatory mechanism."

Hanafusa's interest in cellular genes and oncogenesis—the topic of the series of Darwin Lectures he delivered at Rockefeller in 1985—began some thirty years ago, when he was working on the Rous sarcoma virus as a postdoctoral fellow at the University of California, Berkeley. It was 1961, a time when the very foundations of molecular biology were being laid. Newly arrived from his native Japan, where he received his B.S. and Ph.D. degrees in biochemistry from Osaka University, Hanafusa almost immediately took up where Peyton Rous, who in 1911 had isolated the chicken tumor virus that bears his name, left off.

STUDYING THE ROUS SARCOMA VIRUS

Rous had been invited in 1909 to The Rockefeller Institute, as it was then called, to continue studies of transplantation of tumors. Fortunately, he didn't heed the advice of a mentor, who told him earlier "not to commit deeply on cancer problems." A few years later Rous described an infectious agent which would turn out to be a retrovirus. But Rous didn't pursue his find because cancer research was too primitive, and there was little knowledge of viruses in general, let alone the genetic materials that composed them. Indeed, the first electron microscopic photographs of Rous's virus were not available until 1947. They were made at Rockefeller by Albert Claude and Keith Porter.

At Berkeley, Hanafusa's interest in the Rous virus peaked ("We had the technology now to pay more attention to the implications of Rous's groundwork," says Hanafusa), and soon he had made several pioneering contributions that Rous

John Langone, former medical writer at *Discover* and *Time* magazines, is working on a book about research and education at the Harvard Medical School.

himself would live to see. One was the finding that for the Rous virus to replicate, it required a protein provided by a helper virus. This notion of a "defective" Rous virus—defective in the sense that it was unable to produce an essential envelope glycoprotein on its own—presaged what scientists refer to as transduction—the transfer of genetic material from one cell to another—of oncogenes. After they found oncogenes in viruses, scientists would also uncover, in animal cells, genes with exact counterparts to the viral oncogenes. Researchers would also find segments of DNA related to the v-*src* oncogene in the normal DNA of uninfected chickens. Today, scientists know that viruses can hijack bits of cellular DNA and incorporate them, sometimes damaged, into their own genetic material; and, more important, that cancer-causing genes are present in normal cells before the cells are infected by retroviruses. "If we had pursued the basis of defectiveness," says Hanafusa, "we could have reached the current idea of transduction of oncogenes much earlier." (Hanafusa didn't do so because soon after he discovered the defectiveness of the Rous virus, some nondefective versions were found in viruses kept in Europe. It turned out that they were, as Hanafusa puts it, "exceptional viruses.")

Hanafusa is, in a sense, an engineer trying to determine the cause of a communications breakdown: he searches for flaws in a cell's "wiring," for a malfunction in the equipment that sends, relays, and receives the chemical messages a cell needs to function smoothly.

LEADING THE FIELD IN RNA TUMOR VIRUS RESEARCH

Hanafusa left Berkeley, and after stints as a visiting scientist at the College de France in Paris and as a member of New York City's Public Health Research Institute, he joined Rockefeller as a professor in 1973. Perhaps it was his Ph.D. thesis research on the protein chemistry of enzymes that spurred his later interests and accomplishments, among them his descriptions of the mechanism of genetic information in normal cells that complement defective viruses, and his isolation of mutants that provided evidence for the role of a viral protein in transformation. Whatever it was, Hanafusa "has been the acknowledged leader in the study of the genetics of RNA tumor viruses," observed Purnell W. Choppin, head of the Howard Hughes Medical Institute and former professor and dean at The Rockefeller University, in his introduction to Hanafusa's Darwin Lectures.

While the evidence for virus-induced cancers in humans is still lacking, viruses like the one isolated by Rous have enabled scientists to analyze the mechanism of cell transformation. Says Hanafusa: "Studies of these viruses have had a profound impact on cancer research when the viral genes responsible for the transforming activity were found to have originated from cellular genes, the expression of which is critical in carcinogenesis."

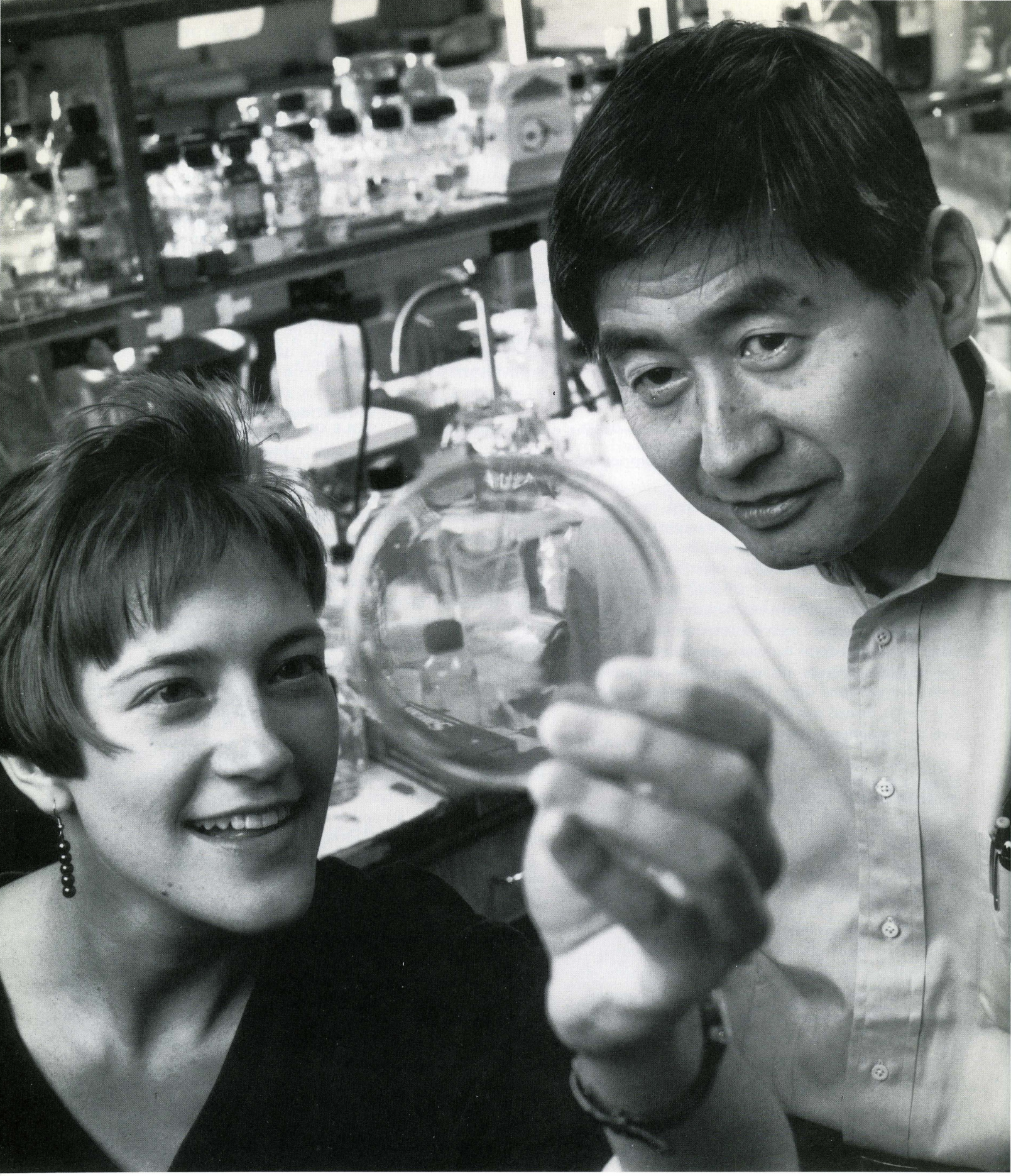
INVESTIGATING THE ROLE OF THE SRC GENE

For that reason, Hanafusa has long been interested in the v-*src* (pronounced "sark") oncogene that was originally found in the Rous sarcoma virus. The gene, like some other oncogenes, encodes a protein tyrosine kinase that is solely responsible for initiating and maintaining the many different changes that accompany cellular transformation. Hanafusa has been investigating the role the *src* gene plays in the cell's signaling apparatus, and where it gets involved along the signaling track. The signaling process is a complicated one involving a chain of intracellular messages and interactions known as phosphorylation.

Hanafusa has found that upon infection with Rous sarcoma virus, many cellular proteins become phosphorylated on tyrosine, which is associated with alterations in a number of cellular structures, and functions such as cell growth.

Hanafusa has also been hunting for a *src*-phosphorylated protein that does its relay work on serine or threonine. This one is most important because, according to Hanafusa, serine/threonine kinases are generally active close to the cell's nucleus, near the end of the signaling process. Hanafusa's team has discovered such a *src*-serine/threonine connection that may play a key role in cell regulation and which might help to explain the runaway division process that turns a cell savage and, thus, cancerous.

Hanafusa has also identified a novel oncogene, *crk*, in an avian sarcoma virus, which was isolated in the early 1920s by Albert Claude, another pioneer of cell biology at The Rockefeller Institute. It encodes a protein that has no known catalytic func-



Graduate student Heidi Greulich and her faculty adviser, Hidesaburo Hanafusa, viewing a colony of transformed cells.

tion, but surprisingly induces tyrosine phosphorylation of some cellular proteins, and causes cancer. Just how the *crk* oncogene interacts with other proteins to transform a normal cell into a cancerous one is currently under intense investigation, as is the role of its mystery protein in normal cells. It is the research of this protein that initiated the current surge of interest in the interaction between phosphotyrosine-containing proteins and a peptide sequence known as SH2.

SETTING THE STAGE FOR SOLVING THE CANCER PROBLEM

Hanafusa's research, like that of all scientists who work at the molecular level, is not directly related to the treatment of cancer. No more than one turned-on protooncogene relates to the transformation of a healthy cell into a cancerous one. However, both the research and the role of the oncogene are steps—essential ones—toward something. The activation of a protooncogene or the deactivation of an anti-oncogene contribute to the development of cancer amid a whole range of genetic changes, outside influences, and collaboration with other genes and oncogenes. The myriad molecular events that are examined piecemeal in Hanafusa's and other labs set the stage for successful treatment that will surely come one day. Without basic research in cell and molecular biology, biochemistry, and biotechnology, it wouldn't be possible to make other advances, such as drugs that block the interactions or change the signals that contribute to a normal cell's transformation to a cancerous one; drugs that work against the protein products of oncogenes; or a way to repair the machinery that has gone awry in a tumor suppressor gene.

Hanafusa, like his colleagues in other Rockefeller cancer labs, voices hope that these advances will soon take place. Reflecting on his years in the field, Hanafusa observes, "Since I started to work in this area, there have been many surprises that will help us solve the cancer problem."

One indication that Hanfusa is the right man for the job is the many awards he has received: the Lasker Award for Basic Medical Research, the Howard Taylor Ricketts Award, the Asahi Prize, and the Clowes Memorial Award of the American Association of Cancer Research. Another is the description of the man and his contributions by one of his fellow tumor virologists:

"Everything that Hidesaburo does has substantial impact on the field. He has a unique talent for sensing the important, and avoiding the trivial." **RU**

Rockefeller's Transgenic Service Laboratory

by Susan Blum

"Oh brave new world, that has such people in't."
-William Shakespeare,
The Tempest

The Rockefeller University's new Transgenic Service Laboratory is a busy hub of activity on the fifth floor of the Laboratory Animal Research Center (LARC). The lab serves as the university's core facility for the creation and maintenance of all transgenic animals, the freezing and preservation of mouse embryos, the refinement and development of new transgenic techniques, and the training of university personnel.

Since the laboratory opened recently, inquiry calls have been coming in from research institutions around the country. "We're unique in providing so many different services in one facility. People want to learn more about what we're doing," says LARC director Michael Hayre.

The interest is great because transgenic techniques are playing an ever-increasing role in biological research. These techniques allow researchers to change an animal's natural genetic endowment by adding or subtracting virtually any genes they desire. Such manipulations permit a wide range of studies, from basic research into a gene's function to the creation of animal models for diseases. So far, most transgenic studies use mice, but other animals such as birds and fish also offer promise for productive investigations.

In one transgenic method, the gene of interest is inserted into fertilized mouse eggs, which are then implanted into "surrogate" mouse mothers. Some of the offspring of these surrogates carry the added gene in every cell of their body. This method, though extremely useful, can present certain drawbacks. For example, researchers cannot control where the gene will be inserted into each egg's chromosomes, so they cannot be sure it will have the same effect in transgenic animals descending from different eggs. A newer transgenic method, called "gene targeting," is more complicated but allows for greater control. By exploiting chromosomes' natural propensity to shuffle, or recombine, it allows researchers to completely debilitate one of an animal's normal genes or to replace it with another of their own devising.

The skilled staffers at Rockefeller's transgenic service lab are expert in both types of transgenic techniques, providing an unusual combination of capabilities that is a boon to researchers. The facility primarily serves the Rockefeller community, but scientists from other institutions are also welcome to use it; researchers from as close by as Memorial Sloan-Kettering Cancer Center in Manhattan, and as far away as the University of Hong Kong, have already done so.

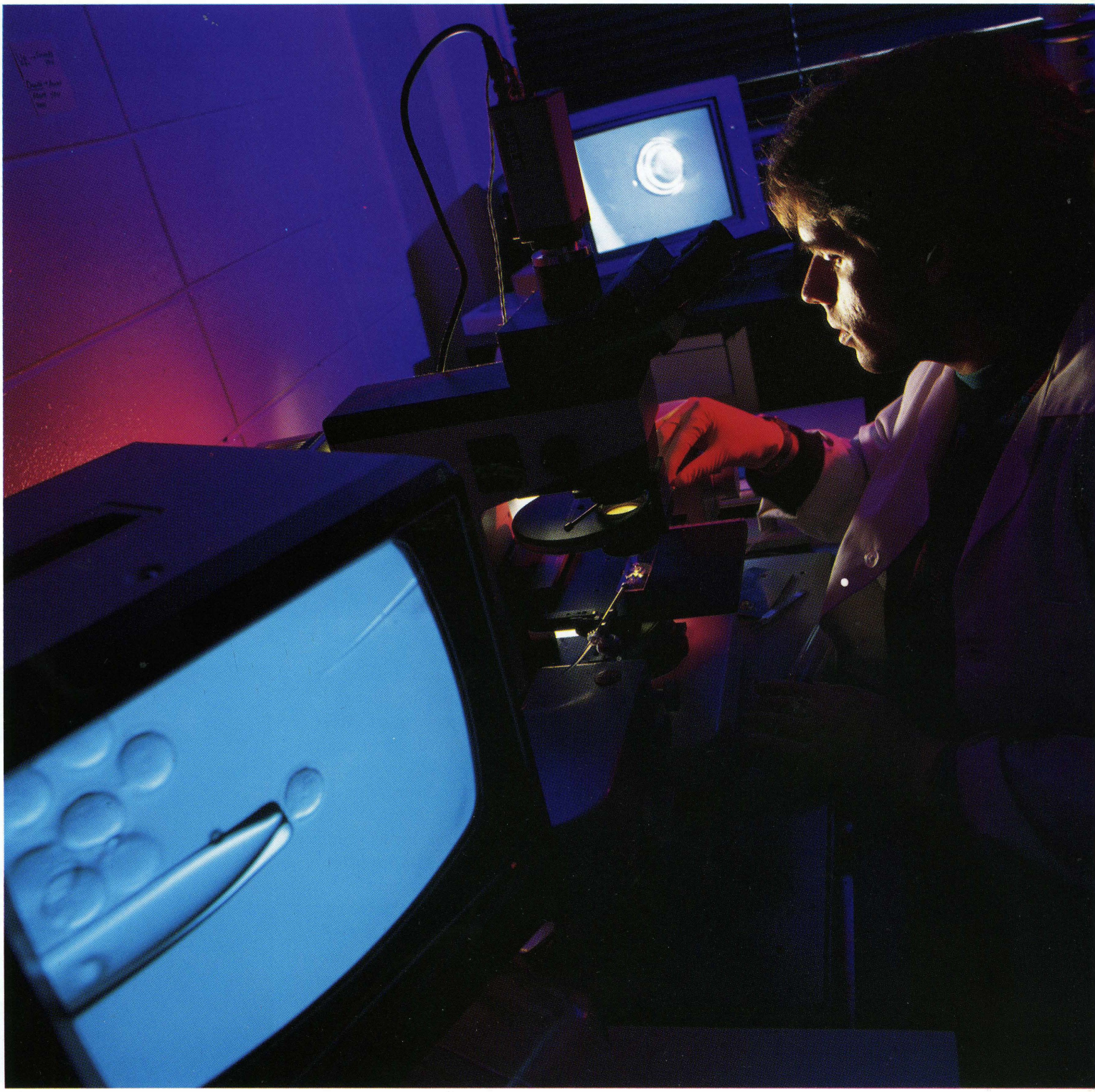
Transgenic techniques are extremely demanding and time-consuming. Now that the new facility is open, researchers will be able to enjoy the benefits of the methodology without having to cope with its complications. "In most cases, if investigators give us well-prepared DNA, we'll be able to give them back transgenic mice," says Annemarie Walsh, director of the Transgenic Service Laboratory. For researchers who prefer to perform the genetic manipulations in their own labs, the staff of the facility stands ready to provide any training that may be required.

In addition to creating transgenic animals, the facility is one of the few nationwide to freeze and preserve transgenic mouse embryos. This "cryopreservation" cuts research costs substantially—and reduces the use of laboratory animals—by minimizing the number of breeding animals that must be maintained. The technique also ensures that genetically altered lines of mice are protected from the infections, accidents, and "genetic drift" that can threaten precious transgenic strains. When transgenic mice are required for research, the embryos need only be thawed and implanted in surrogate mothers. Studies recently completed in the lab show that cryopreservation does not harm the embryos in any way.

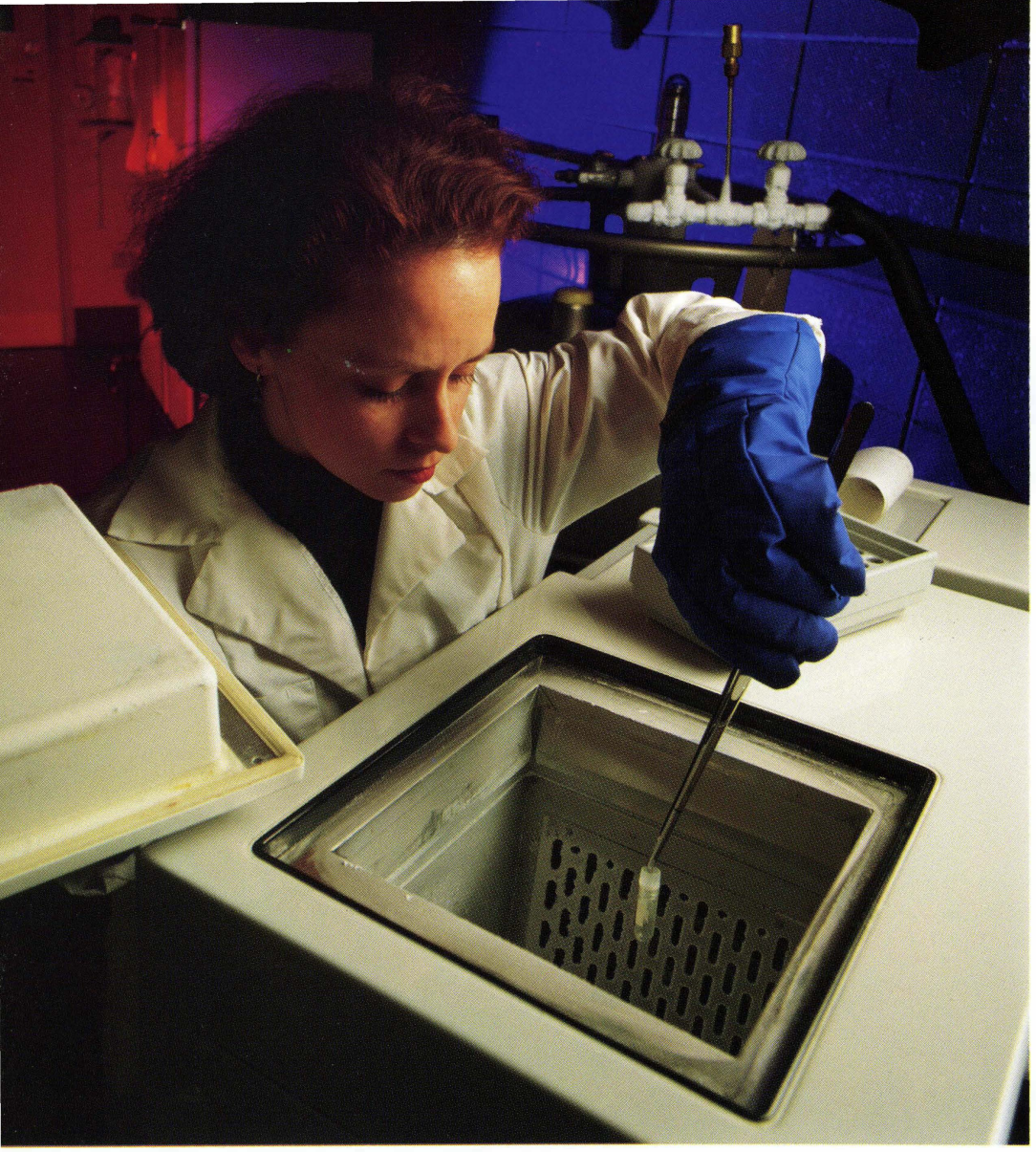
Lab members are also researching better methods to freeze mouse sperm—an accomplishment that, like cryopreservation, would help save money

Susan Blum is a science writer in The Rockefeller University Public Affairs Office.

Robert Reichert



Above, Research Assistant Kirk Economides microinjects mouse eggs with foreign DNA to produce a new strain of transgenic mice that will help researchers understand the



Robert Reichert

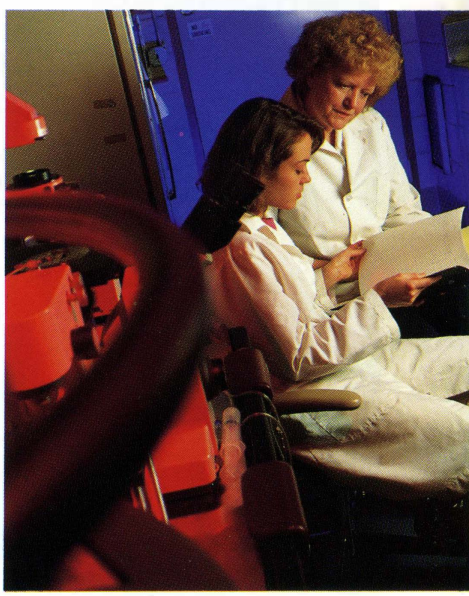
genetic endowment would further enhance the insights such studies might provide. Though the characteristic internal structure of avian sperm and eggs has so far thwarted the development of transgenic birds, the team at the Transgenic Service Laboratory believes the obstacles can ultimately be overcome.

Development of the Transgenic Service Laboratory was facilitated by a gift of $150,000 from the Schering-Plough Research Institute, the research division of the major pharmaceutical company in New Jersey. Michael Hayre has long-standing ties with Schering-Plough, having served as the company's associate director of animal care before becoming LARC's director in 1991. "We are enormously pleased that Schering-Plough has made such a generous contribution to our new facility," Hayre said. "My ties of affection and admiration for both Rockefeller and Schering-Plough are enormous, and I'm delighted that we have been able to build this bridge between the two institutions." **RU**

and reduce the number of lab animals used. It has long been possible to freeze the sperm of many other mammals from rats to humans, but for reasons that remain unknown the sperm of mice is much harder to freeze. The researchers at Rockefeller are using new techniques developed in England to surmount the difficulties of this tricky procedure.

That project is just one of many now under way or planned for the future at the new Transgenic Service Laboratory. Currently, for instance, Walsh and Carol Novotney, a veterinary postdoctoral fellow at LARC, are exploring methods to create transgenic quail. Most other groups involved in such efforts are interested in benefiting the poultry industry. But the researchers at Rockefeller believe transgenic birds would be a boon to the biomedical research community, too.

As the studies of Rockefeller scientists such as Fernando Nottebohm and Arturo Alvarez-Buylla have shown, birds serve as excellent models for neurobiological studies and for research in basic biology. The ability to manipulate birds'



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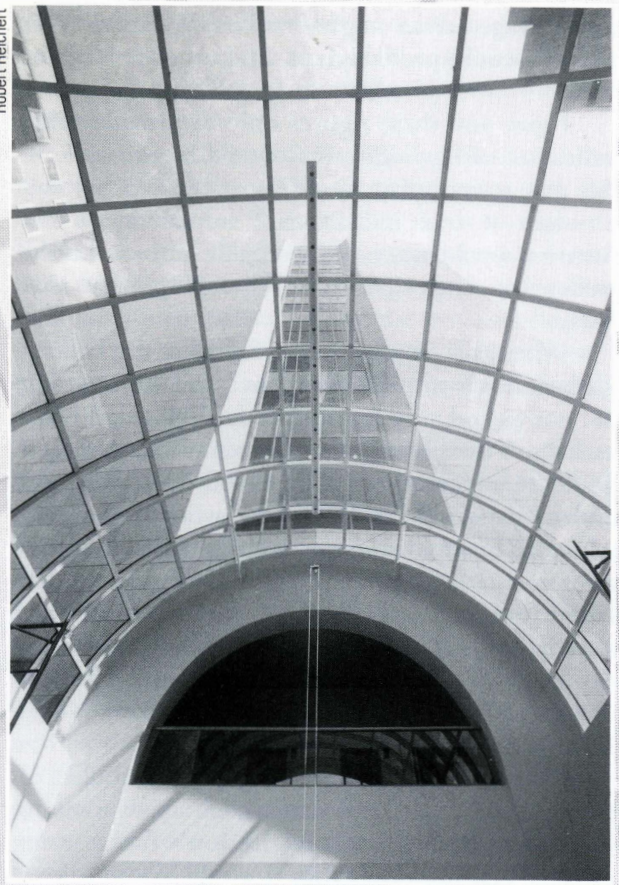
Top, Susan Powell, director of cryogenic preservation services, retrieves a vial of frozen mouse embryos. *Bottom,* Research Assistant Michelle Inserra, left, and Annemarie Walsh, right, director of the Transgenic Service Laboratory, review data

Dedication of the John D. Rockefeller, Jr. and David Rockefeller Research Building



Robert Reichert

Looking up through the atrium of the new research tower.

The new John D. Rockefeller, Jr. and David Rockefeller Research Building officially opened its doors at a dedication ceremony September 23, 1992. The twelve-story limestone and granite structure, which took eight years to complete, increases campus laboratory space by over twenty-five percent. It will house research groups undertaking major studies in fields such as cell and molecular biology, immunology, chemistry, and the neurosciences.

The dedication of the new building was part of a four-day program of activities at the campus. Among the highlights of the ceremonies were:

- **The keynote address delivered by Walter E. Massey, Director of the National Science Foundation**

Massey's thoughts on the new building, the enduring legacy of the university, and the future of philanthropy and research in this country are reprinted on the pages that follow.

- **Participation of the Howard Hughes Medical Institute**

The new research building was funded with major assistance from HHMI, the nation's largest private philanthropy, which, like The Rockefeller University, focuses primarily on the biomedical sciences. Purnell W. Choppin, president of HHMI, was on hand to discuss the unique role of the Howard Hughes Medical Institute in American science and its fruitful method of collaborating with other institutions. A history of HHMI, founded in 1953 by the late billionaire Howard Hughes, is also included, along with photos of four dedication speakers, each of whom referred to the significance of this historic partnership: Rockefeller University President and Nobel Prize winner Torsten Wiesel; Chairman of the Rockefeller University Board of Trustees Richard Furlaud; Rockefeller University Executive Committee Chairman David Rockefeller; and Dr. Choppin.

- **A poster exhibit, "From Microbes to Molecules: A Century of Science at Rockefeller"**

Among the special exhibits mounted as part of the four-day celebration was a display in the atrium of the new building entitled "From Microbes to Molecules: A Century of Science at Rockefeller." The exhibit links the historic growth of the buildings on The Rockefeller University campus with the growth and development of scientific inquiry. The exhibit—a series of photographs with accompanying text, shown in the following pages—discusses the origins of the university then known as The Rockefeller Institute for Medical Research and depicts its early battles to conquer infectious diseases, as well as some of its subsequent scientific breakthroughs and the key figures associated with them. An accompanying timeline highlights when and why major buildings were constructed, and traces the evolution of the campus.

Dedication Ceremony

Keynote Address

by Walter E. Massey
Director, The National Science Foundation

I have often thought that if I had to live life over again I would become a historian. I have made a hobby of learning history because I believe passionately that we must know history in order to understand and appreciate current events, and to inform our decisions about the future. In this new research building, I see lots of history; and it also inspires me to think about the future.

Both mystery and certainty are at work here. We cannot predict what new knowledge will be unveiled within the walls of this building. But we also are certain that great advances will come forth from within these walls sooner or later. Some man or woman, perhaps someone here today, might someday discover a cure for AIDS, or an affordable pollution-free energy source, or any number of less dramatic discoveries that bring added convenience and enjoyment to daily life. This mystery—that we cannot predict precisely what we will learn—combined with the certainty that great things will occur, is the essence of scientific and technological progress. It underlies all of the contributions that science and technology have given to society throughout history—from the first wheel to the most advanced supercomputer.

I also believe that the historical importance of this dedication extends far beyond this building and the research it will house. This building is a vivid reminder that science in America owes much of its development to the farsighted individuals who devoted their fortunes to the progress of knowledge.

It staggers the mind to try to imagine what it would take today to match the accomplishments of the Rockefellers, Carnegies, Stanfords, and a generation later, Hughes. Such individual largesse erected universities, research institutes, and facilities that enabled the nation to begin its ascendency in fundamental science and engineering.

The dollar amounts behind these efforts of a century ago—generally in the millions or tens of millions—may not sound great by today's standards. But it is worth remembering that when this great institution was founded in 1901, the entire Federal budget totaled only a few hundred million (and, by the way, it even ran a surplus in some years), a successful wage-earner might draw ten dollars a week, and you could probably still find a good five-cent cigar.

I give you these figures only to provide some indication of how difficult it would be to duplicate this generosity today. Yet without the wisdom and foresight of these individuals, I am convinced that America would not have been able to become the wellspring of progress and knowledge that it is today.

When this institution was founded, the Federal government's interest in science and engineering did not extend very far beyond surveying and mapmaking. Virtually all of fundamental research and graduate education was supported by private and philanthropic sources. Years later, when the government had matured enough to recognize the need for a continuous supply of new knowledge and scientific talent, the research infrastructure fortunately was already in place. Since then, this research and education enterprise has laid the foundation for an unbelievable string of discoveries, inventions, Nobel Prizes, and economic progress.

Whenever an institution engages in a project of this size and scope, it is natural and appropriate to ask questions about the institution's future role, mission, and responsibilities. I would like to offer a couple of thoughts about the future of The Rockefeller University.

First, never lose sight of the unique capabilities of this institution. The value to the nation of a pure research institution cannot be matched anywhere else. By providing an unfettered atmosphere, the nation's best minds are free to follow their imagination and curiosity. It is truly amazing to have all of this in the middle of the city that never sleeps.

Second, and closely related, is the fact that the frontiers of science today often fall along the boundaries of existing disciplines. The Rockefeller University realized this early in its history. Although it was founded as a medical institute and is still largely focused on human health, it recognized the need to have scientists from other disciplines—physicists, chemists, engineers—on campus. This has helped give rise to such promising areas of science as biophysics and biochemistry. The future of

science requires that this process of integration continue, and I fully expect this university to remain at the forefront.

I believe that this process of integration will be a guiding force in the future for all of science. And once again, my thoughts are inspired by what I have learned about this building. Since I arrived on campus to join in these festivities, more than one person has said to me that this may well be last time we see a research building of this capacity built entirely with private funds.

The construction of this building combined the forces of two names which are synonymous with the can-do attitude that made America great: Rockefeller and Hughes. The nation is very fortunate for that. But we have reached an age where even with such stature behind the project, the end result is just a shell in many respects. To put it simply, somebody else has to buy the furniture for half of the floors in this building.

I expect that the somebody who buys the furniture and instruments will be a combination of all of us—government agencies like the National Science Foundation and the National Institutes of Health, the city and state governments may choose to participate, and without a doubt so will private corporations and industrial groups that need advanced knowledge for comparative advantage. The opening of borders around the globe could also bring forth new partnerships.

The challenge of furnishing this building is symbolic of the future of the entire research enterprise. I believe that the future of research will involve increased cooperation, partnerships between institutions, sharing knowledge, exchanging ideas, and combining resources more than ever before.

There are changes occurring that make it clear we cannot continue supporting research as we have in the past. We are witnessing a growth in cost and scale unlike anything in history: laboratories, like the ones we see here for example, require the most modern controls on wastes and emissions to comply with government regulations. We have also moved decades beyond the days when equipping a laboratory was a simple as putting a microscope on a lab bench.

And, when it comes to the administration of research, sometimes it seems we are just running in place. At NSF, we reject almost twice as many proposals as we fund. And those we fund receive only a bare minimum in terms of support; the average grant generally enables a senior scientist to hire just one graduate student. Some people say more human energy is expended reviewing research proposals than conducting the research itself.

Despite these disconcerting facts, however, the knowledge generated by investments in research and education is more vital and valuable to the nation than ever. There is great excitement about the potential that many recent discoveries hold for the nation's future: areas like superconductivity, which could reduce energy consumption and lead to new forms of transportation; or biotechnology, which holds the promise of new drugs and technologies to clean the environment.

All of this adds up to a complicated picture of the research enterprise as it approaches the twenty-first century—dynamic and vital, but also disgruntled and pessimistic.

Robert Reichert

The picture of the future of research would not be complete without saying something about the end of the cold war. No one of us can deny that superpower tensions shaped many of our national research and development priorities—from the space race to Star Wars. Many disciplines, especially in physics and engineering, grew up as offshoots of weapons programs. Many areas of research in the life sciences as well, including the human genome project, have roots in national security objectives. Even today, three years after the fall of the Berlin Wall, almost sixty cents of every dollar the govern-

Above right, Walter Massey, Purnell Choppin, and Torsten Wiesel at the dedication ceremony for the John D. Rockefeller, Jr. and David Rockefeller Research Building last September

John Sholtis

ment spends on R&D is earmarked for defense, the same level as a decade ago.

With the rapid decline of the Soviet Union at a time of steady growth in economic power in Europe and Asia, there are new expectations for research in this country. Many of the underlying rationales for public support of science are changing. At the height of the cold war, people viewed science as insurance against technological surprise from an adversary. Today, the nation increasingly looks to science as the source of the technological advance necessary for economic prosperity and an improved quality of life.

The research enterprise should not try to insulate itself from these forces of change. To do so would not only be a mistake, it would be impossible. The future vitality of research depends on our ability to be as creative and forward looking in the future as people like John D. Rockefeller were a century ago.

At the National Science Foundation, we have begun a very thorough process of identifying the most effective ways to continue serving the nation and promoting the progress of science and engineering. I am certain that whatever NSF does in the future must be premised on continued strong support for the fundamental research that is so valuable to the country. We must build on this strength and help the nation capitalize on its preeminence in fundamental science and engineering.

We must develop strategies that continue to give academic researchers the independence they need in order to achieve success. But we must do more to move quality research quickly to those who can use it for innovative applications. Cooperation, integration, and exchange of ideas—this is the hallmark of research in the future...and also what I believe will put furniture in this building.

John F. Kennedy once said that "History. . . has no present, only the past rushing into the future. To try to hold fast is to be swept aside."

The dedication of this building gives us the chance to celebrate a slice of the history of science in America. It also serves as a reminder of the challenges and opportunities that the future will bring.

Above left, The Rockefeller Research Building dedication ceremony, September 1992

The Rockefeller University and The Howard Hughes Medical Institute

Collaborating to Further Scientific Discovery

The opening of the John D. Rockefeller, Jr. and David Rockefeller Research Building marks a major collaboration in modern science. The structure symbolizes the joined forces—and shared philosophy—of two prominent institutions dedicated to biomedical research—The Rockefeller University and the Howard Hughes Medical Institute (HHMI), the largest private philanthropy in the nation, which contributed over $33 million to the cost of the new building. Says Torsten Wiesel, Rockefeller's president, the institutions' common outlook "strikes to the heart of the whole scientific enterprise: Find the most talented researchers possible, and then give them the facilities and the freedom to pursue their studies wherever they might lead."

The collaboration is particularly meaningful for both institutions because HHMI's president, Purnell W. Choppin, spent much of his career as a research scientist, dean, and scientific administrator at The Rockefeller University.

"Among those to whom this occasion means something very special I certainly count myself," said Choppin at the building's dedication ceremonies last September. "I cannot avoid some very personal feelings because I have been privileged to have long personal associations with both the very special place that The Rockefeller University is, and another unique and great institution, the Hughes Institute."

Before joining HHMI as vice president and chief scientific officer in 1985, Purnell Choppin spent twenty-eight years at The Rockefeller University studying the mechanisms by which influenza and measles viruses produce cell injury and disease. When he left the university he was a senior physician and the Leon Hess Professor of Virology, and served as vice president for academic programs and dean of graduate studies.

"Clearly my years there imbued me with respect for thoroughness and excellence," Choppin explains, "and the importance of unfettered time to perform research. If one comes from an institute of that order, he looks on research with the highest possible standards."

Robert Reichert

Right, Purnell Choppin, head of the Howard Hughes Medical Institute (HHMI), and his wife, Joan, flank Nathaniel Heintz in his laboratory in the new Rockefeller research building. Heintz, an HHMI investigator, was the first university faculty member to move his lab into the new facility, funded in part through HHMI

HHMI SUPPORTS RESEARCH AND LAB SPACE

The relationship between The Rockefeller University and The Howard Hughes Medical Institute exemplifies HHMI's method of support. Once HHMI enters a collaborative agreement with a host institution, it not only brings faculty scientists onto its research staff, but arranges for their laboratory space either by leasing existing facilities or by participating financially in the construction of a new building and then occupying some of the new facilities. An arrangement for new construction was reached between Hughes and The Rockefeller University at the time of their contractual agreement in 1985. At that time, HHMI pledged funds toward four floors of the new research facility that opened its doors this fall.

"There is no other institution in the United States that operates quite like Hughes," says Choppin. "As an operating medical research organization, HHMI enters into partnership with outstanding universities and medical centers, collaborations to which each brings important resources—human, environmental, and financial. It is an unusual arrangement in which HHMI investigators become Institute employees but remain as faculty members of the host institutions, carrying out normal teaching and other faculty responsibilities. It is complex, but it works—and we at HHMI are appreciative of the manner in which our partners, such as The Rockefeller University, work with us."

Robert Reichert

ELEVEN RU SCIENTISTS ARE HUGHES INVESTIGATORS

At Rockefeller University, the Howard Hughes Medical Institute supports eleven scientists whose research will soon be carried out on four floors of the new John D. Rockefeller, Jr. and David Rockefeller Research Building.

HHMI selects investigators according to the quality of their research. Scientists do not apply for HHMI support; they are chosen. They are offered renewable appointments for varying periods of time, depending on the rank of the scientist at the host institution. Assistant professors are appointed for terms of three years, associates for five years, and full professors for seven years. HHMI investigators heading labs at Rockefeller University are Günter Blobel, Stephen K. Burley, Claude Desplan, Michael W. Young, Thomas Sakmar, Michel C. Nussenzweig, Jeffrey M. Friedman, Nathaniel Heintz, John Kuriyan, Jan Geliebter, and Yongwon Choi. An additional eighty-one people—postdoctoral associates, technicians, and other support staff—who work on the Rockefeller campus are on the Hughes payroll. In fiscal year 1992, HHMI's operating budget for its Rockefeller University projects was $7.8 million, according to Choppin.

"Hughes is very generous," says geneticist Michael Young. "The institute takes you in and gives you ample support that is realistic to the cost of science. There is money for supplies and salaries for junior members of the lab. Postdocs can work on two-, three-, or four-year independent projects that relate to the larger project, and Hughes pays for their work and supplies. Money from public and private agencies is tight now and a grant is often barely enough to cover a portion of your work. Hughes is more realistic and has more awareness of the costs of research."

A VISION FOR THE FUTURE

The joint efforts of HHMI and The Rockefeller University are expected to result in significant contributions to scientific research. Walter E. Massey, director of the National Science Foundation, said in his keynote address at the dedication ceremony for the new building (reprinted in its entirety on pages 24–26): "Both mystery and certainty are at work here. We cannot predict what new knowledge will be unveiled within the walls of this building. But we also are certain that great advances will come forth from within these walls sooner or later. Some man or woman, perhaps someone here today, might someday discover a cure for AIDS, or an affordable pollution-free energy source, or any number of less dramatic discoveries that bring added convenience and enjoyment to daily life." That is the hope—and the anticipation—of this philanthropic mission that David Rockefeller says is "aimed at supporting top-quality re-search that only the very best in science are qualified to conduct."

Right, Peggy and David Rockefeller enter the new Rockefeller research tower after the ribbon-cutting ceremony at the building's

Robert Reichert

"This occasion calls for celebrating the past that has informed us and shaped our aspirations for the future. It was only ninety years ago that John D. Rockefeller, Jr., David Rockefeller's father, convinced his father, John D. Rockefeller, Sr., to invest $20,000 each year for ten years to support scientists in a new institution for medical research to help solve dramatic health problems so evident in New York City at the turn of the century—and I might add—as they are today....

"This building could not have become a reality without the tremendous support of another philanthropist, Howard Hughes, whose medical institute provided more than $30 million for the continuing funding for eleven senior scientists who will be its first occupants. This is, of course, pursuant to our mission and the institute's mission to further basic knowledge in sciences that underlie essentially all diseases: cell biology, genetics, immunology, neuroscience, and structural biology."

-Richard M. Furlaud

"The similarity between the Howard Hughes Medical Institute and The Rockefeller University transcends the parallel use of private fortunes for the public good. Both share a philosophy that strikes at the heart of the whole scientific enterprise: Find the most talented researchers possible, and then give them the facilities and the freedom to pursue their studies wherever they might lead....

"As a neuroscientist, I am particularly excited that in addition to the floors housing Howard Hughes investigators, our new research building also will be home to a Center for Neuroscience—an area of strength at the university."

-Torsten Wiesel

From Microbes to Molecules:

A CENTURY OF SCIENCE AT THE ROCKEFELLER UNIVERSITY

Above, Schermerhorn Farm: Site of the future Rockefeller University campus. *Inset,* Frederick T. Gates and Simon Flexner.

The Rockefeller Institute for Medical Research was incorporated in 1901, and immediately gained local attention by finding (as the headlines of the *New York Herald* put it) "Germs Swarming in City's Purest Milk." The next year, Simon Flexner, a young, eminent pathologist at the University of Pennsylvania, was appointed the nascent institute's first director. It was Flexner's personal venture into the universe of deadly microbes during a 1904–1905 epidemic of cerebrospinal meningitis that established both The Rockefeller Institute's lasting fame and the enduring confidence of its benefactor, John D. Rockefeller.

Text by Geoffrey Montgomery
Photos are courtesy of The Rockefeller University Archives

American,
New York City,
June 1st, 1908.

TELLS HOW FLEXNER WON $500,000 GIFT

Dr. Holt Explains Why Institute Gets New Hospital from John D. Rockefeller.

MENINGITIS CURE DID IT

Through New Discovery 70 to 75 Out of Every 100 Recover from Disease.

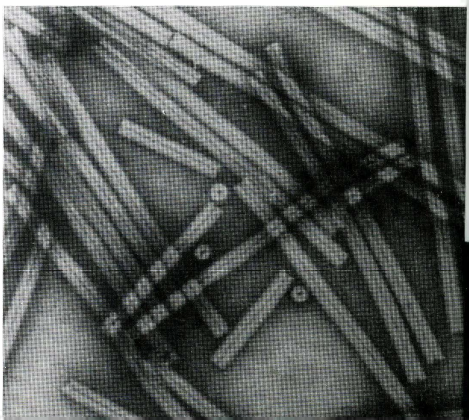
"Recoveries from cerebro-spinal meningitis to-day are from 70 to 75 per cent. During the epidemic in New York in 1904-5 the mortality averaged 76 per cent. This tremendous change has been wrought through the serum found by Dr. Simon Flexner, director of the Rockefeller Institute, and it is because he is convinced of the permanent value of Dr. Flexner's discovery that John D. Rockefeller has given the institute an additional half a million."

This was the statement made last night

American, New York City, June 1, 1908.

Under the leadership of this master microbe hunter, the mission of The Rockefeller Institute both widened and deepened. In 1910, as construction was completed on a new hospital, Flexner recruited the experimental biologist Jacques Loeb, an apostle for a physico-chemical explanation of life's great conundrums—heredity, embryogenesis, and mind. One of Flexner's first appointments to Rockefeller, Phoebus Levene, revealed the chemical formulas of the ill-understood nucleic acids. And in 1935, Wendell Stanley, applying methods developed by his Rockefeller colleagues working on protein chemistry, succeeded in crystallizing the virus responsible for tobacco mosaic disease.

Stanley's crystalline microbe caused a sensation. This virus that could be turned to crystal while retaining its self-replicating powers seemed to exist on the twilight border between the living and the dead, between reproducing organisms and lifeless molecules. Its protein capsule seemed to hold the promise of a true chemical understanding of life. Stanley, like Loeb, Levene, and nearly all biochemists of the age, thought that the elements of reproduction—genes—must be made of protein. Yet a strange fact soon emerged. Coiled within the capsule of Stanley's magic crystal was the molecule Levene had first analyzed—a nucleic acid.



Above, Jacques Loeb. *Below*, Tobacco mosaic virus.

1901–1934

The cornerstone of Founder's Hall, which housed The Rockefeller Institute for Medical Research's first permanent laboratories, was laid on December 3, 1904. The Institute's Board asked

for a building that would be commodious but without frills: its style should "be as simple as is consistent with its present purpose, future additions, and general utility." Founder's Hall was

opened on May 11, 1906. Within its six floors of brick and stone resided three departments that represented the core disciplines of the early institute: chemistry, pathology, and bacteriology.

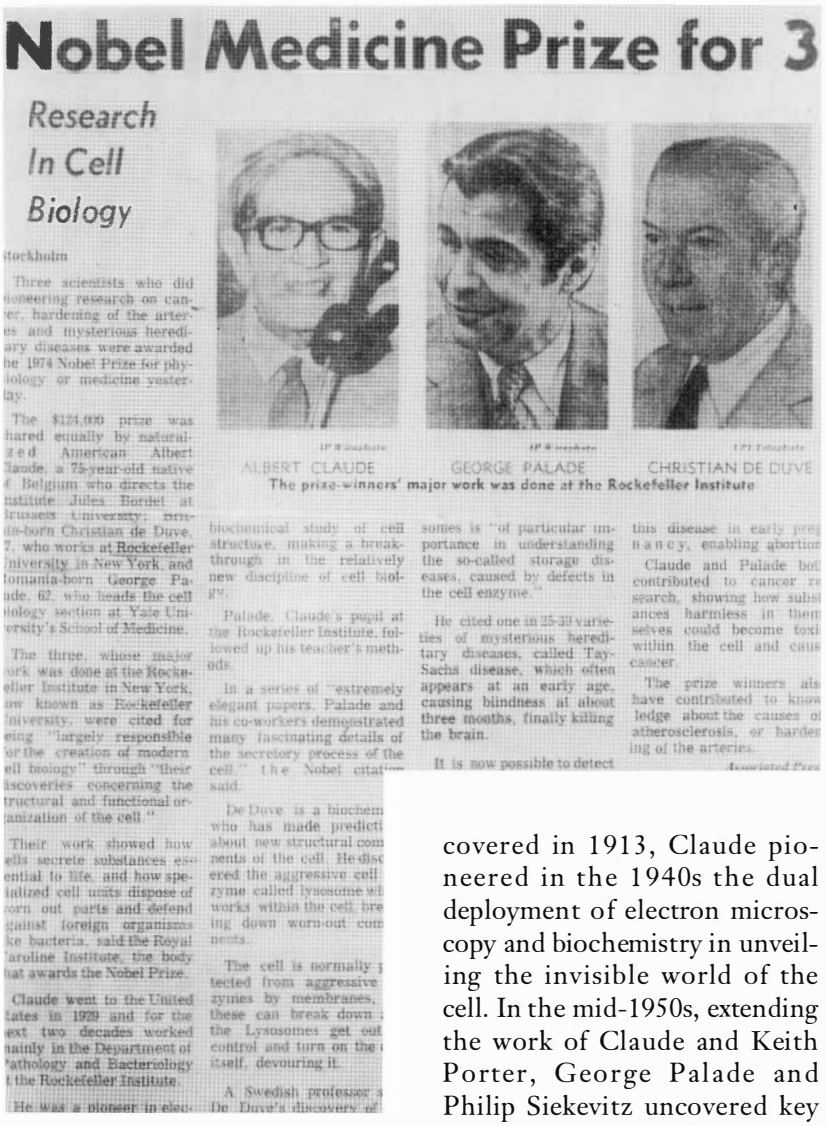
1945–1959

President Detlev W. Bronk, with Board Chairman David Rockefeller, led the institute's evolution into a university. In 1954 Rockefeller was given the power to grant graduate

degrees by the University of the State of New York.

Caspary Hall/Abby Aldrich Rockefeller Hall—a single integrated building despite its dual name—was completed in 1958. It con-

tains the office of the president and other administrators, a small library, the Faculty and Student's Club, a dining room, and guest accommodations. Connected to Caspary is the university's domed auditorium.



Nobel Medicine Prize for 3

Research In Cell Biology

tockholm

Three scientists who did ioneering research on can- er, hardening of the arter- es and mysterious heredi- ary diseases were awarded he 1974 Nobel Prize for phy- iology or medicine yester- lay.

The $124,000 prize was hared equally by naturali- zed American Albert laude, a 75-year-old native f Belgium who directs the nstitute Jules Bordet at russels University; brit- in-born Christian de Duve, 7, who works at Rockefeller niversity in New York, and omania-born George Pa- ade, 62, who heads the cell iology section at Yale Uni- ersity's School of Medicine.

The three, whose major ork was done at the Rocke- eller Institute in New York, ow known as Rockefeller niversity, were cited for eing "largely responsible or the creation of modern ell biology" through "their iscoveries concerning the tructural and functional or- anization of the cell."

Their work showed how ells secrete substances es- ential to life, and how spe- ialized cell units dispose of orn out parts and defend gainst foreign organisms ke bacteria, said the Royal aroline Institute, the body hat awards the Nobel Prize.

Claude went to the United tates in 1929 and for the ext two decades worked ainly in the Department of athology and Bacteriology t the Rockefeller Institute.

He was a pioneer in elec-

ALBERT CLAUDE GEORGE PALADE CHRISTIAN DE DUVE

The prize-winners' major work was done at the Rockefeller Institute

biochemical study of cell structure, making a breakthrough in the relatively new discipline of cell biology.

Palade, Claude's pupil at the Rockefeller Institute, followed up his teacher's methods.

In a series of "extremely elegant papers, Palade and his co-workers demonstrated many fascinating details of the secretory process of the cell," the Nobel citation said.

De Duve is a biochem who has made predicti about new structural com nents of the cell. He disc ered the aggressive cell zyme called lysosome wi works within the cell, bre ing down worn-out com nents.

The cell is normally tected from aggressive zymes by membranes, these can break down the Lysosomes get out control and turn on the itself, devouring it.

A Swedish professor De Duve's discovery of somes is "of particular importance in understanding the so-called storage diseases, caused by defects in the cell enzyme."

He cited one in 25-30 varieties of mysterious hereditary diseases, called Tay-Sachs disease, which often appears at an early age, causing blindness at about three months, finally killing the brain.

It is now possible to detect this disease in early pregnancy, enabling abortion

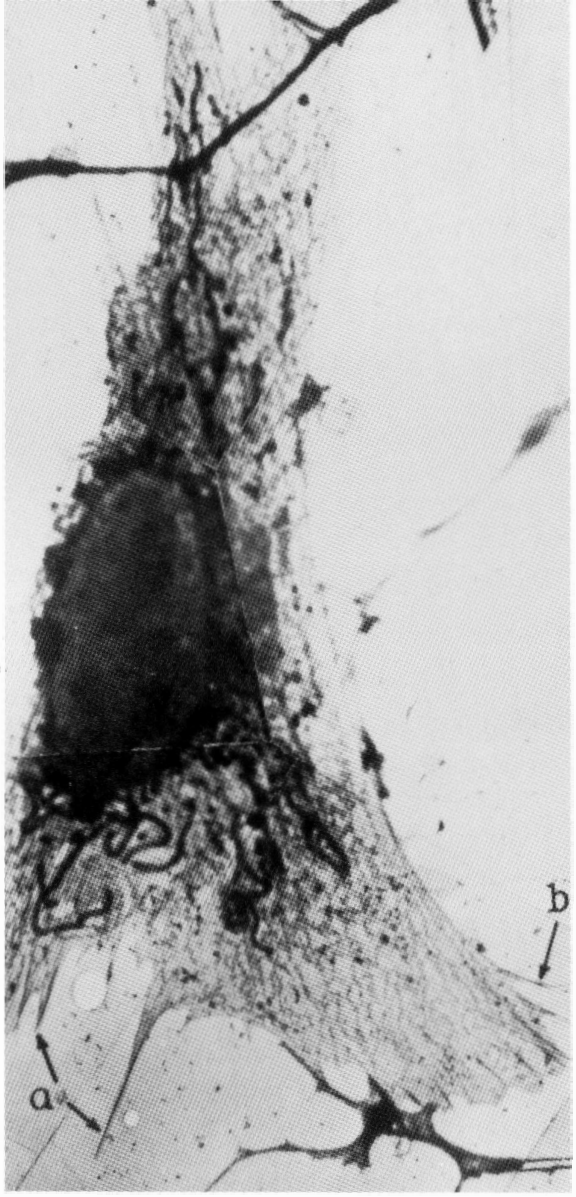
Claude and Palade bot contributed to cancer re search, showing how subst ances harmless in them selves could become toxi within the cell and caus cancer.

The prize winners als have contributed to know ledge about the causes o atherosclerosis, or harden ing of the arteries.

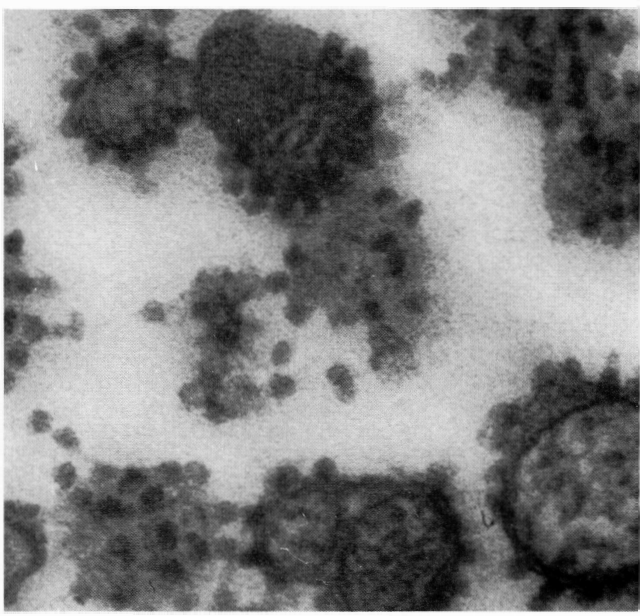
Associated Press

While Avery the microbe hunter discovered that DNA is the stuff genes are made of, another microbe hunter, Albert Claude, led science's entry into the fine structures residing in the cell's gelatinous interior. Trying to isolate the famous cancer-causing virus that Peyton Rous had discovered in 1913, Claude pioneered in the 1940s the dual deployment of electron microscopy and biochemistry in unveiling the invisible world of the cell. In the mid-1950s, extending the work of Claude and Keith Porter, George Palade and Philip Siekevitz uncovered key aspects by which DNA's code is translated into proteins—the cogs, gears, and girders by which cells function.

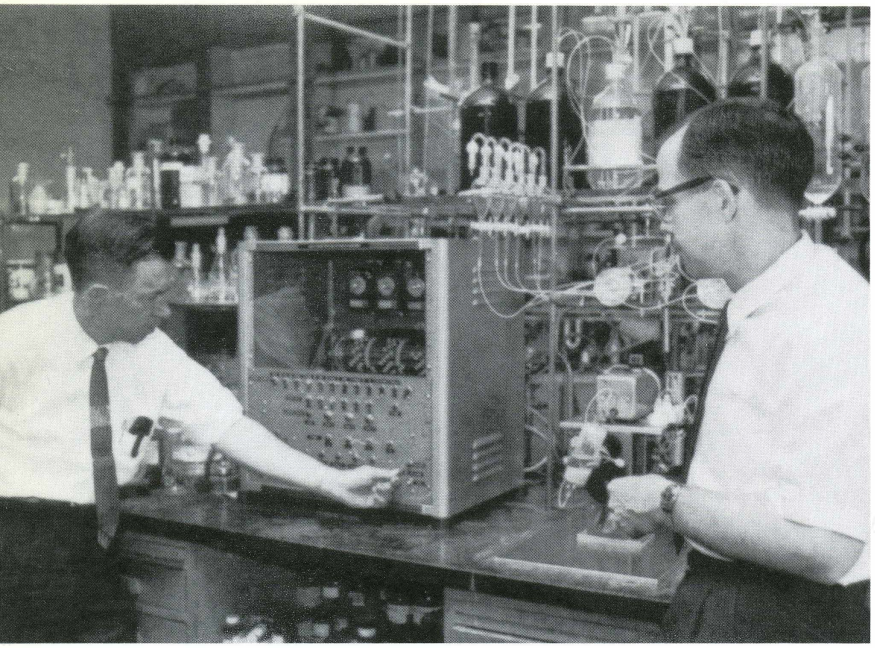
For founding modern cell biology, Claude, Palade, and Christian de Duve shared the 1974 Nobel Prize for Physiology or Medicine.



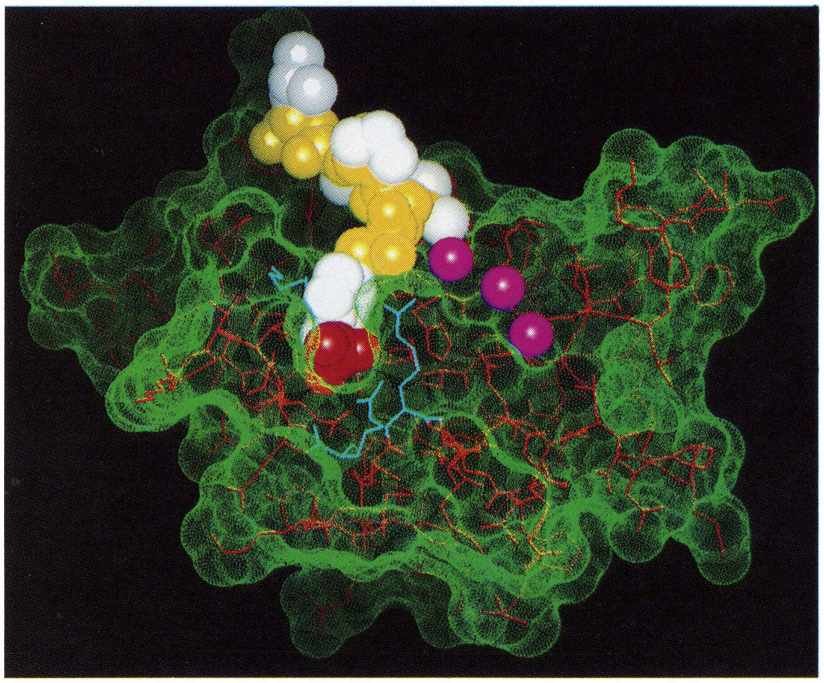
First electron micrograph of a cell.



Ribosomes–factories for making proteins.



Bruce Merrifield and his protein synthesizer.



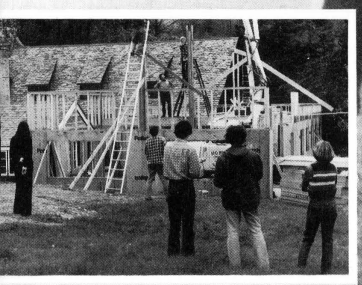
John Kuriyan

SH2 domain coded by Rous sarcoma virus oncogene

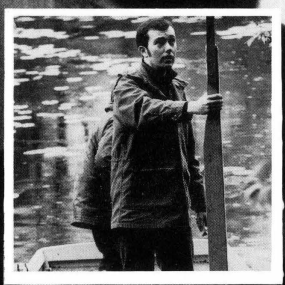
In 1972 Stanford Moore and William H. Stein received the Nobel Prize for their chemical analysis of the protein ribonuclease; and in 1984 Bruce Merrifield won the Prize for artificially synthesizing this same protein. Between 1940 and 1980, Rockefeller scientists voyaged from the center of the cell and its DNA to the vital protein structures DNA encodes.

In addition, the discoveries of Rockefeller's earliest microbe hunters continue to bear fruit. Just this summer, in a seminal collaboration, the labs of four Rockefeller professors—David Baltimore, David Cowburn, Hidesaburo Hanafusa, and John Kuriyan—along with Marilyn Resh of the Memorial Sloan-Kettering Cancer Center revealed the crystal structure of a key cancer-causing protein segment, isolated from the tumor virus Rockefeller scientist Peyton Rous first cultured eighty years ago. Through such work from its current researchers, Rockefeller's glorious past remains very much alive.

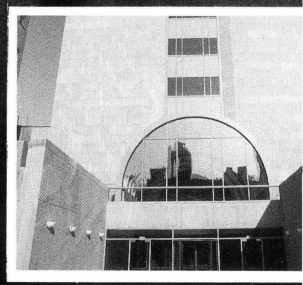
1960–1992



In 1971, the Mary Flagler Cary Charitable Trust donated a tract of land in Millbrook, New York, that now serves as the university's Field Research Center for Ecology and Ethology.



The John D. Rockefeller, Jr. and David Rockefeller Research Building was opened in 1992.



1991–92 Annual Report

From the President

by Torsten Wiesel

Just over a year ago I accepted the responsibility of becoming president of The Rockefeller University. Most of my nearly forty years as a scientist had been devoted to research; my previous administrative experience consisted of serving as chairman of the Harvard Medical School's neurobiology department, as well as a few other small assignments. Yet my transition from the laboratory to the president's office went smoothly, thanks in no small part to the relationships I had formed in my decade on the Rockefeller faculty. The faces on the campus were familiar; many belonged to close colleagues and friends. These personal, trusting relationships, especially with members of the faculty and the trustees, provided a solid foundation for leading this university.

The university's finances have been greatly strengthened, and we have been able to recruit an outstanding senior professor and five superb junior professors.

I have been fortunate: this has been an auspicious period for Rockefeller. The university's finances have been greatly strengthened, and we have been able to recruit an outstanding senior professor and five superb junior professors. The Rockefeller University Hospital has received new leadership and new resources; we have added a sixth faculty search committee, in physics; and we have witnessed the opening of our magnificent new tower, the John D. Rockefeller, Jr. and David Rockefeller Research Building, with 50,000 square feet of laboratory space ready for immediate use, and another 50,000 to be developed on the top six floors.

These successes, of course, did not arrive miraculously in this first short year of my presidency; they were planned, prepared, and begun under the leadership of my predecessors, Joshua Lederberg and David Baltimore, and were nourished by the crucial support of the Howard Hughes Medical Institute. Under Dr. Baltimore's administration, Fred Bohen, our executive vice president, helped to chart a sound course for The Rockefeller University's financial future by setting in place a coordinated program of management and financial reforms. This tougher-minded allocation of the university's resources has continued during my presidency, and it has already resulted in a striking decrease in our operating deficit—the shortfall between income and expenses that has eroded the university's financial strength over the last five years. At the same time, the gifts and pledges given to the university from private sources have increased dramatically, rising from $11.3 million in fiscal 1990–91 to $28.5 million in fiscal 1991–92, and this growth has continued in the months thereafter.

The first decades of this university's existence happily coincided with the development of an entirely new field, molecular biology, which brought together the skills and insights of medical scientists, biologists, chemists, and physicists. Through gene therapy and molecular medicine, molecular biology now offers a remarkable and unprecedented range of diagnostic technologies and treatment possibilities for many of our most-feared diseases: cancer, AIDS, heart disease, and antibiotic-resistant tuberculosis, to name only a few. This new era of molecular medicine was born at The Rockefeller University Hospital, and we continue to allocate resources to revitalize the hospital and keep it at the forefront of this ever-expanding scientific frontier. In February 1992, Zanvil Cohn was appointed Vice President for Medical Affairs; at the same time, Jules Hirsch became the hospital's Physician-in-Chief, and Rudy Leibel, a longtime collaborator with Dr. Hirsch in studying the biological basis of obesity, was named Head of Laboratory. A challenge grant from the Herzog Foundation provided crucial support for our Clinical Scholars Program, which furthers the careers of outstanding physician-scientists. These developments, as well as the efforts of our search committee for medical scientists, will help to maintain the hospital's central place in this essential field.

The university continues to expand its basic core areas of biomedical research. Three members of our faculty have been promoted to Head of Laboratory: the structural biologist David Cowburn, the medical researcher Shigeru Sassa, and the cell biologist Sanford Simon. Three scientists from outside the university have been appointed to our junior faculty: Kenji Adzuma, a molecular geneticist; Yongwon Choi, an immunologist; and Seth Darst, a structural biologist. Our search committees in biochemistry, chemistry, and structural biology, in cell and developmental biology, and in immunology and microbiology continue to seek out outstanding junior and senior faculty to join us at The Rockefeller University. I have always felt that it is important for the university to maintain and develop our small but active chemistry and physics programs, and two visiting committees have concurred with me. The university's core

mission remains biomedical research, but as I mentioned above, the participation of physicists and chemists has been crucial to the revolution in cell and molecular biology, and the presence of physical scientists will remain an essential part of our scientific community.

Most biomedical scientists will agree with me when I say that the next great biological frontier is an increased understanding of the workings of the brain, the most complex organic structure in the known universe. The Rockefeller University is already among the world's foremost research facilities in neuroscience, with top-notch laboratories investigating the basic mechanisms underlying perception, memory, learning, development, and such disorders of the brain as depressive illness, schizophrenia, and Alzheimer's disease. We have a search committee in neurobiology seeking neuroscientists whose work will complement that of our laboratories. The committee's activity has already led to the appointment of two new junior faculty members: Robert Darnell, whose research on the brain sheds light on problems in immunology and cancer, and Joseph Atick, a young physicist who is developing mathematical models of sensory perception. A major initiative of my administration has been the development of a Neuroscience Center, to be housed in our new research building, which will integrate and strengthen the university's efforts in neurobiology. The newest member of our senior faculty—Mary Beth Hatten, a leading developmental neurobiologist—will play a key role as part of this interactive research center.

The creative life of our scientific community requires a strong administrative and support team, and here, too, the past year has brought us great successes. We were able to attract a superb and experienced administrator, Ingrid Reed (who was formerly at Princeton's Woodrow Wilson School), to assume the critical roles of Vice President for Public Affairs and Corporate Secretary. Ingrid serves as liaison among the Board of Trustees, the faculty, and the Office of the President; in addition, she organizes publications, lectures, and special events for general audiences as part of an ever-growing effort to reach out to the larger community of which our university is a part. (Our high school outreach program for science education, which was formally instituted last May, is another critical component of this effort.) Frank Lees, our new Chief Information Officer, comes to us from the State University of New York in Albany. He has already emerged as an important member of the university's staff through his help in integrating the campus's computer and communication-services networks.

In my first year as president, I have discovered how fortunate we are to have a Board of Trustees that is genuinely committed to the scientific and operational principles on which the university was founded. David Rockefeller has served on the board for over fifty years, and the steadfastness of his leadership and support should serve as a model for all other research universities. Richard Furlaud, Chairman of the Board of Trustees, has been a friend, a partner, and a constant source of guidance. I would like to welcome those trustees who have recently joined our board: Edward S. Cooper, D. Ronald Daniel, Evelyn G. Lipper, Ernest Mario, Frederick A. Terry, and Alair Townsend.

One of my great pleasures in this past year has been the opportunity to meet and work with people from every part of the university: trustees, faculty, students, administrators, and support staff. I believe we are all working together in harmony and with a sense of common purpose. As we look toward the future in an ever-changing and increasingly competitive world, we must continue to set our goals high and be guided by the compass of the past. Discoveries at The Rockefeller University have played a crucial role in changing the course of scientific history: they have added to our understanding of nature and of human disease, and have laid the foundations for contemporary molecular medicine. Our task is to build on these achievements and, through our efforts, enhance this noble legacy for those who succeed us.

Above, President Torsten Wiesel talks with students on The Rockefeller University campus.

1991–92 Annual Report

From the Executive Vice President

by Frederick M. Bohen

The Rockefeller University accomplished several major operational objectives during the course of 1991–92, even as presidential leadership passed, without advance planning but nonetheless smoothly and cordially, from Dr. David Baltimore to Dr. Torsten Wiesel. The university measurably strengthened its financial foundations by significantly cutting its operating costs and achieving dramatic advances in private fund-raising for research.

Among the operational highlights of the year, the university:

- Completed construction in June 1992 of a state-of-the-art, twelve-story research facility—the John D. Rockefeller, Jr. and David Rockefeller Research Building. This extraordinary $88 million facility adds 100,000 square feet to the university's productive research space, increasing it by more than 30 percent. The building was completed in less than 24 months, slightly ahead of schedule, and more than $4.5 million under the total budget authorized by the university's trustees.

- Consummated the first combined taxable/tax exempt long-term debt financing undertaken by an institution of higher education in New York State. With the assistance of the New York Dormitory Authority, the university borrowed $50 million in July 1991, to cover its share of the construction costs of the new Rockefeller Research Building, at a blended taxable/tax exempt interest rate of 7.1 percent. Even after this $50 million debt issue, the university's very favorable endowment-debt ratio continues to place it comfortably among the half-dozen research universities in the nation with the strongest balance sheets, and sustains its Triple-A credit rating.

- Purchased and installed a new AT&T-manufactured telephone system which replaced a creaky rented system that had lasted for more than a decade. The university simultaneously recabled the campus with high-capacity fiber-optic wire that provides a backbone network for state-of-the-art information and computing services. These improvements were accomplished through financial arrangements that held future annual amortization of the capital investment involved below the annual cost of the equipment and services that were replaced.

- Invested more than $1.1 million, including a major grant from NIH, to upgrade the heating, ventilation, and air conditioning systems and made other physical plant improvements in the Laboratory Animal Research Center (LARC). These improvements will ensure that the university maintains an outstanding animal care and use program.

In April 1992, Dr. Michael Hayre, the Director of LARC, and his staff, received a three-day reaccreditation review and assessment by The American Association for Accreditation of Laboratory Animal Care (AAALAC). The university's strengthened program and improved animal-based research facility won high marks and received continued full accreditation.

- Modernized research laboratories in the Tower Building; expanded the protein sequencing service facility in the Smith Hall research building.

- Successfully renegotiated with the federal government the university's rate for reimbursement of necessary overhead and research support costs, following extensive independent audits for the years 1986–90 that revealed no material overbilling of the government for unauthorized or inappropriate expenses.

Fiscal year 1991–92 also marked the moment when the university decisively narrowed the gap between overall expenses and income that had widened steadily during the five previous years. As illustrated by the graph that accompanies this report, the shortfall between income and expenses grew from $11.6 million in 1988–89 to $14.0 million in 1989–90, and $15.8 million in 1990–91 before dropping sharply to $8.6 million in 1991–92. This movement toward financial balance is expected to continue in 1992–93.

Also in 1991–92, the university's fund-raising from private sources (organized foundations, individual donors and private corporations) soared to an historic high of $28.5 million in new gifts and pledges. This compared favorably with $9.1 million in 1989–90 and $11.3 million in 1990–91. The dramatic increase in funds from private resources not only helped reduce the annual operating deficit, but enables the university to continue a multi-year process of expanding and strengthening its faculty.

The university's record achievement of $28.5 million in new gifts and pledges during 1991–92:

- resulted in cash receipts of $17.9 million, an increase of $4.9 million, or 38 percent above the level of the previous year;

- added $11.7 million in current and future gifts to strengthen our permanent endowment;

- enabled the university to plan continuing recruitment and expansion of the research faculty by assuring $7.6 million in new gifts that will be received in the years immediately ahead, and will be applied to underwrite the university's plans to expand its research faculty.

The university received several seven-figure leadership gifts which reflected an increased outreach to new friends led by members of the Board of Trustees, The Rockefeller University Council, and the Committee on Trust and Estate Gift Plans:

- a $2 million challenge grant from a current trustee to

members of the RU Council to double the private giving over the next two years by attaining a $10 million goal. During FY92, the first year of the challenge grant period, Council giving reached a record $5 million, representing a doubling from prior years;

- a $1.9 million challenge grant from The Carl J. Herzog Foundation to raise endowment funds for the Clinical Scholars Program at The Rockefeller University Hospital. The grant provides $1 for every $2 contributed to the endowment by other university friends;

- $3.6 million for arthritis and diabetes research from a trust which paid a donor lifetime income and terminated on her death, and a $1 million bequest in support of research on schizophrenia. Both gifts were made possible by the superb efforts of volunteers from the university's Committee on Trust and Estate Gift Plans.

While dramatically stronger fund-raising has been essential to the university's financial turnaround, so, too, has been a determined effort to control and reduce expenses—to make do with less—in all facets of university operations, especially in administration and support services. Initiated by former President David Baltimore, and firmly continued and enforced by President Torsten Wiesel, this "austerity" initiative asked everyone in the Rockefeller community to share in sacrifice by forgoing routine salary increases for academic year 1991–92, to live with the limitations and frustrations of an employment freeze, and to engage cooperatively in office-by-office reviews that would rationally, carefully, but decisively downsize both the scale of functions, activities, and services, and the university's investment to support them. The result of this "austerity" initiative (as illustrated in the table accompanying this report) is that the university's total expenditures of $107 million in 1991–92 dropped $6.5 million below the amount spent in 1990–91.

Within this overall framework of cost limitation and reduction in 1991–92, the university reduced:

- the annual costs of general administration and institutional management from $13.7 million to $12.3 million—an absolute reduction of 10 percent;

- the annual costs of Facilities Management and Planning from $14.9 million to $14.3 million—an absolute reduction of 4 percent;

- the annual costs of auxiliary service functions, particularly residential housing and food services, from $15.9 to $14.9 million — an absolute reduction of 6.3%;

- expenditures for routine capital needs from $4.8 million to $1.2 million—an absolute reduction of 75 percent.

As it faces the scientific challenges and opportunities of the future, the university has the continuing need to contain and cut its overhead and support expenses, to constantly test concepts of improved or enhanced services against the discipline of "affordability," and to focus new administrative expenditures on support needs of the university community that simply must be met. In the new environment of scarcity, controlled management of resources is not merely desirable, but absolutely essential and inescapable. The university's leadership believes it met this demanding standard during 1991–92. It looks to the future with confidence in its capacity to protect and advance the university's scientific quality, while sustaining the recent gains in financial stability and strength.

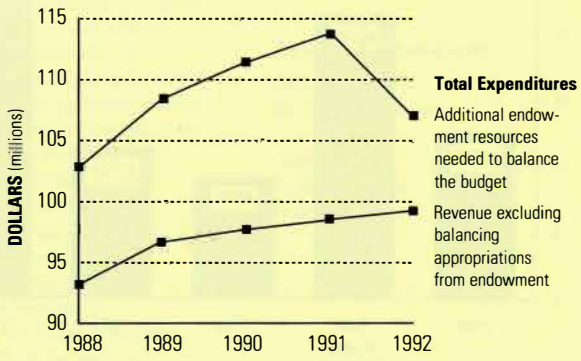
Statement of Expenditures and Resources Utilized
Five Years Ended June 30, 1992
(000's omitted)

	1988	1989	1990	1991	1992
Expenditures					
Research and education	$59,100	61,200	63,600	62,900	63,000
Operations and maintenance of plant	12,300	14,100	14,600	14,900	14,300
General administrative and institutional	10,400	12,000	12,800	13,700	12,300
Auxiliary enterprises	11,100	12,400	14,700	15,900	14,900
Debt service	1,200	1,200	1,300	1,300	1,300
Capital expenditures	8,600	7,700	4,500	4,800	1,200
Total Expenditures	$102,700	108,600	111,500	113,500	107,000
Resources Utilized					
Government grants and contracts	$37,700	41,500	37,100	36,800	38,000
Private gifts grants and contracts	19,500	18,300	20,100	18,700	17,400
*Endowment income	24,200	24,500	25,000	25,100	24,400
Auxiliary enterprises	8,500	9,600	12,200	13,800	14,300
Other sources	3,100	3,100	3,100	3,300	4,300
Total income	$93,000	97,000	97,500	97,700	98,400
Additional endowment resources needed to balance the budget	9,700	11,600	14,000	15,800	8,600
Total Resources Utilized	$102,700	108,600	111,500	113,500	107,000

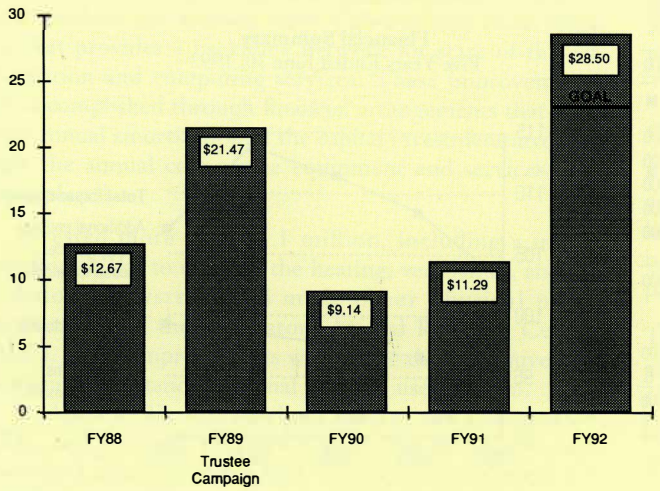
*Endowment income is defined as five percent of a three-year average market value

The University uses annual audited statements. A copy for 1992 can be obtained from the Controller's Office, The Rockefeller University, 1230 York Avenue, New York, NY 10021.

Financial Summary
Five Years Ended June 30, 1992



The Rockefeller University
Development Program
New Gifts and Pledges
Fiscal Years 1988–1992
(in millions)



Pledges and Gifts to Operating Support and Facilities

July 1, 1991–June 30, 1992

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AE Charitable Foundation
Altman Foundation
American Medico-Legal Foundation
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Endnotes

Factors Favorable for the Continued Advance of Science

by Frederick Seitz

Dr. Frederick Seitz, president emeritus of The Rockefeller University and former president of the National Academy of Sciences, considers the future of scientific research in the following excerpt from his new book, The Science Matrix: The Journey, Travails, Triumphs *(New York: Springer-Verlag, 1992).*

INNATE CURIOSITY

The most important factor assuring the continued advance of basic science lies in the combination of earnest curiosity regarding nature and the desire for self-expression that resides in many talented and imaginative young people—deeply ingrained human traits. These traits have been instrumental in the evolution of science from its beginning. Indeed, such curiosity can continue unabated for a lifetime in the well-initiated, not least in the professional scientist, in spite of varying levels of creativity.

Alongside this we now possess, as a result of nearly five centuries of experience, knowledge of the combination of experiment, logical analysis, speculative theory and institutional structure needed to form a solid platform for the advance of science. None of these guarantee the appearance of that flash of inspired insight from a great mind that is occasionally necessary to introduce a major new evolutionary concept in some field. In this respect we will apparently always depend upon the arrival of the appropriate level of genius at the active scene during special periods in the development of a field. Fortunately, such pregnant moments seem to attract the appropriately gifted sooner rather than later. One can only hope that this will continue to be the case indefinitely.

PRACTICAL NEED, NATIONAL PRIDE

Also on the positive side, it seems clear at present that under normal circumstances the advanced industrial societies will have a continuous need for the further infusion of new scientific knowledge for several good reasons. Some of the need will arise from a basic interest in the revelations of science, some from its educational value, and some from issues such as the improvement of public health, industrial competitiveness, defense and what might be called replacement technology—such as finding substitutes for materials in dwindling supply.

Then, too, there is national pride, which has been a significant motivating factor in the past and which will probably be significant as long as we have a diversity of ethnic and cultural groups on an international scale....

GLOBAL ISSUES

Finally, it is likely that there will be global problems that require the encouragement of reasonably coordinated basic as well as applied research at many centers on a worldwide basis. Issues such as concern about the global environment or problems related to health such as cancer and acquired immune deficiency syndrome (AIDS), not to mention as yet unforeseen but inevitable pandemics, will require enlisting scientists from many institutions who are prepared to work at the most basic levels of current understanding. It is, in fact, remarkable that the worldwide epidemic of AIDS occurs just when our ability to achieve understanding of the disease is possible and when detailed scientific investigations can be carried out internationally in a concerted way. This is undoubtedly not the last time that the international scientific community will be called upon in a similar manner.

Then too, there will be less life-threatening scientific adventures which can benefit from international cooperation. The coordinated research programs in the antarctic provide one present-day example. The development of very high resolution astronomical observatories on the moon, including extended arrays which might observe planets on neighboring stars, could provide such an international adventure in the near future.

SEARCH

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The university viewed from Roosevelt Island, across the East River. Visible in center, the new John D. Rockefeller, Jr. and David Rockefeller Building, dedicated last September (see related story, page 23).