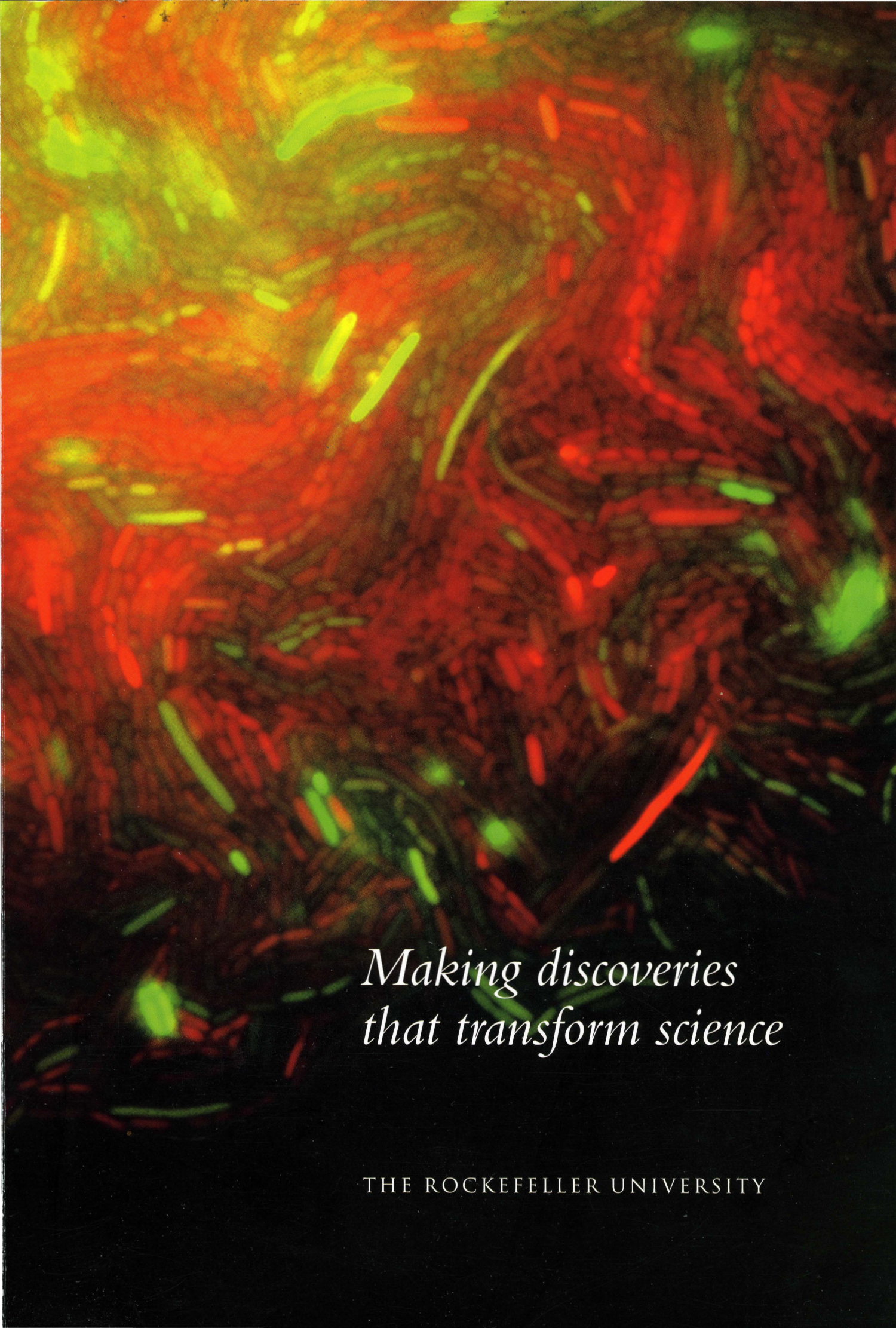
2002

Making Discoveries that Transform Science

The Rockefeller University



Making discoveries that transform science

THE ROCKEFELLER UNIVERSITY

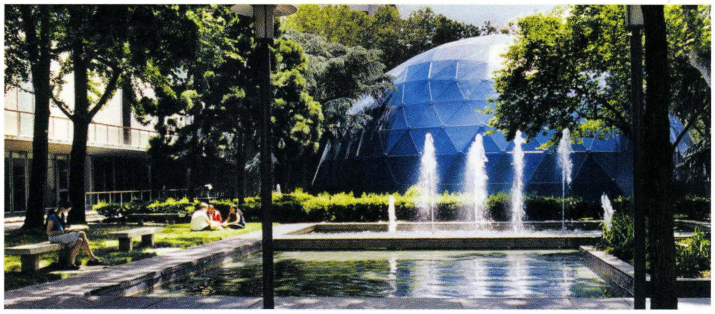
The Rockefeller University, founded by John D. Rockefeller in 1901 as the nation's first institute for medical research, has a unique laboratory-based organizational structure that encourages interdisciplinary research and collaboration.

On the cover

A colony of a special strain of *E. coli* bacteria, containing copies of the "Repressilator" — a synthetic genetic network designed by Stan Leibler, Ph.D., head of the Laboratory of Living Matter and the Gladys T. Perkin Professor at Rockefeller, and Michael Elowitz, Ph.D.

In this artificial system, two different fluorescent proteins, shown here in green and red, are made to oscillate out of phase with one another in a periodic fashion. As the image shows, most cells are either red or green, but not both (i.e., yellow). But at the same time, a great deal of variation is also evident. Is this variation the result of random molecular events, or "noise"? And if so, how can this noise be reconciled with other highly reproducible behaviors exhibited by cells?

The researchers hope to answer these questions next — and to improve our understanding of the rules, or "design principles," underlying the behavior of cells.



WHO WILL LEAD SCIENCE?

"Science is driven by creative individuals. Given room and scope, scientists develop new ways of thinking, new methods and new approaches to attacking problems."

Nobel laureate Torsten Wiesel, M.D.
President Emeritus, Rockefeller University

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Making discoveries that transform science

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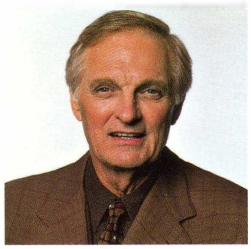
WHAT FACTORS PROMOTE KNOWLEDGE?

A conversation among

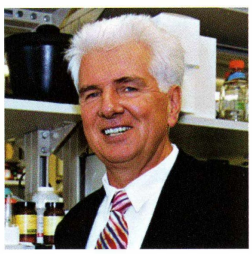
ACTOR AND SCIENCE ENTHUSIAST
Alan Alda

NOBEL LAUREATES
Günter Blobel
Paul Greengard
Torsten Wiesel

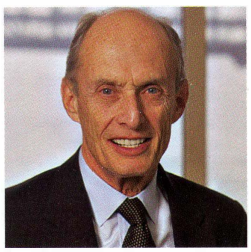
ACTING PRESIDENT
Thomas P. Sakmar



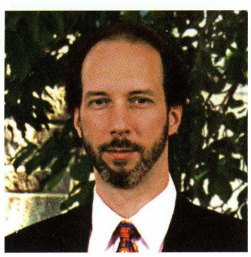
Alan Alda



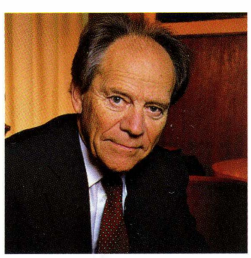
Günter Blobel



Paul Greengard



Thomas P. Sakmar



Torsten Wiesel

The discussion begins with actor Alan Alda engaging the Rockefeller scientists in a conversation about the value of basic science, and the role of creativity and risk taking in research discoveries.

Torsten Wiesel (TW): Most of the money spent since the 1970s as a result of President Nixon's "war on cancer" went into basic molecular biology and genetics, which laid the groundwork for the developments we are going to see in the next few decades.

Alan Alda (AA): Although the goal was to cure cancer, research money went into pure science, which is undirected and goes wherever it's led?

TW: It's not that it went undirected. The way science works, you can't direct it too much because scientists must be free. But the goal of trying to understand the basic mechanisms — cell differentiation, cell growth and how cells become cancerous — is very basic. And that was addressed in the years after the "war on cancer."

AA: What factors promote new knowledge?

TW: The best of science has always been creative, a reason why art and science belong together. They are not 9-to-5 jobs, in which you have certain things you do and then you go home and think about something else. You always think about what you are doing in science. Work is part of you when you are a scientist, as it is for you, Alan, as an actor.

Science is driven by creative individuals who are given room and scope to develop new ways of thinking, new methods, new ways of approaching problems, and to take risks to create new knowledge.

Tom Sakmar (TS): And let's not forget that knowledge is the goal of science, and that information isn't always translated directly into knowledge. Sequencing the human genome was a great advance, but putting that sequence information to practical use requires a much more detailed understanding of basic mechanisms than we now have.

Günter Blobel (GB): For example, it's shocking how little we know about how a cell works, even a primitive bacterial cell. And that will take a long, long time to figure out.

TS: So you can assemble groups of people like the Human Genome Project did and have large collaborative projects to accumulate information, but innovation and creativity come from the initiative of individual scientists.

Paul Greengard (PG): The research of 90 percent of scientists recognized by a Nobel Prize went against the current thinking. If it hadn't, it wouldn't have been novel, and it wouldn't have made a major contribution.

AA: How do you know you're not wasting your time?

PG: Most scientists who contributed creative ideas didn't have any doubts and were happy that so many other scientists didn't think they were right, because this gave them time to develop and test their ideas. While you feel bad when researchers say nasty things about you after you give a speech, it doesn't affect your conviction that you're right.

GB: In my own research, it was nice to realize that others thought I was wrong (*laughter*) because it left me time to work it out myself.

AA: When did you know you were right?

TW: It's very intuitive, actually.

GB: You have to do a few experiments to test your idea. You also have to have the ability to let your idea die if there is the slightest evidence that it is not supported by experiments.

AA: How do you make sense of the human genome data?

GB: We need the help of physicists and mathematicians to mine the vast amount of sequence data of the human genome. For example, Rockefeller University physicist Eric Siggia looks for sequence elements that might be involved in the regulation of transcription.

AA: Which research field is becoming exciting?

TW: Stem cell research is certainly one area in which a lot of progress should occur in the next decade.

GB: We will have to understand how to make from these stem cells the heart cells or cartilage cells or whatever other cells we want to replace in patients. It may take an entire generation of scientists before we can do this.

AA: Will scientists answer these questions with new tools and new ways of calculating?

PG: The tools today are enormously more powerful than they were 10 years ago. Rockefeller has made tremendous contributions in methodologies — in electron microscopy, for example. This drives the research. There's an old German saying: "Die Methode ist alles," or "methods, tools are everything." Incredible discoveries are going to be made just by this knocking out and removing one gene after another and finding out what they do.

TW: Industry is moving very powerfully, interacting with academic research. For example, genome sequencing became an industrial project, and now proteomics is, with the sequencing and description of proteins. Industry is going to dominate there.

AA: Günter, why are you shaking your head at that?

GB: Proteins are not as simple as DNA. Proteins are very complicated in their interactions and how they are organizing each other in the cell. Companies will be able to do some proteomics, but will never do the more exciting things like what Rod MacKinnon, a scientist at Rockefeller, has achieved in solving the atomic structures of two very important ion channels (*see page 8*).

AA: When he won the Nobel Prize, Günter talked about proteins that carry signals that act like ZIP Codes in a cell. That sounded to me like a laudable, deliberate effort to make clear the research.

GB: I don't think there is any concept that you can't make understandable to the educated lay public. I always tell my students and postdocs — if you can't explain to your grandmother what you are doing, probably you don't understand it yourself properly.

DISCUSSION PANEL

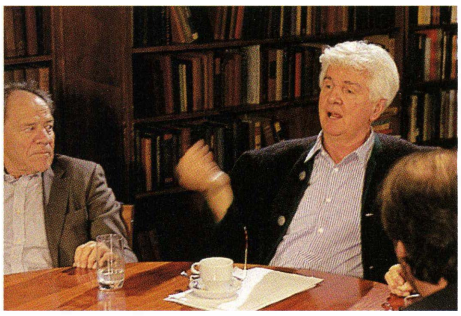
Alan Alda
*Best known for his role in the popular TV series "M*A*S*H," he portrayed Nobel laureate and physicist Richard Feynman in the play "QED." A regular reader of scientific journals, he interviews researchers for the TV program "Scientific American Frontiers."*

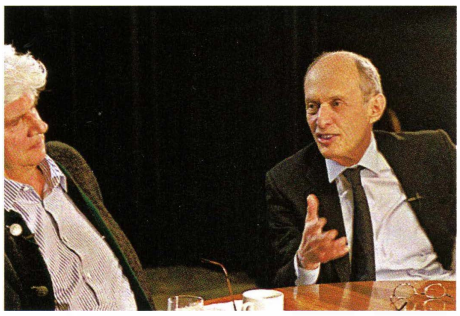
Günter Blobel, M.D., Ph.D.
Head of Laboratory of Cell Biology
John D. Rockefeller Jr. Professor; Investigator, Howard Hughes Medical Institute (HHMI)
Nobel Prize in Physiology or Medicine, 1999

Paul Greengard, Ph.D.
Head of Laboratory of Molecular and Cellular Neuroscience
Vincent Astor Professor
Nobel Prize in Physiology or Medicine, 2000

Thomas P. Sakmar, M.D.
Acting President
Head of Laboratory of Molecular Biology and Biochemistry
Richard M. and Isabel P. Furlaud Professor; Associate Investigator, HHMI

Torsten Wiesel, M.D.
President Emeritus
Vincent and Brooke Astor Professor Emeritus
Nobel Prize in Physiology or Medicine, 1981





TS: The issue of educating young students is extremely important. They have to have a level of understanding of how things have progressed and how things were 20 years ago compared to now, and some perspective that knowledge is not static. In public lectures, I put my own personal history in context — what I was taught in high school, and what I'm learning now. How so many fields that I now use routinely in my own work didn't exist 25 years ago. Science is progressive; knowledge is passed from generation to generation.

"Science is the art of the soluble, as Peter Medawar told us. You make hypotheses that are testable and that can be disproven.

It is difficult to predict what will happen in the next 20 or 30 years. There could be revolutionary developments that will catalyze quantum leaps and provide information that we could not even dream of now."
Günter Blobel

AA: Is the future of science going to be brighter if there is this excommunication between conservative and traditional-thinking scientists and people who are probing into the dark unknown?

PG: No, because science selects for certain personalities — people who want to find truth. If the researcher with the crazy idea seems very smart, the typical approach is "let him or her have a shot at it."

AA: And yet there are these revolutions in the way we view reality. That's true in acting as well. When Brando came in, actors who had thought that they were realistic suddenly realized that they were very stagey. Brando helped introduce a new version of reality.

GB: This happened at Rockefeller with Oswald Avery, who discovered in 1944 that DNA carried genetic material. But many scientists opposed this. Avery died before his research was recognized as one of the most monumental discoveries of the last century.

PG: If another scientist comes along with a new way of thinking, and says that your way is all wrong, and "this is the way it works," it's very upsetting intellectually. So there is a tendency, an emotional response, to resist those new ideas. It's not an admirable response, but that's the reality of being human.

AA: An outsider expects science not to squabble about protecting territory or intuitions.

TW: Scientists are people. Time is your best friend, because if you do good work, even if it's opposed by other scientists, with time it's going to be recognized.

AA: What if the territory changes? How does a research institute deal with a "hot" new area that demands rethinking an old question or an entire field?

GB: Rockefeller doesn't have departments. If a scientist who heads a lab retires, we don't have to continue the lab like most universities continue a department. We can create new laboratories to rapidly address the next questions because we don't have to deal with the burden and boundaries of departments. That's unique to Rockefeller.

AA: A very creative way to organize. Did the Nobel Prize that you each received help your field of science in any way?

PG: It helps the people in the field feel good because the entire field is recognized.

AA: With all that you know about the brain, do you sense that computing will ever approach what the human brain can do?

PG: Oh, much more. The interesting question to me is whether computers will do creative things in the way we do.

AA: What's the thing about wanting to get there first?

TW: It's a matter of seeing for the first time something that nobody knew before and you didn't either. That's a powerful imprinting thing, and with a few conditioning events you are hooked for good to search for new discoveries.

AA: I'm very grateful to have been asked to come talk with you folks, because it's been a delightful afternoon for me.

"Scientific knowledge advances when scientists have concentrated time to focus on their research. It took me three years of investigation to report any results. That wouldn't be possible in most universities."

Bruce Merrifield, Ph.D.
John D. Rockefeller Jr. Professor Emeritus
Nobel Prize in Physiology or Medicine, 1984

The art of the soluble

Rockefeller University empowers its stellar faculty with the time, freedom and resources to follow the science wherever it takes them. Where is it taking them?

The following pages spotlight pathbreaking research of a few of the university's 75 major laboratories.

RODERICK MACKINNON
John D. Rockefeller Jr. Professor, HHMI investigator

Seeing proteins' beauty and function in their form

"Imagine you want to wiggle your finger," says Roderick MacKinnon, M.D., slowly moving a finger of his right hand to illustrate his explanation about the importance of ion channels in body cells.

"Electrical signals, little impulses, go all the way from your brain down the long extended nerve fibers to induce the contraction of the muscles in your finger.

"The same sorts of electrical signals allow me to move and breathe, my heart to beat and for all of us to have all the thoughts that we have," he continues. "Those impulses come from ions moving across the cell membrane."

Because so many life-sustaining functions begin with ions crossing membranes of cells, MacKinnon conducts his research there too. He has solved the structure of the potassium ion channel and a chloride ion channel. Without detailed images of these channels, researchers cannot begin to understand how even the transmission of nerve impulses actually works, and how it malfunctions, contributing to health disorders and drug side effects.

When MacKinnon decided to "solve" the structure of the potassium ion channel, some scientists cautioned him to reconsider. After all, many others had spent years and had failed to visualize this specialized protein, a gatekeeper as well as a gateway for potassium ions.

Ignoring the skeptics, MacKinnon persevered — and succeeded in solving the structure of the potassium ion channel in 1998, only two years after joining The Rockefeller University.

When MacKinnon and his colleagues reported this research in *Science*, its editors illustrated the cover of that issue with a three-dimensional, high-resolution image of the potassium channel. *Science* later declared the study one of the year's "breakthroughs."

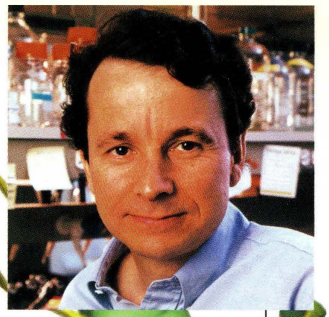
Subsequent research revealed the channel's inner characteristics, homing in on viewing the atomic-scale parts of the channel and understanding better how the structure forms mechanistic features: in effect, learning how function and form are intertwined in the channel's design.

In 2002, in a remarkable follow-up to their potassium ion channel research, and this time featured on the cover of *Nature*, MacKinnon and his colleagues published the structure of yet another channel — a chloride channel. A distinctive hourglass shape, seen for the first time in MacKinnon and colleagues' research, defines the chloride channel, and provides a striking contrast to the pyramid-shaped cavity of the potassium ion channel.

To visualize the structures of these ion channels, MacKinnon's lab uses X-ray crystallography, a multi-step process resulting in a diffraction pattern from a crystal, which is then rendered as a three-dimensional picture. The result offers literally an atom-for-atom image of the ion channels in question — a view of a beautiful evolutionary solution to the problem of moving things across solid membranes.

That nature could come up with something so ingenious is one of the breathtaking marvels of basic research, and exemplifies why MacKinnon and many of his colleagues and students at Rockefeller undertake their work — for the sheer joy of discovery.

When then President Torsten Wiesel, M.D., asked him to join the university's faculty, MacKinnon says, "Rockefeller told me, in essence, that they like scientists who take risks and they were willing to take me on in that attempt. It is rare that an institution can offer that kind of support."



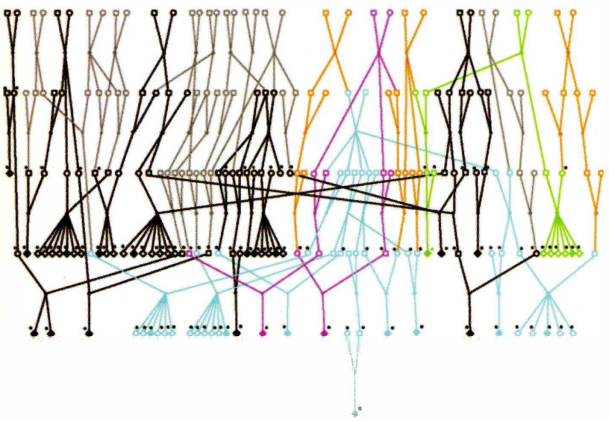
A protein has a sophisticated architectural plan created by nature. Solving protein structures — visualizing their shapes — is an ongoing, and important, activity of basic science researchers.

In addition to their canny beauty, protein structures provide us with an understanding of the process of life. Each protein's shape corresponds with its function, whether it is to "shake hands" with other proteins, or to serve as a passage for small molecules in the body moving from one place to another. Pictured here, the structure of a chloride ion channel, a specialized protein, shows that it permits two streams of chloride ions (shown in red) to flow through its center, moving tens of thousands of ions per second from one side of a cell wall to the other.

For an interactive illustration of an ion channel, visit www.rockefeller.edu/discovery.

MARIA KARAYIORGOU

Genetic clues to schizophrenia



The chart above is one of the research tools that help Maria Karayiorgou study the inheritance of genes that confer susceptibility to schizophrenia. Charts — also called pedigrees — show family members' relationships to each other. This pedigree links together 27 schizophrenic patients from the Micronesian island of Kosrae.

Maria Karayiorgou, M.D., heads one of the few laboratories in the world that searches for the genetic causes of schizophrenia by looking at people with the disease before studying lab animals.

"It's the other way around in most labs," says Karayiorgou, head of The Rockefeller University's Laboratory of Human Neurogenetics. "All of our hypotheses and studies begin with human patients."

Her unique approach has led to the identification of several genetic mutations that may underlie schizophrenia — as well as to possible clues about how to better diagnose and treat this disease.

Afflicting two million Americans, schizophrenia is characterized by disordered thinking and deficits in emotional and social behavior. Like heart disease and diabetes, it is triggered by multiple genes whose activity patterns in specific body cells change, often in reaction to one or more unknown environmental influences.

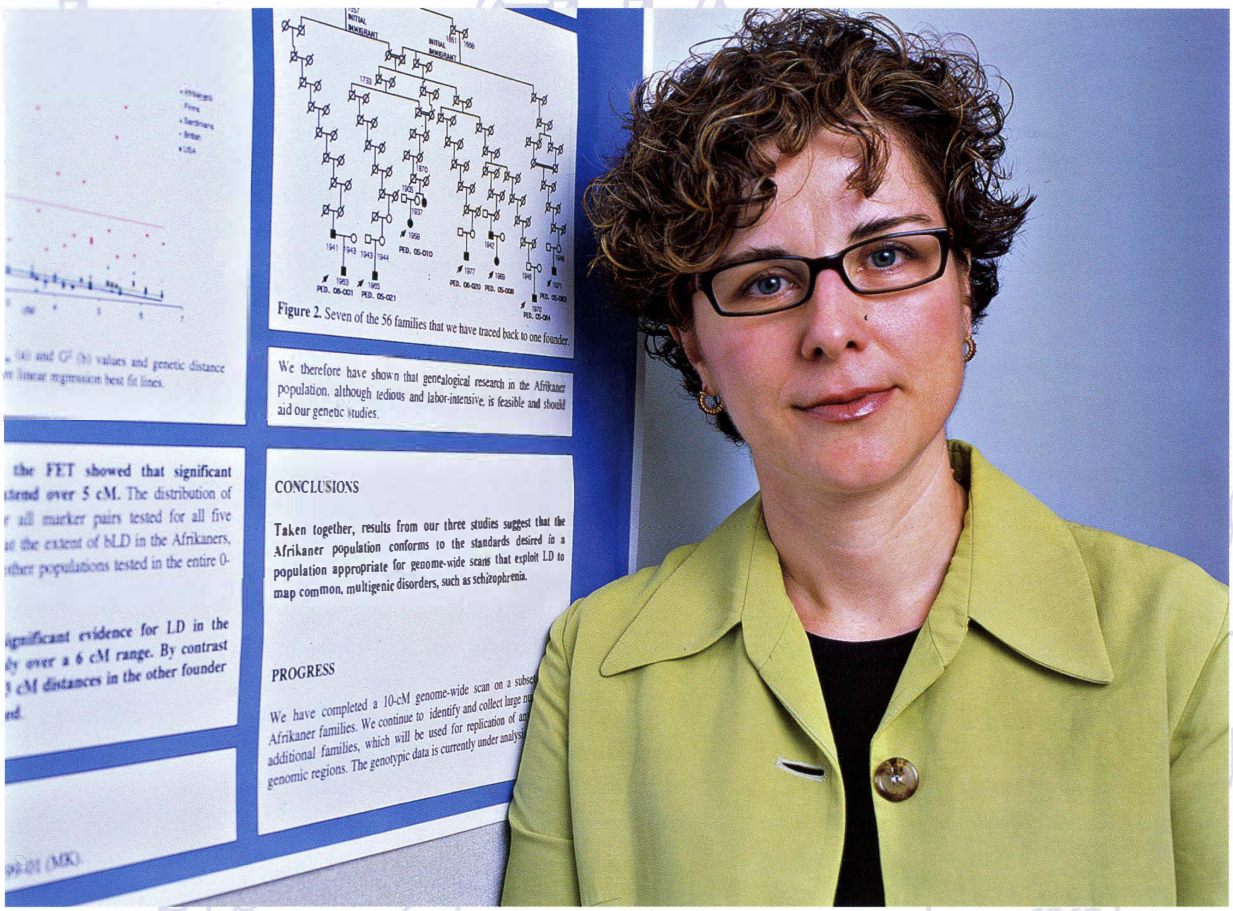
Before Karayiorgou joined Rockefeller in 1996, her search for the identity of these genes led her to a small region of human chromosome 22. This particular patch of DNA, she discovered, was lacking, or "microdeleted," in people with schizophrenia: of the 100 unrelated people with the disease whom she studied, all possessed these microdeletions, while all 200 healthy "control" subjects did not.

At Rockefeller, she and other researchers created the first animal model of schizophrenia by deleting or "knocking out" a gene called *PRODH*. It codes for an enzyme that regulates levels of the amino acid proline, a crucial brain chemical required for proper functioning of neurons. Mice lacking this gene possess a hallmark of human schizophrenia: inability to filter the multitude of sensory inputs, such as sounds, to focus on only one stimulus at a time.

Karayiorgou continues to explore chromosome 22. Recently she and collaborators published a systematic study using DNA from three independent populations: children with childhood-onset schizophrenia, and adult North Americans and South African Afrikaners with schizophrenia. Of the 13 genes studied, two conferred susceptibility to schizophrenia — one of which turned out to be *PRODH*.

"This was an interesting finding because the particular pathway in which *PRODH* is involved is largely undescribed," says Karayiorgou. "It is a novel pathway that will open up several different avenues for new drug development."

Through this pedigree, Maria Karayiorgou's research team traced to one person – or founder – seven of the 56 South African Afrikaner families whom the scientists are studying as part of their research on the genetics of schizophrenia.



Female ○

Males □

Deceased Female ⌀

Deceased Male ▯

Filled symbol shows a family member affected by schizophrenia.

ELAINE FUCHS
HHMI investigator

Skin and hair: Means to a genetic end

Skin and hair proteins fascinate Elaine Fuchs, Ph.D., who heads the university's Laboratory of Mammalian Cell Biology and Development.

From proteins that act like glue to hold together skin to those that form a tough outer barrier to keep harmful pathogens out and essential fluids in the body, Fuchs's research goal is the same: understand how skin proteins function at the level of the cell. While unraveling the secrets of our body's largest organ, she finds clues to the genetic origins of skin diseases, including cancer.

Fuchs is addressing one of today's crucial biological questions: "What are the amazing properties of stem cells of the body that enable them to develop into tissues and organs?"

Her lab studies how skin stem cells are able to divide and churn out skin cells in a Petri dish, a process used to treat burn victims. "If we understand enough about the biology of skin stem cells, and how they can make both hair and skin, will we be able in the future to coax stem cells of the skin or hair into becoming something that they normally would not become, such as a blood vessel to the heart, neurons for the brain, or pancreatic islet cells?" she asks.

These tissues can be severely damaged by, respectively, heart attack, Alzheimer's and diabetes. If skin stem cells can be persuaded to become other tissues, they could be the basis for new treatments.

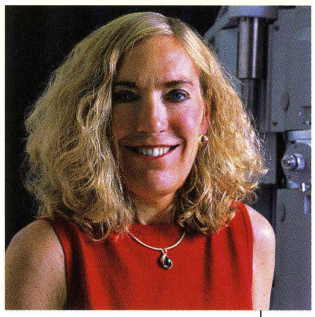
Scientists must first thoroughly understand normal stem cells. "There is much promise for stem cells in revolutionizing medicine, but there is so much we must first learn about stem cells before we can reach the stage of even knowing whether this might be possible," she points out.

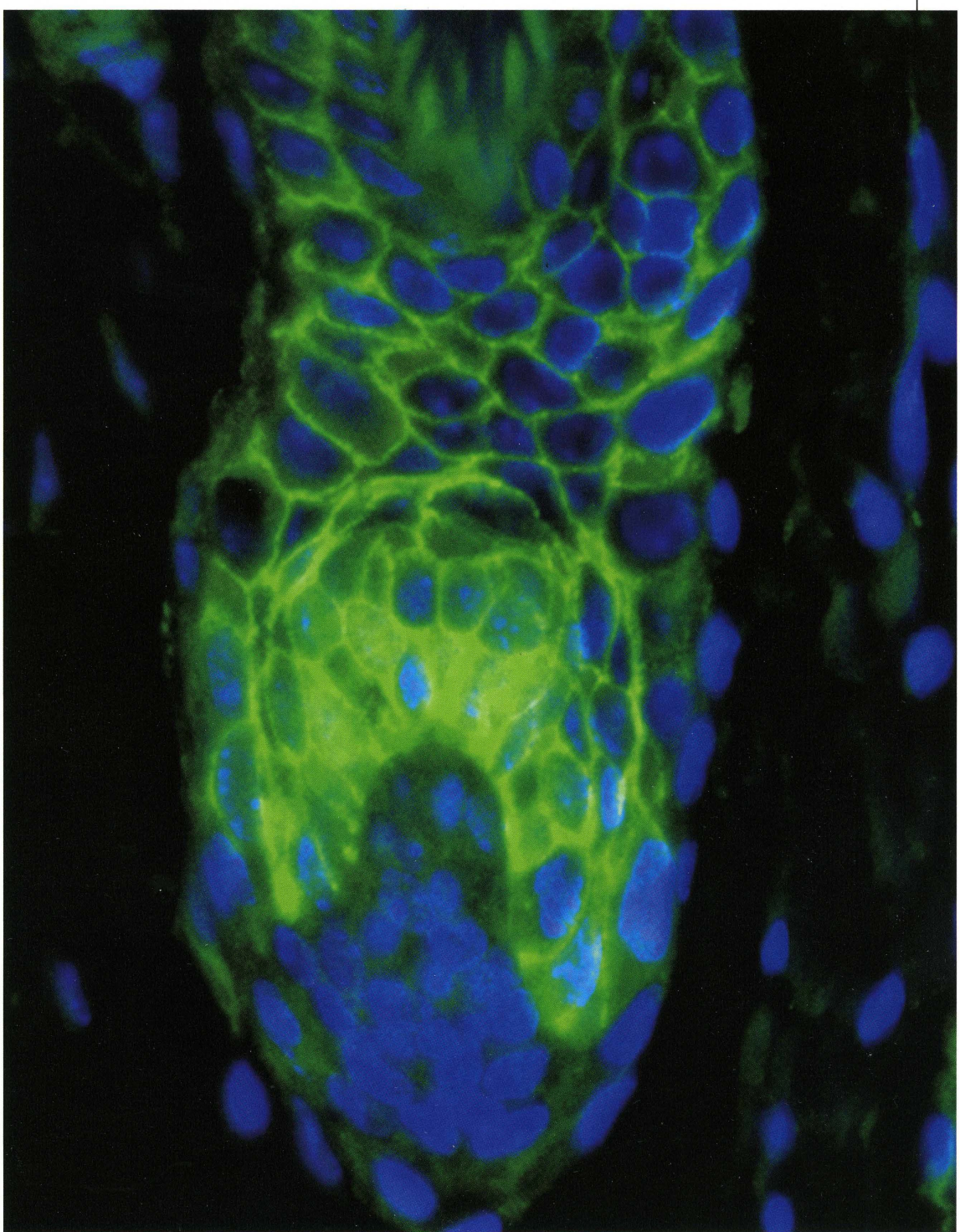
Unlike other stem cells, skin stem cells can be cultured easily in the lab. With these lab cultures, Fuchs and her research team study stem cells and learn about how they choose between making skin epidermis or making hair. Employing modern molecular biology techniques, the scientists trick stem cells into making one choice — for example, to become hair. The scientists test their findings by introducing small mutations in specific skin genes in laboratory mice. More often than not, this key step has guided them to the genetic bases of human skin disorders.

Fuchs's lab has determined the genetic basis of a type of skin tumor that affects the scalp. The lab hopes to understand the genetics of squamous and basal cell carcinomas, the most common types of human cancers in the world. "Because of their extraordinary self-regenerating properties, stem cells, when gone awry, are the likely cause of many if not most types of human cancers," says Fuchs.

While her goal is to unravel the biology of normal cells, not the causes of skin diseases, Fuchs's results exemplify the unexpected benefits of basic research to medicine as well as science.

Skin cells' durability comes from the protein keratin. This protein also makes up the bulk of hair cells. To switch on hair keratin genes and turn cells into keratin factories, hair precursor cells need a signal to tell them to make a transcription factor between beta-catenin and a partner protein. The hair follicle at right is stained with antibodies to reveal the presence of beta-catenin (lime green). In blue are the cells' nuclei. Beta-catenin normally stays at the cells' borders, but the hair precursor cells (at base) have received their signal and begun to move with their partners to the nucleus.





JAN BRESLOW
Frederick Henry Leonhardt Professor

JEFFREY FRIEDMAN
Marilyn M. Simpson Professor, HHMI investigator

MARKUS STOFFEL
Robert and Harriet Heilbrunn Professor

"Syndrome X" genetics on island of Kosrae

The cluster of disorders known as "Syndrome X" is relatively unfamiliar to the public. It is not a new disease, but a new name for a collection of health problems — obesity, diabetes, high blood pressure and high blood cholesterol. Tens of millions of people have one or more of these four disorders.

Because all four conditions simultaneously can affect the same individual or many family members, a common set of flawed genes may trigger the syndrome. To look for a possible common thread in all four, and to find the genetic roots of each disease, Rockefeller University laboratories that specialize in research on obesity, diabetes, hypertension and heart disease are jointly conducting research on Syndrome X.

Their partner is the Department of Health on the Pacific island of Kosrae in Micronesia, about 5,400 miles from Los Angeles.

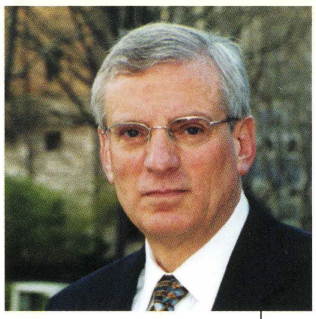
The Rockefeller scientists have turned to this remote population of over 3,000 people for two reasons. One, most Kosraeans can trace their heritage to a relatively small "founder" population of about 50 people who came from Polynesia about 1,000 years ago. Later, in the mid- to late-19th century, Caucasian whalers visited and in many cases settled on the island, and so today many Kosraeans can trace their ancestry to both groups.

The second reason the Kosraeans are ideal for studies of Syndrome X involves the more recent "westernization" of their lifestyles. For most of their thousand-year history, Kosraeans were active. They ate native foods and were reported to be relatively lean. But in the years following World War II, most began leading a sedentary lifestyle while eating foods with high salt and fat contents. Subsequently, a disproportionate percentage of people on the island have developed one or more conditions associated with Syndrome X.

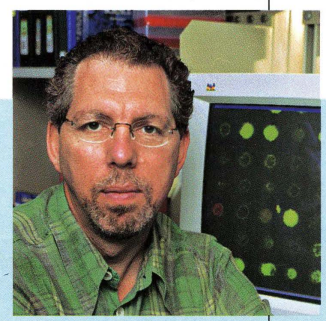
By analyzing the genetic inheritance patterns of the entire Kosraean population, Rockefeller scientists Jan Breslow, M.D., Jeffrey Friedman, M.D., Ph.D., and Markus Stoffel, M.D., Ph.D., hope to solve the ongoing mystery of why some people develop these diseases, while others with the same lifestyle do not.

They have conducted a comprehensive epidemiological and genetics study involving over 90 percent of the adult population — or 2,188 men and women — on Kosrae. For each Syndrome X disorder, Friedman and his Rockefeller colleagues are scrutinizing DNA samples provided by volunteers in Kosrae to identify genes involved in each disease and to verify previous findings of candidate genes from their research with lab animal models or human patients in the United States.

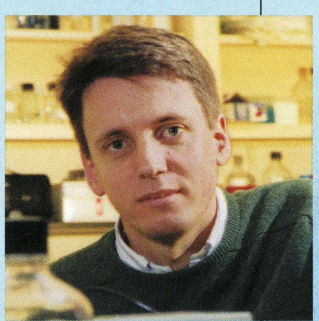
Blood samples were provided willingly, because Kosraeans want to understand why they are so vulnerable to the Syndrome X disorders. "People on the island should benefit from this study because they have become more aware of these health problems," explains Friedman, director of the Starr Center for Human Genetics at Rockefeller. "This awareness is a starting point for prevention as well as treatment."



Heart disease
Jan Breslow



Obesity
Jeffrey Friedman

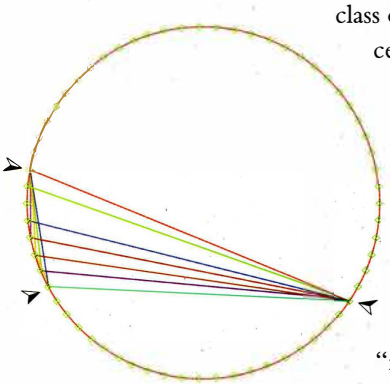


Diabetes
Markus Stoffel

The island of Kosrae

TERRY GAASTERLAND

Theater of the cell



Genes were biology's command performers during the last decade of the 20th century. We expected their monologues to tell us much about life. Today, genes are but one class of actors in the theater of the cell. Other leading parts go to proteins and complexes that become active when genes, or groups of genes, tell them to do so.

Terry Gaasterland, Ph.D., has the singular qualifications to help us understand these actors' "motivations," revealing their mechanisms of communication and transit within the cell.

Gaasterland's tools for studying genes and other molecular actors are computers, not pipettes or Petri dishes.

"I examine data generated by gene sequencing labs all over the world," says the head of Rockefeller's Laboratory of Computational Genomics. "I knit the data together with gene expression data and other sources to form a picture of the biological systems inherent in all organisms. Whole genomes, or the maps of all genes for organisms like human, fly and mouse, have given us much more information to work with."

New ways of visualizing information come with the new territory of computational genomics. Gaasterland devised the above "ball of yarn" system that depicts genes' interactions with one another when they are expressed, or turned on. Here, several genes in the bacteria Vibrio cholera *interact when substances necessary for the organism's metabolism are present. All the points along the circle's circumference represent genes. Arrows indicate genes consistently co-expressed — in this case, during metabolism.*

This information helps scientists identify families and homologues of proteins and their structures.

Proteins, molecules scripted and regulated by genes, are the essence of cellular life. They're the workhorses that send and receive signals, bind with receptors and meet up with other proteins to play important roles in the body. Complexes — groups of proteins or proteins mixed with other cellular products — perform jobs only when they are activated, or turned on.

Why is this important? Major diseases from cancer to cystic fibrosis are based on mistakes in the structure or composition of one or more proteins. Ultimately, knowing more about which genes turn on and off for which disease, and how the corresponding proteins (individually or in key groups) malfunction, allows scientists to see the entire "cast" performing in a disease. This knowledge provides the means for designing new drugs to intervene with the proteins and recast disease-causing players.

As part of their research, Gaasterland and her colleagues build software tools to infer relationships and to model protein systems. These intricate role-playing exercises help scientists understand how disease evolves in the body.

Because scientific interactions at Rockefeller are not restricted by traditional departmental structures, Gaasterland's computational insights are quickly transferred to the university's many biology labs. The fluid boundaries between disciplines help to clarify existing biological research and prompt new measurements to be taken in the laboratory.

A protein's structure often reveals something about its role in the body, depending on the counterparts with which it performs. Terry Gaasterland compares the "readout" of an organism's gene expression data (background) with protein structures (foreground) to learn more about proteins' functions. Her comparisons often suggest new experiments for biologists working with traditional tools.

MADHAV DHODAPKAR
Irene Diamond Assistant Professor

Tailor-making a cancer vaccine for people with multiple myeloma

People with multiple myeloma rarely get well even after undergoing chemotherapy and transplants of stem cells from their own bone marrow. However, a cure to this pernicious blood cancer is being nurtured in the "translational" research of Rockefeller University physician-scientist Madhav Dhodapkar, M.D.

Like several of the university's scientists, Dhodapkar traverses the worlds of patient care and basic research, translating the accomplishments of each to improve public health. Dhodapkar's scientific journey begins and ends with the patient with multiple myeloma, which develops when immune system cells go awry.

From his patients with this disease, Dhodapkar retrieves immune cells, including one called the dendritic cell. The cells are isolated and processed to develop a tumor vaccine specifically tailor-made for each patient.

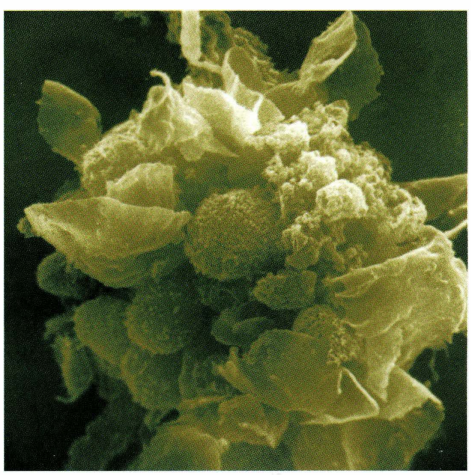
Dendritic cells — discovered by Ralph Steinman, M.D., who is the Henry G. Kunkel Professor at Rockefeller and head of the university's Laboratory of Cellular Physiology and Immunology — normally call into action the "killer T cells" of the body's immune system. To guide killer T cells to their precise targets — which typically are bacteria or viruses that have invaded the body, or cancerous tissue in the body — the dendritic cells engulf some of the target. Dendritic cells then display on their surfaces various proteins or other substances from cancers or foreign bodies.

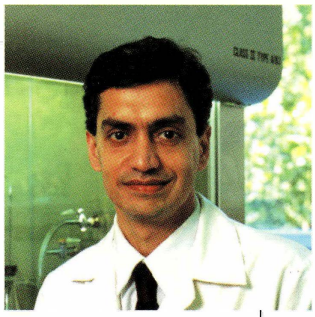
However, because they often escape the attention of the dendritic cells, cancers are not always attacked as they should be by the powerful killer T cells.

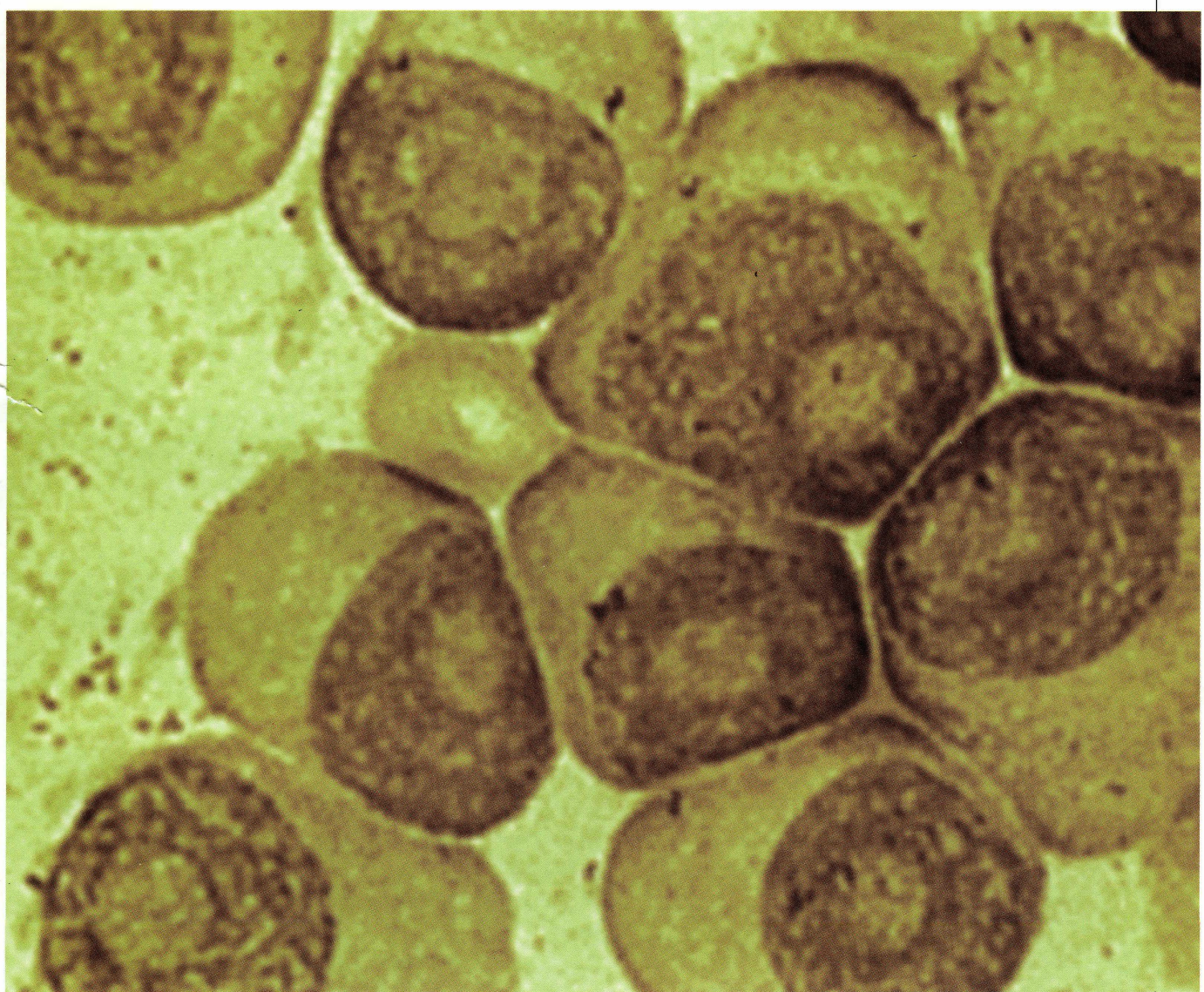
To insure that the dendritic cells recognize the cancer, Dhodapkar's lab primes a sample of these cells from a patient with multiple myeloma. The cells are "treated" with a substance known to activate killer T cells. During carefully monitored clinical research at The Rockefeller University Hospital, patients with multiple myeloma are then injected with the primed dendritic cells.

If over time it proves safe as well as effective in persuading the killer T cells to recognize and destroy multiple myeloma in a large group of patients, this new experimental treatment may become a "cancer vaccine."

Cluster containing dendritic cell and other immune system cells.







Multiple myeloma cells in the blood (above) can't be removed by surgery the way most tumors in the body can, and they're resistant to conventional chemotherapy and radiation. In a novel treatment, Madhav Dhodapkar amplifies patients' own immune cells, including the dendritic cell (opposite), in the lab. He then returns them to the body with a bonus — an experimental cancer drug. Enhancing the immune cells, and using them as a delivery system, forms the basis of a potential new treatment for this and other incurable cancers.

MARY E. HATTEN
Frederick P. Rose Professor

NATHANIEL HEINTZ
HHMI investigator

Building a genetic atlas of the brain

Two Rockefeller scientists are shooting time's arrow forward at the rate of about a decade a month as they "map" the 10,000 genes active in the human brain in record time.

If not for their novel research method, the remainder of this century would be needed to pinpoint when and where in the brain gene expression, or activation, occurs. The "bacterial-transgenic" method used by Nathaniel Heintz, Ph.D., and Mary E. Hatten, Ph.D., accelerates this goal with rapid-fire precision.

"We can analyze up to 500 genes per year, and we've already done so on about 200," says Heintz. "We'll cover all the well-known genes in the first couple of years."

Why create a map of the genes that are active in the brain? "The actual pattern of gene expression can give you a first inference into the function of a gene," Heintz explains.

When a gene is active, it expresses a signal — a messenger molecule to specific cells in the brain. The messenger instructs the cells to manufacture a specific protein. Depending on its genetic recipe, that protein can help form another brain cell or one of the many chemical substances, or neurotransmitters, through which brain cells communicate with each other.

When neurological diseases such as Alzheimer's occur, one or more proteins are misshapen, too abundant or insufficient. Finding and scrutinizing the genes responsible for these protein mistakes provide clues to the origins — and possible treatment — of the disease.

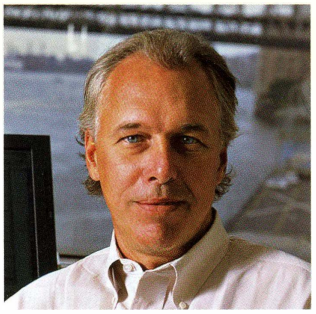
When their National Institutes of Health-supported project is complete, Hatten and Heintz will deliver to the worldwide scientific community a free, unrestricted, comprehensive database on gene expression in the brain.

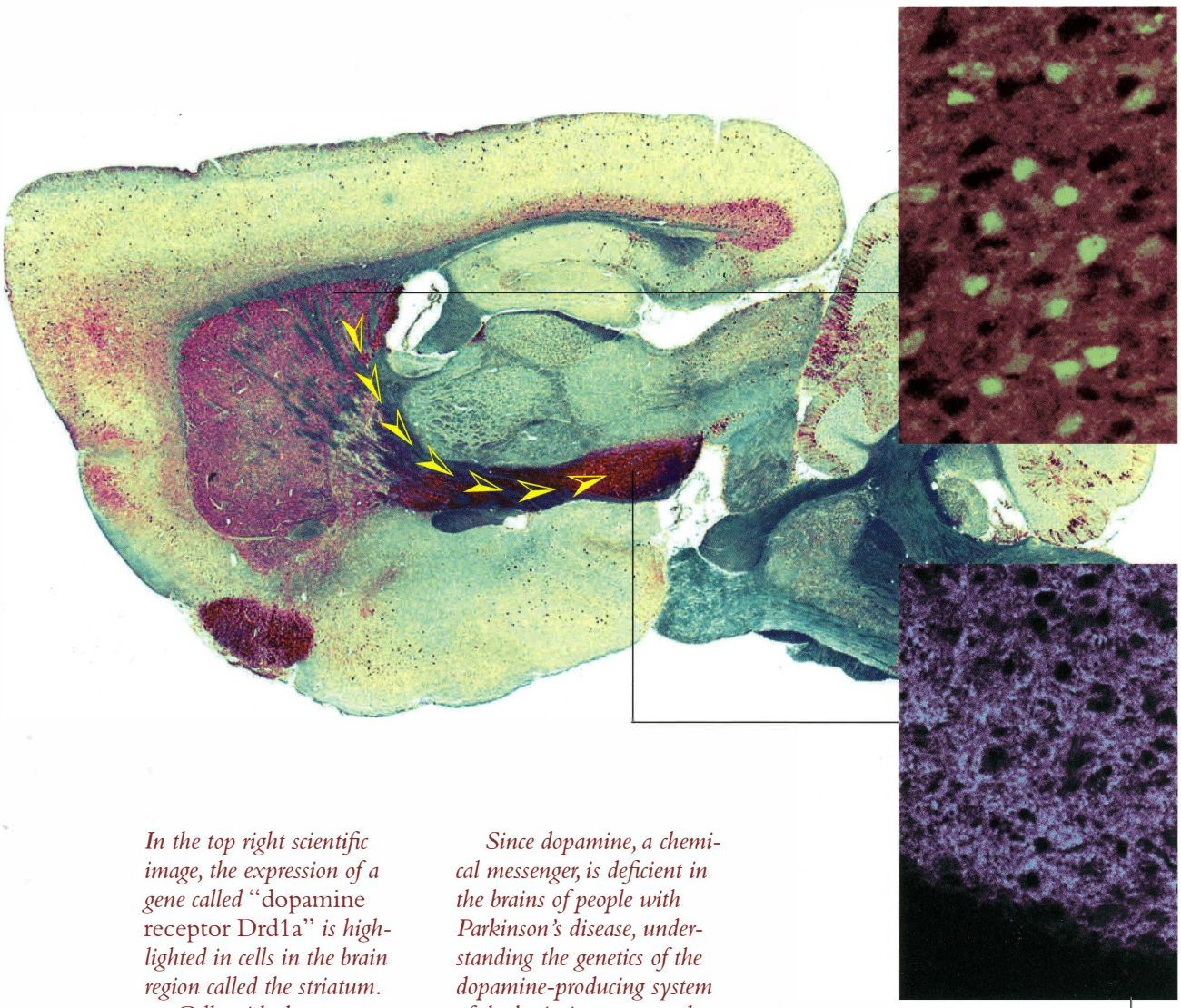
For Hatten and Heintz, both neuroscientists, their genetic atlas recreates for all scientists the experience of sitting down at a microscope and seeing thousands of cells and their corresponding structures. The atlas will benefit neuroscientists in every conceivable basic and clinical research field, because it will give unprecedented levels of insight on neurological development and stroke, Alzheimer's and Parkinson's disease.

"We know this atlas will be important," says Hatten. "Our initial work already has provided us with intriguing new information about cell migration, the specialized movement of cells in the brain, that we never would have found using existing techniques."

Hatten and Heintz have named their ambitious project "GENSAT," for Gene Expression Nervous System Atlas. This acronym is meant to invoke LANDSAT, a satellite system for investigating vast terrain in close detail.

The difference is that Hatten and Heintz's research "topography" is the brain.





In the top right scientific image, the expression of a gene called "dopamine receptor Drd1a" *is highlighted in cells in the brain region called the striatum.*

Cells with these corresponding receptor proteins, which were manufactured as a result of the gene's activation, project fibers (see arrows in large image, above left) to another area of the brain, called the substantia nigra *(detail, lower right).*

Since dopamine, a chemical messenger, is deficient in the brains of people with Parkinson's disease, understanding the genetics of the dopamine-producing system of the brain improves understanding about the origins of this neurological disorder. Mapping the expression, or activity pattern of a single gene, such as Drd1a, *over time reveals the cells associated with that gene and the other cells in the brain with which they interact.*

TOM MUIR

Creating "molecular Legos®" by snapping together natural and synthetic molecules

Tom Muir, Ph.D., brings a different set of tools to the study of biology — those of organic chemistry.

While organic chemists manipulate molecules to create a test tube full of a desired compound, Muir goes one step further: his creations are designed to study precise biological problems in the test tube and the cell.

"Not only can we use these sophisticated approaches to manipulate the structure and function of genes and proteins in the test tube, but we can increasingly do this in living cells or whole animals," says Muir, who heads the Selma and Lawrence Ruben Laboratory of Synthetic Protein Chemistry.

Called "chemical biology," this emerging field allows Muir and other scientists to rapidly ascertain functional information about key biological molecules, including those involved in cancer, Alzheimer's disease and other disorders, and to create systematically novel drugs for the possible treatment of these diseases.

One of the new relatively easy-to-use tools that has emerged from Muir's lab stacks together chunks of proteins in a technique called "expressed protein ligation."

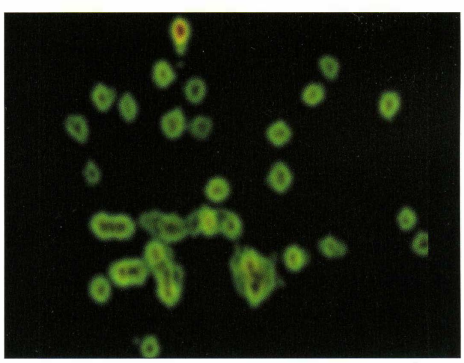
This novel approach — available to all scientists, not just those at The Rockefeller University — provides for the first time a technique to synthesize a full-sized protein, an important tool in understanding any protein's overall function in a cell.

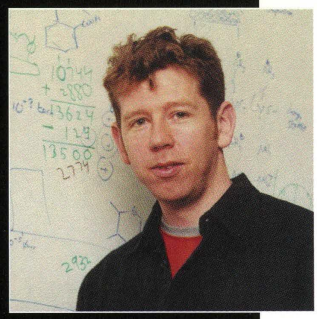
Recently Muir's lab has applied similar protein-linking technology to study protein folding. Newly made proteins — which typically adopt a linear topology, or form, with dangling ends like those of a string — cannot function properly until they fold into the correct three-dimensional shape. Indeed, misfolded proteins are associated with Alzheimer's, cystic fibrosis and "mad cow" disease.

But some proteins adopt a circular topology, leading Muir to ask what effect such an altered form might have on protein folding. Like a true chemist, Muir tackled the problem by artificially linking the two free ends of a protein together into a circle, then observed it fold. He found that the new molecule folded into the same shape as its natural linear form, but more intriguing, it did so more quickly.

"This suggests that topology plays a very important role in protein folding, which is an emerging theme in the protein folding field," says Muir.

Muir's overriding goal, however, is to develop chemical tools that any researcher can use. "After all," he asks, "what good are the tools if only a few people can use them?"





Understanding how the machinery of the cell works can yield important information about biological processes such as tumor growth. Biologists use a technique called nuclear magnetic resonance spectroscopy to observe molecules as they float in solution, using powerful magnetic fields and high-frequency radio waves to probe molecules and advanced computers to interpret the data. But large proteins often limit the amount of information that can be obtained.

Tom Muir's "molecular Legos®" give biologists the tools of chemistry to "label" a region, or domain, of a protein to generate structural information about a particular domain in the context of the whole protein. The background image is a detail of a nuclear magnetic resonance spectrum (left) of a bacterial protein that regulates gene expression.

Translating research into human health

"I like donating my cells to science," explains Susan, a clinical study volunteer at The Maurice R. and Corinne P. Greenberg Hospital of The Rockefeller University.

The first in the nation dedicated to clinical research, the 92-year-old hospital serves as a bridge connecting the university's basic research labs to the world of human health, to people with diseases. People like Susan.

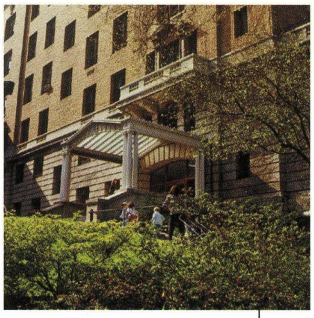
Susan is afflicted with a common autoimmune disorder. Rockefeller physician-scientists' studies of the disease in Susan inspire the direction of many laboratory investigations, and help translate hard-won lab discoveries into potential health care and biomedical research achievements.

The hospital, where paintings by Frank Stella and other renowned artists hang in the hallways and patient rooms, bustles on most days with the activity of physician-scientists, nurses and other health care professionals, and M.D.-Ph.D. students in the top-rated joint program Rockefeller offers with Weill Medical College of Cornell University and Memorial Sloan-Kettering Cancer Center.

On any day, the most important people there are the study participants, all of whom are involved in approved clinical research protocols.

"The patients' altruism is vital to medical progress," says Barry Coller, M.D., David Rockefeller Professor and the hospital's physician-in-chief. "We owe them a great debt and must make their safety our highest priority. Everyone at Rockefeller views this commitment as a sacred trust."

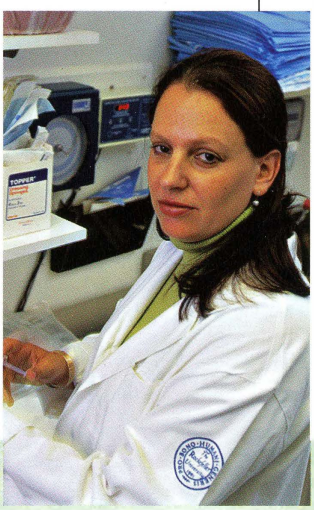
Susan concurs: "I would not volunteer if Rockefeller was not such a supportive environment. The hospital cares for the total person — clinically, mentally and emotionally."

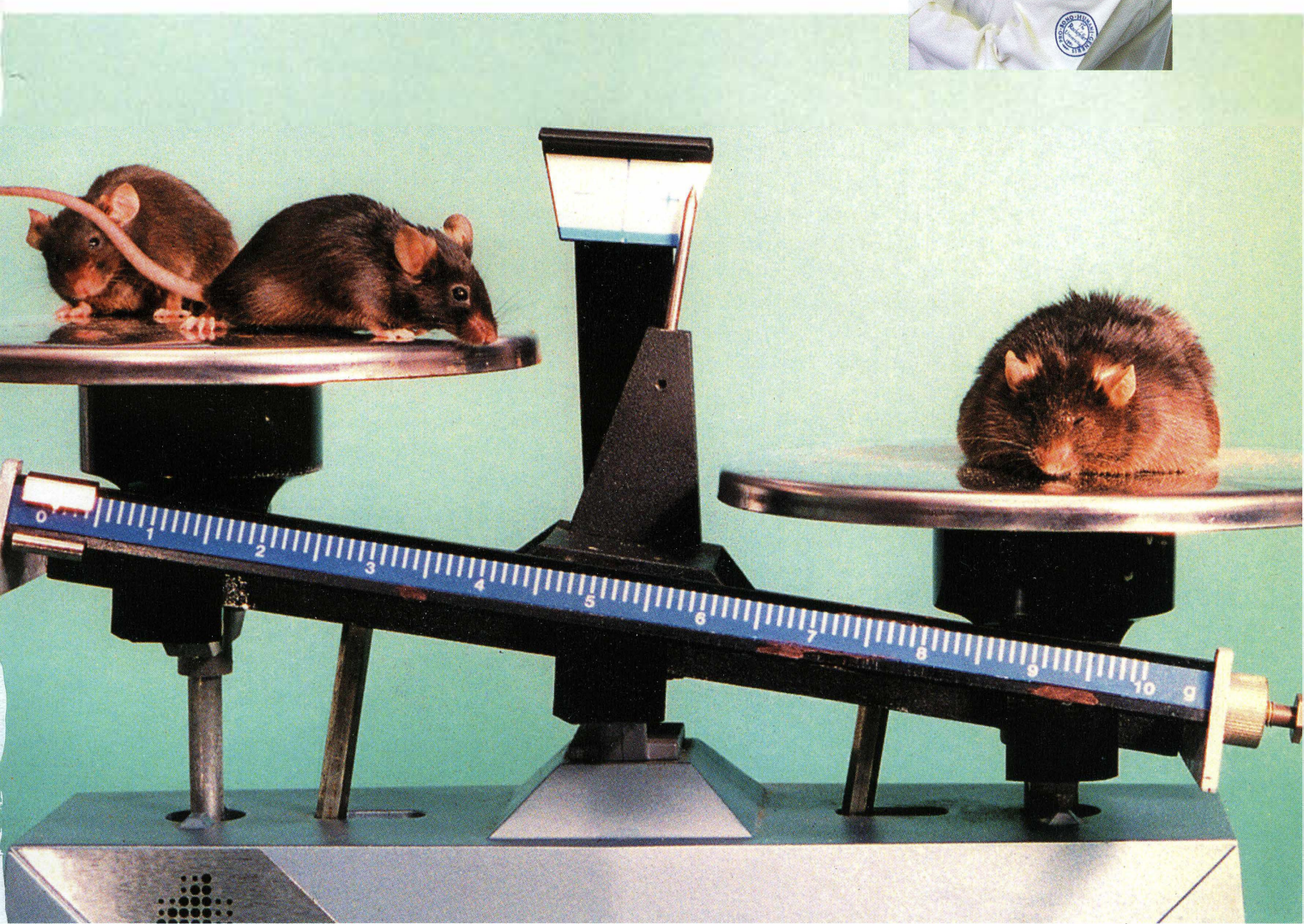


When overweight lab mice or humans lose weight due to dieting, their bodies' metabolism changes. Diet-induced weight loss results in a decline in blood levels of leptin, the protein byproduct of the "obese" (or "ob") gene discovered by Jeffrey Friedman, M.D., Ph.D., at The Rockefeller University.

What other metabolic changes occur in diet-induced weight loss? Will leptin treatments keep the hormone at normal levels in the dieters' bodies and help accelerate weight loss, or lessen some of the unwanted effects of a low-calorie diet?

Since low leptin levels may be a potent stimulus to weight gain, Friedman and Sagit Zolotov, M.D. (right), are evaluating the effects of leptin treatment on overweight women on a low-calorie, healthy diet. This project, one of the "translational research" programs at The Rockefeller University Hospital (above), is the most comprehensive study ever conducted on the metabolic changes that occur in dieting.





Hepatitis C research: Whatever it takes

The body's immune system holds the key to eliminating hepatitis C, the source of a hidden epidemic in the U.S. Locating that key depends on scientists' learning why many people's immune systems fail to mount an effective response to hepatitis C, while others' rise to the viral challenge.

Charles Rice, Ph.D., director of the Center for the Study of Hepatitis C at the university, aims to do "whatever it takes" to combat this illness because of its devastating toll on the people of New York City and around the world.

Only a quarter of the four million people in the United States infected with hepatitis C know they have the virus. The life-threatening liver disease that occurs with infection takes decades to develop, and for those in the final stage of disease, liver transplant remains the only treatment. If more people with the virus were tested and sought treatment, scientists could better understand the immune system's interaction with the virus. Creating a metropolitan center for clinical and basic research advances the research — and aids more patients.

In the three years that Rice has headed the new center, the basic research has blossomed.

"Immunologists are having a heyday now," says Rice. "We know that the immune response in individuals chronically infected with hepatitis C has a strong antibody component, but a very weak cellular component." Figuring out how to boost the cellular component could be an important part of future therapy or vaccination.

The center's basic research focuses intensively on the immune system's white blood cells (T and B cells) that attack and destroy invading microbes.

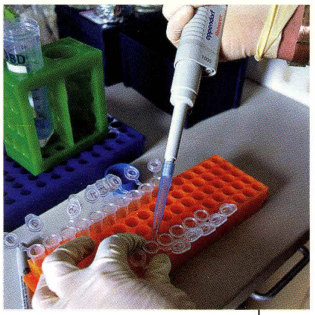
"More people than we thought clear the virus from their system, and we need to understand how they do this," adds Rice. "Having the center's home base in New York City serves the research well: we have a large pool of people receiving clinical care for hepatitis C, as well as a clinically challenging sub-group also infected with HIV. But we'd like to treat, and study, more people."

A new clinical research component of the center supports pediatric sufferers of hepatitis C. "We need to know more about when and how to treat children," says Margaret R. MacDonald, M.D., Ph.D., co-founder of the Center for the Assessment and Treatment of Children Infected with Hepatitis C.

While hepatitis C immunology is yielding clues about the disease, other areas demand intense research attention. "We really need to get the virus's replication cycle going in cell culture," says Rice. "With this next phase of the research worked out, we'll be able to examine many aspects of the virus that we can't understand right now and open new avenues for drug development."

Rice's record demonstrates that he gets results. In 1997, before joining Rockefeller, he led the team that made the first infectious clone for the virus, demonstrating that the hepatitis C virus alone — not one of its brother or sister hepatitis viruses — is sufficient to cause the disease. In 1999, he and his colleagues discovered mutations in the virus that allow it to replicate its genome in cell culture — another milestone in research on the disease.

Charles Rice (right), Maurice R. and Corinne P. Greenberg Professor and director of the Center for the Study of Hepatitis C, and postdoctoral fellow Arash Grakoui study the entire life cycle of the hepatitis C virus.



Learning science by doing science

"At Rockefeller, nobody boxes you in as a scientist," says fourth-year graduate student Tshaka Cunningham, describing the university's uniquely unstructured, highly successful training of students to become leaders and innovators in biomedical science.

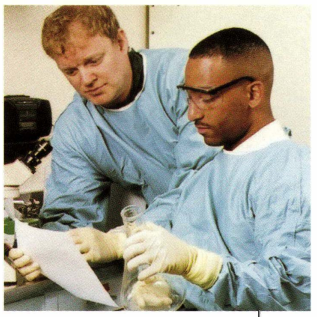
Cunningham, recipient of the university's prestigious David Rockefeller Fellowship in 2002, is learning by "doing science" in one of the world's top AIDS research labs: the Aaron Diamond AIDS Research Center, directed by David Ho, M.D., Irene Diamond Professor at The Rockefeller University.

Students at Rockefeller quickly get into the nuts and bolts of conducting scientific research because coursework is minimal, unlike most other graduate training programs in the life sciences. At Rockefeller, graduate training often is described as an "apprenticeship with a master scientist."

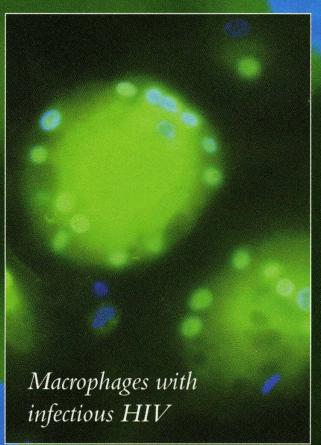
From the master scientist, or mentor, as well as the other researchers in the lab, the student learns a framework for asking the crucial scientific question, designing an experiment to answer the question and interpreting the results.

Cunningham, an apprentice with Mark Muesing, Ph.D., is training for a scientific career in HIV/AIDS research. With his colleagues, Cunningham has identified a possible platform for gene-therapy-based vaccines

"As a Rockefeller graduate student, my mind moves quickly and my hands keep pace in the lab," says the Princeton University graduate. "What's my incentive? In my area of research on HIV/AIDS, 40 million people will potentially benefit if we make a major breakthrough."



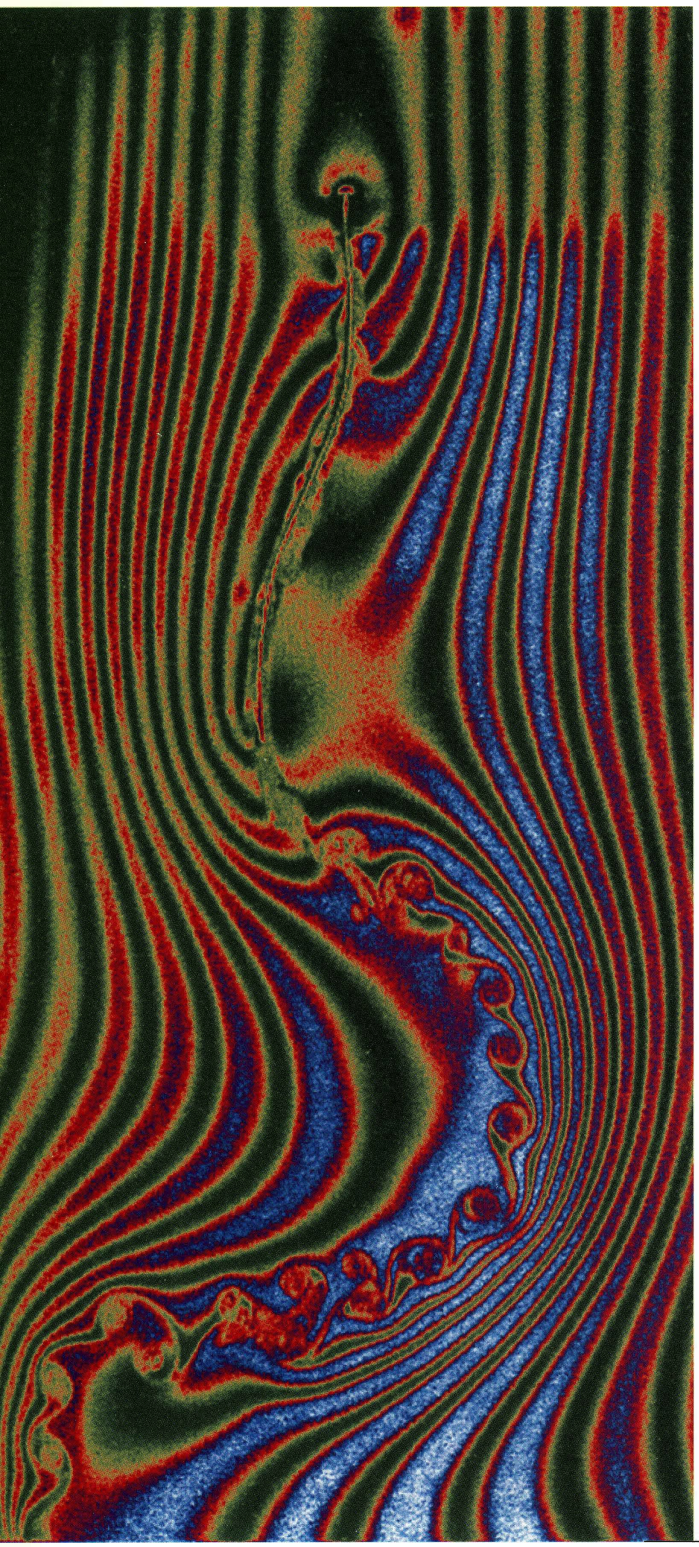
The creation of protease inhibitors in the 1990s changed the treatment arc of HIV infection for the better. But additional treatment options are still needed for people living with HIV/AIDS. A new class of drug, called "integrase inhibitors," looks promising in the laboratory. Integrase inhibitors work by thwarting integration, the crucial phase of HIV's replication in which the virus combines its DNA with human DNA in a cell's nucleus. In tandem with testing the new class of drugs for its preventive effectiveness, Rockefeller graduate fellow Tshaka Cunningham (above right) and Assistant Professor Mark Muesing (above left) must establish what unintegrated, or failed, HIV looks like and how it behaves. To this end they infect macrophage, a type of immune system cell, with a mutant strain of HIV that does not integrate (large image). They compare the characteristics of unintegrated HIV with those of the successful virus, whose ability to spread infection is revealed by luminescent markers on its infectious particles (small image). Green markers appear only after the integration phase of the virus's life cycle occurs. Many of the macrophages in these images contain two nuclei because HIV's "envelope," or coating, causes two regular immune system cells to fuse.



Macrophages with infectious HIV

Macrophages with noninfectious HIV

The laws of living matter



For mathematicians or physicists seeking potential biomedical applications of their highly specialized training, 21st-century "biology provides almost an embarrassment of riches," says Erik van Nimwegen, Ph.D., a postdoctoral fellow at the Center for Studies in Physics and Biology.

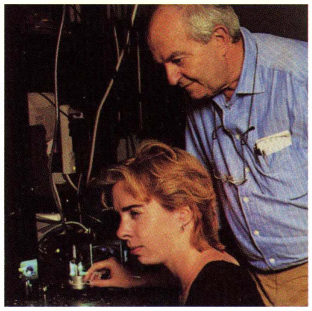
Biology is "like another civilization; the whole way of thinking is very different from physics," adds Tsvi Tlusty, Ph.D., another fellow at the center, presciently established in 1994 at The Rockefeller University.

These and other young physicists and mathematicians study the civilization of biology as part of the university's plan to build more bridges, and more opportunities for collaboration, between the disciplines.

While biologists eagerly clear space at their lab benches — and computers — for mathematicians and computer scientists to help organize and analyze the complex data of the DNA code and the proteins that genes determine, physicists open new avenues for understanding "living matter." Studying how a cell behaves, for example, reveals as much as knowing what it contains. Biology depends more and more on physicists to explain symmetry and change, or stability and instability within living organisms down to single molecules.

Silk and soap settle a century-old flap, and encourage physicists to study turbulence in living organisms.

Here the movements of a silk filament in liquid soap, research by Rockefeller scientist Albert Libchaber in collaboration with several colleagues, reveal the dynamics of how flexible objects move in fluid forces. The group of scientists discovered that, technically, a flag could fly straight rather than constantly flap, given the right conditions. This also applies to understanding how fish swim in water.



One of the center's scientific leaders, Albert Libchaber, Ph.D., the university's Detlev W. Bronk Professor, trained in condensed matter physics and pioneered the field of complexity theory. Libchaber views biology as a model frontier that will help establish new physics and mathematics.

Where some may see physics and mathematical contributions as a form of applied science, Libchaber and his colleagues take an inverse view. Biology offers a universe as vast as the Milky Way, revealing laws undiscovered in other natural systems.

Several years ago, Libchaber began a project to learn more about fluid dynamics. To create a simple version of a "fish swimming" phenomenon, Libchaber, along with his Rockefeller students and postdocs and his colleagues at New York University's Courant Institute of Mathematical Sciences, studied silk filaments in soap film, revealing the four main conditions of an object moving in water or air.

The resulting publication in *Nature* revealed for the first time how flags flap in the wind. The findings served as a starting point for a more elaborate project studying tigerfish as they move through water. Information about the turbulence effects of the aquatic animals' movements may become the cornerstone of new developments in physics.

Using a similar approach, Libchaber and his lab members study DNA, but not for its biological functions. They study the physics of DNA — how it is structured, broken down and reassembled during replication — to theorize new means of computing. DNA provides a more complex set of information-processing methods than any computer ever conceived by humans.

As well as new theories, new tools emerge from the interface between physics and biology. For several years, Benoit Dubertret, Ph.D., a postdoctoral fellow who works with Libchaber, has been searching for biological applications of quantum dots — crystals of only a few hundred atoms that are visible with a single wavelength of light.

With another Rockefeller scientist, Ali H. Brivanlou, Ph.D., head of the Laboratory of Molecular Vertebrate Embryology, Dubertret has succeeded in applying quantum dots to illuminate how embryonic frogs develop into a whole organism.

Could quantum dots also illuminate a healthy human cell's change to malignancy? Only a physicist working with a biologist may ever answer the question.

Using molecular beacons, Noel Goddard (above left) studies rigidity of single-strand DNA. As a graduate student in the Laboratory of Experimental Condensed Matter Physics, she combines her formal training in physics with an apprenticeship in molecular biology mentored by laboratory head Albert Libchaber (above).

The university's graduate program is "very effective," says Nobel laureate and former Rockefeller President Torsten Wiesel, M.D. "A student spends time in a lab and learns from and interacts with a master scientist."

Rockefeller University has many educational partners, including Weill Medical College of Cornell University and Memorial Sloan-Kettering Cancer Center. With them, it offers a highly rated M.D.-Ph.D. program to train physician-scientists for the future. Through New York University's Courant Institute of Mathematical Sciences, Rockefeller offers students curricula linking the disciplines of biology, physics, mathematics and computation, providing young scientists with tools to understand the patterns of life.

Selected prizes and awards
2001–2002

BRIAN T. CHAIT
Frank H. Field and Joe L. Franklin Award for Outstanding Achievement in Mass Spectrometry (American Chemical Society)

Academy Fellow, New York Academy of Sciences

JOEL E. COHEN
Mayor's Award for Excellence in Science and Technology

BARRY S. COLLER
Warren Albert Foundation Award

JAMES E. DARNELL JR.
Albert Lasker Award for Special Achievement in Medical Science

Academy Medal for Distinguished Contributions in Biomedical Science (New York Academy of Sciences)

TITIA DE LANGE
Paul Marks Award for Cancer Research

MADHAV DHODAPKAR
New York Community Trust Scholar

Damon Runyon-Eli Lilly Clinical Investigator Award

JEFFREY M. FRIEDMAN
Bristol-Myers Squibb Award for Distinguished Achievement in Metabolic Research

HIRONORI FUNABIKI
Searle Scholar Award

CHARLES GILBERT
Fellow, American Academy of Arts and Sciences

PAUL GREENGARD
NARSAD Julius Axelrod Neuroscience Award (shared with Eric Kandel and Arvid Emil Carlsson)'

A. JAMES HUDSPETH
Fellow, American Academy of Arts and Sciences

JOSHUA LEDERBERG
Benjamin Franklin Medal for Distinguished Achievement in the Sciences (American Philosophical Society)

BINGWEI LU
Arnold and Mabel Beckman Award

Alfred P. Sloan Research Fellow

RODERICK MACKINNON
Gairdner Foundation International Award

BRUCE S. MCEWEN
Edward J. Sachar Award (Department of Psychiatry, Columbia University College of Physicians and Surgeons)

JOHN MCKINNEY
Ellison Medical Foundation New Scholar Award in Global Infectious Disease

FERNANDO NOTTEBOHM
Ellison Senior Scholar Award in Aging

F. NINA PAPAVASILIOU
New York Community Trust Scholar

ROBERT G. ROEDER
Dickson Prize in Medicine (University of Pittsburgh)

MICHAEL P. ROUT
Presidential Early Career Award for Scientists and Engineers

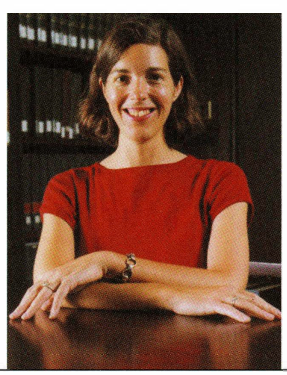
SHAI SHAHAM
Sidney Kimmel Cancer Scholar Award

EREC STEBBINS
Burroughs Wellcome Fund Investigator Award in Pathogenesis of Infectious Disease

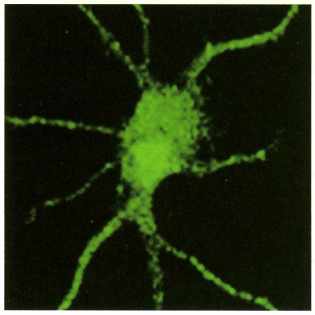
RALPH M. STEINMAN
Member, Institute of Medicine

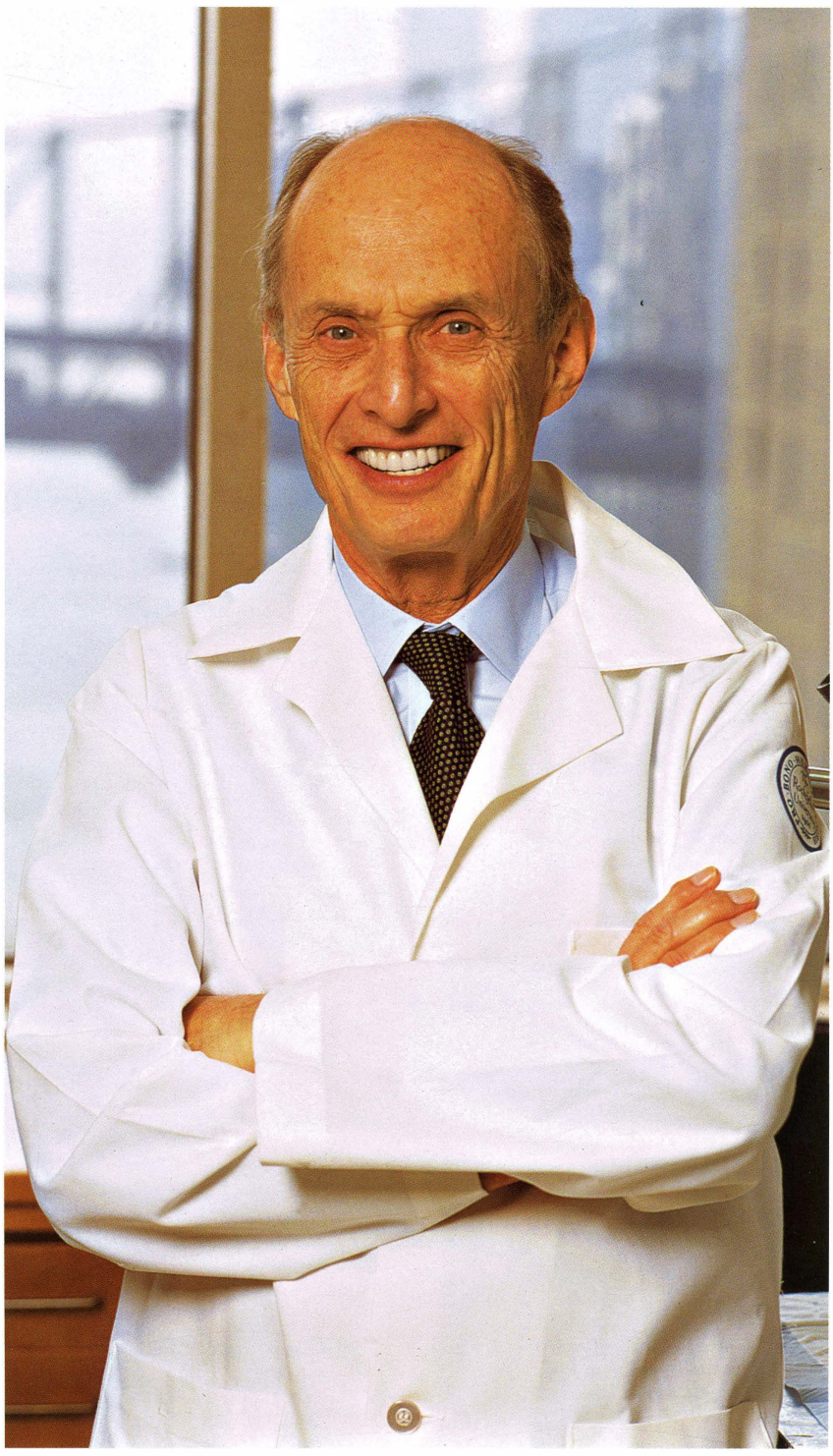
MARKUS STOFFEL
Bristol-Myers Squibb Unrestricted Grant Award for Metabolic Diseases

LESLIE B. VOSSHALL
Presidential Early Career Award for Scientists and Engineers



Leslie B. Vosshall, Ph.D. (right), and Mike Rout, Ph.D., are the most recent of five Rockefeller scientists to have been honored with the PECASE (Presidential Early Career Award for Scientists and Engineers) since the award was established in 1996.





In laboratory cultures of human and rodent brain tissue, Nobel laureate Paul Greengard, Ph.D. (left), and his Rockefeller University colleagues showed that the hormone estrogen prevents the accumulation of "senile plaques" that build up in the brains of most people with the devastating disease Alzheimer's.

Above is a neuron, the most common type of brain cell in humans and most animals. This image of a rat neuron was stained to identify the locations of proteins forming the "senile plaques."

The plaque-forming proteins are located primarily in a part of the neuron called the Golgi compartment (bright area of image) — a part of the cell responsible for manufacturing, warehousing and shipping certain cellular products. Greengard found that estrogen scoots the plaque-forming proteins out of the Golgi compartment. Scientists hypothesize that the longer these proteins stay in the Golgi network, the more likely they may be to develop into the beta amyloid of "senile plaques."

From DNA to a postgenomic world: Discoveries that (continue to) transform science

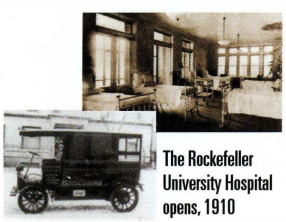
With the 50th anniversary of the discovery of DNA's double-helix structure by James Watson and Francis Crick at Cambridge University upon us, the world of science eagerly anticipates a season of celebratory conferences and honors marking the occasion. Rockefeller University will join the festivities, to honor its own chapter in the textbook of DNA history.

In 1944, Rockefeller scientists Oswald Avery, Colin MacLeod and Maclyn McCarty showed for the first time that DNA *is* the chemical substance of heredity. This crucial finding set the stage for Watson and Crick's unveiling the physical structure of this double-stranded molecule nine years later.

Half a century later, DNA has become a cultural phenomenon in its own right, with ripple effects that reach far beyond the research lab and into every area of human endeavor — business, philosophy, ethics, the arts. For scientists working in our own so-called postgenomic era, the span of less than 60 years since The Rockefeller University's discovery is uncanny.

Visit any of The Rockefeller University's 75 major laboratories today and you will find scientists writing new chapters in the textbook of DNA history. Among them: Robert G. Roeder, Ph.D., the Arnold and Mabel Beckman Professor and head of the Laboratory of Biochemistry and Molecular Biology, who stands at the center of research to reveal the basic principles of mammalian transcription.

Transcription is the process by which the identical sets of genetic instructions contained in each of the body's 200 distinct types of cells are

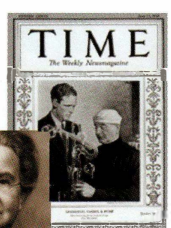


The Rockefeller University Hospital opens, 1910

June 14, 1901
Rockefeller Institute for Medical Research incorporated

Florence Sabin, renowned anatomist and histologist, becomes first female member of Institute, equivalent to full professor, 1925

Peyton Rous discovers virus can cause cancer, 1911



Charles Lindbergh and Alexis Carrel appear on "Time" magazine cover with their perfusion apparatus, which keeps organs alive in the lab for two weeks, 1938

Oswald Avery, Colin MacLeod, and Maclyn McCarty discover DNA carries hereditary information, 1944

WWII: Rebecca C. Lancefield's expertise in identifying bacterial types assists war effort, early 1940s

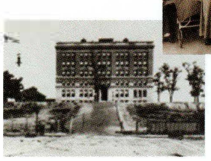
1901 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955

Rockefeller researchers collaborate with New York City Board of Health to reduce bacteria in city's milk supply, 1902

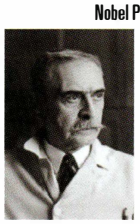
Simon Flexner develops serum to treat epidemic cerebrospinal meningitis, 1907

Donald van Slyke perfects apparatus to analyze blood gases, 1921

WWI: Rockefeller scientist and Nobel laureate Alexis Carrel trains surgeons to clean and suture wounds at the front

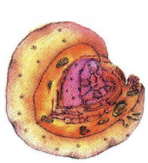


Founder's Hall completed, 1906



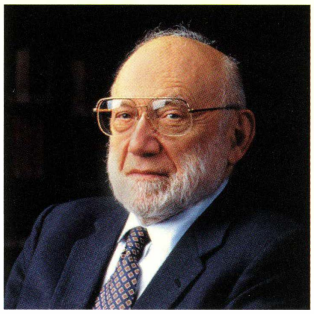
Karl Landsteiner receives 1930 Nobel Prize for classifying blood groups; he later discovers Rh blood factor

Wendell Stanley shows a virus can be crystallized, 1935; he shares 1946 Nobel Prize with John Northrop



Electron microscopy reveals inner structure of cells, 1945; for founding the field of cell biology, Albert Claude, Christian de Duve, and George E. Palade share 1974 Nobel Prize

Stanford Moore and William Stein describe the enzyme pancreatic ribonuclease, which breaks down RNA, 1959; for this work they receive 1972 Nobel Prize



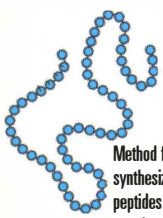
"Because Rockefeller offers its faculty extraordinary resources and freedom, they are able to take scientific risks that would be unimaginable anywhere else."

Joshua Lederberg, Ph.D.
President Emeritus
Raymond and Beverly Sackler Scholar
Nobel Prize in Physiology or Medicine, 1958

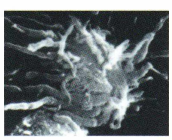
individualized to distinguish, for example, a skin cell from a muscle cell. Through transcription, the cell's machinery issues marching orders of precisely which genes to express, or "switch on." A gene must be "on" to generate recipes for proteins; the particular proteins expressed ultimately determine the cell's function in the body.

And, because diseases such as cancer, Alzheimer's and AIDS can arise when transcription breaks down, understanding how a gene transcribes its instructions accelerates research to create more effective medical therapies.

In 1944, The Rockefeller University ushered biology into the modern age. Today, Roeder is one of the university's 75 scientific leaders making the discoveries that continue to transform science.

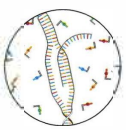


Method for synthesizing peptides and proteins developed by R. Bruce Merrifield, 1963; he wins 1984 Nobel Prize



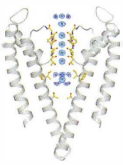
Dendritic cell, vital white blood cell that alerts immune system to presence of foreign invaders in diseases, discovered by Zanvil Cohn and Ralph Steinman, 1973

Mike Young clones *"per"* gene, which affects circadian rhythms, in fruitflies, 1984

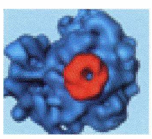


Robert Roeder identifies and clones first gene-specific transcriptional regulatory factor — key to how genetic information in DNA is converted into protein, 1988

Roderick MacKinnon reveals structure of potassium ion channel, shedding light on nerve cell communication, 1998



Günter Blobel awarded 1999 Nobel Prize for discovering proteins are distributed throughout cells by a "ZIP Code" system

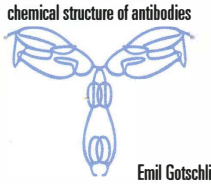


James E. Darnell Jr. awarded 2002 Lasker Award for Special Achievement in Medical Science

1960 1965 1970 1975 1980 1985 1990 1995 2000 2001 2002

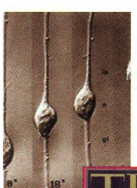
Rockefeller awards Ph.D.s to first graduating class, 1959

Gerald Edelman awarded 1972 Nobel Prize for showing chemical structure of antibodies



Emil Gotschlich receives 1978 Lasker Award for his role in developing vaccine against Group C meningitis

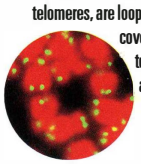
Vincent Dole develops methadone for managment of heroin addiction, 1960s; receives 1988 Lasker Award



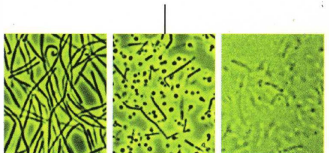
Mary Beth Hatten and Nathaniel Heintz identify gene involved in directing nerve cells to their destinations as brain grows, 1994

Led by David Ho, scientists at The Rockefeller University Hospital and Aaron Diamond AIDS Research Center begin trials of "drug cocktail" that reduces death rates from AIDS in U.S., 1995

Titia de Lange helps determine chromosome ends, called telomeres, are looped, a discovery relevant to cancer and aging, 1999



Paul Greengard awarded 2000 Nobel Prize for discovering how dopamine and other chemical messengers affect brain



Vincent Fischetti develops new anthrax treatment consisting of bacteriophage, or "bacteria-eating virus," anthrax's number-one natural enemy, 2002

75 heads of laboratories
200 research and clinical scientists
300 postdoctoral investigators
850 support staff
134 Ph.D. students
35 M.D.-Ph.D. students
800 alumni

HEALTH CONDITIONS UNDER STUDY

Addiction
Aging
AIDS
Alzheimer's
Antibiotic resistance
Arthritis
Cancer
Diabetes
Heart disease
Hepatitis C
Memory loss with aging
Obesity
Psoriasis
Schizophrenia
Tuberculosis
Visual disorders

BASIC INTERDISCIPLINARY RESEARCH AREAS

Biochemistry, structural biology and chemistry
Molecular, cell and developmental biology
Immunology, virology and microbiology
Medical science and human genetics
Neuroscience
Physics and mathematical biology

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Pels Family Center for Biochemistry and Structural Biology
Center for Studies in Physics and Biology
Christopher H. Browne Center for Immunology and Immune Diseases
Fisher Center for Alzheimer's Disease Research
F. M. Kirby Center for Sensory Neuroscience
Shelby White and Leon Levy Center for Mind, Brain and Behavior
Starr Center for Human Genetics

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Professor

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