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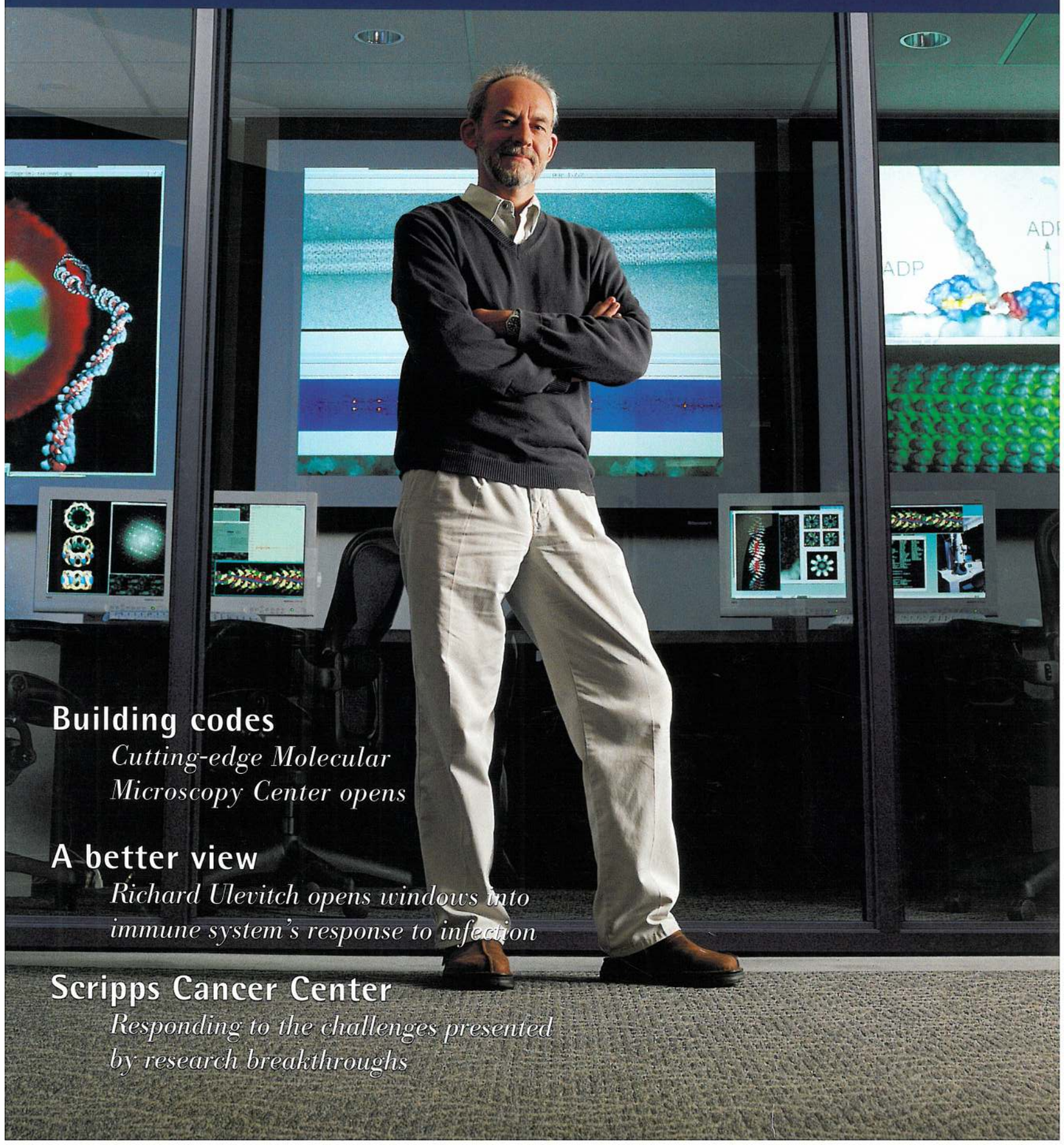
THE SCRIPPS RESEARCH INSTITUTE

Endeavor



Building codes

Cutting-edge Molecular Microscopy Center opens

A better view

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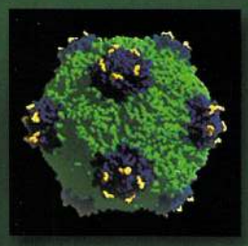
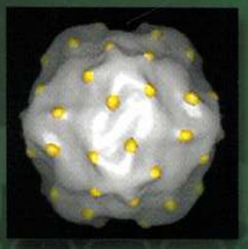
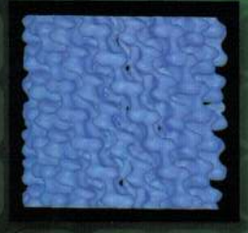
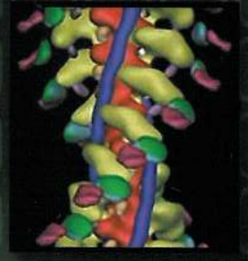
Scripps Cancer Center

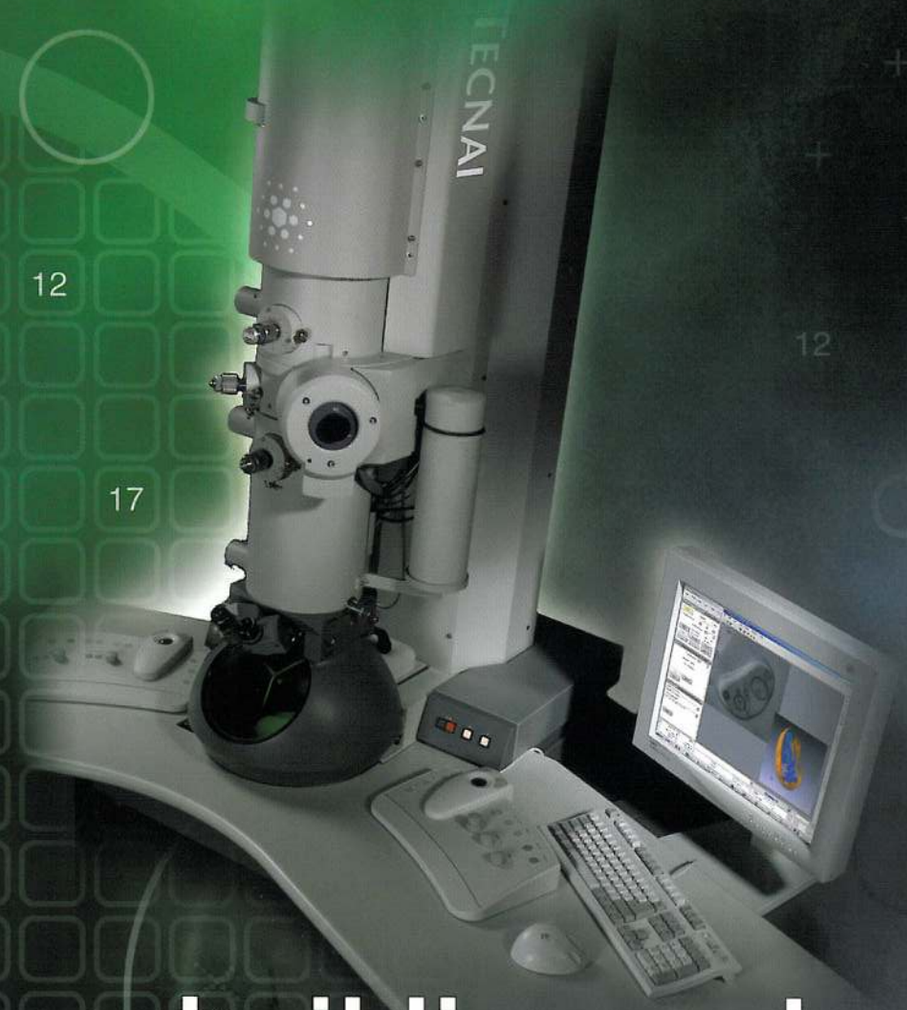
Responding to the challenges presented by research breakthroughs











building codes:

Cutting-edge Molecular Microscopy Center opens

When Associate Professors Bridget Carragher and Clint Potter arrived at The Scripps Research Institute (TSRI) last year, they knew where their laboratory space would eventually be, but they had no idea what the space would be like.

That is, until after they sat down with Professor Ron Milligan and drew up plans on a blank blueprint of the interior of the CarrAmerica B building.

In the following weeks, this became the blueprint for Milligan's dream of one of the most advanced biological microscopy centers in the world — The Center for Integrative Molecular Biosciences (CIMBio) — which officially opened in April. CIMBio is built around its advanced microscopes and open laboratories, and houses several TSRI faculty under one roof.

"We had an almost unique opportunity to design an ideal electron microscopy suite, and we put a lot of effort into doing this," says Milligan.

The design is predicated on six rooms for microscopes, which are at the center of the building. The microscopes are mounted on three-foot-thick concrete slabs isolated from the building's foundation, which protect the instrumentation from vibrations. The rooms are climate-controlled with low humidity to prevent contamination of samples by water vapor, and they are sound-proofed so that noise from the corridors does not cause vibrations. The air supply coming into the rooms passes through a nylon sleeve that breaks up any air currents, and the microscopes can be controlled entirely from a separate room so that the samples can be left alone in the dark inside the microscopes.

"We had an almost unique opportunity to design an ideal electron microscopy suite, and we put a lot of effort into doing this," says Milligan.

"It's quiet, there are no air currents, and the microscopes are sitting on a very stable platform," says Milligan.

MOLECULAR MACHINE MANIA

Milligan, Carragher, and Potter, all members of the Department of Cell Biology, are founding members of CIMBio, which was organized to combine the talents of several groups across campus who have backgrounds in divergent disciplines such as chemistry, biochemistry, structural biology and cell biology but whose interests converge in one area.

The center seeks to speedily obtain and analyze high-resolution structural images of large molecular complexes of the cell by combining the use of x-ray crystallography and electron microscopy (EM) as a means to unravel the structure and mechanism of action of the large molecular assemblies of the cell. These include the transcription complexes that make messages from the genes, membrane channels and pumps that import and export materials, and the tiny molecular tracks and motors that move cells and form important structures like the mitotic spindle.

Phase I of CIMBio is devoted to working out the structure of the proteins and nucleic acids in complexes that carry out the work of the cell. In addition to Milligan, Carragher, and Potter, CIMBio members involved in Phase I include investigators Francisco Asturias, M.G. Finn, Jack Johnson, Elizabeth Wilson-Kubalek, Tianwei Lin, Mari Manchester, Nigel Unwin, and Mark Yeager.

While the individual protein components of these cellular machines may be studied by x-ray crystallography, the machines themselves are compositionally and conformationally dynamic, making them often unsuitable for x-ray methods. They are, however, ideal specimens for electron microscopy. Polymerases, membrane complexes, viruses, and motor proteins can all be visualized

On The Cover:
Ron Milligan, Ph.D., Professor, Department of Cell Biology, Director, Center for Integrative Molecular Biosciences.

in their native environment using EM. Also relocating to the new facility at the end of the year will be Geoffrey Chang, whose expertise in solving the high-resolution structures of integral membrane proteins is a valuable addition to the center.

Phase II will concentrate on the dynamics of cellular machines — their assembly, disassembly, and control over time. Laboratory space for that effort is already under construction, and at the end of the year, investigators Velia Fowler, Klaus Hahn, Clare Waterman-Storer, and Kevin Sullivan will relocate there to lead the Phase II efforts.

The building combines several of these laboratories into large contiguous shared spaces built above and around the microscopes. The laboratories have an open design and some of the facilities — like the microscopes and an imaging area — are shared, something that the CIMBio researchers appreciate.

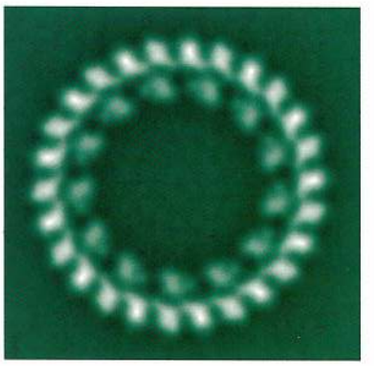
Kinesin I motor molecules caught in the act of depolymerizing microtubule protofilaments. Here the process has been arrested at the curling stage, and the tubulin protofilament has formed a closed ring consisting of 13 tubulin heterodimers (26 outer regions) to which the kinesin motor (13 inner regions) is bound.

EM IMAGING OF BIOLOGICAL STRUCTURES

Electron microscopy, which has been around since the 1930s, uses a beam of electrons to image tiny objects onto a digital camera or a photographic plate. An electron microscope can examine specimens over a very wide range of magnifications, from no more than that which an ordinary microscope can produce, about 60 times, to incredible magnifications of up to 1,000,000 times. CryoEM, which is the technique used for viewing biological materials, requires the samples to be spread into a thin film, frozen with liquid nitrogen and suspended on a copper meshwork grid. Images are then collected using the electron microscope operating in a mode that does not damage the delicate biological specimens.

When combined with the x-ray structures of the component parts of the structures, EM maps can yield a detailed description of the structure and action of the entire machine.

The final products of these electron images are three-dimensional (3-D) maps of the cellular structures at near-atomic resolutions — up to about 3 to 4 angstroms under the best of circumstances (an angstrom is one 254 millionth of an inch). When combined with the x-ray structures of the component parts of the structures, EM maps can yield a detailed description of the structure and action of the entire machine.



Further application of this technique will be an invaluable tool for studying membrane-bound proteins, which are notoriously hard to crystallize. Less than one half of one percent of the structures contained in the Brookhaven National Laboratory Protein Data Bank are of integral membrane proteins, despite the fact that over a third of all proteins in the body are in the membrane.

But EM can be a tedious technique. Calculating an EM structure manually takes weeks or even months.

A single high-resolution image of a sample under an electron microscope has too much noise to yield accurate molecular representation. Images must be averaged together with their counterparts to reduce noise. To build a 3-D map, one must take many images and build a structure by looking at all the different angles of all the different molecular assemblies imaged.

In this way, building a 3-D map is like looking at a piece of sculpture in a gallery. Only by walking around the piece and viewing its various sides and angles can the brain build a mental image of the art and fully comprehend its dimension, perspective, and scale. The same is true using a computer; only by piecing together many different views of a molecule from a microscope can a computer build a model of the molecular assembly.

And the molecule that is being imaged gets destroyed in the process, so the next image must be captured from some other part of the sample holder grid. This has always required a person to choose different spots on the grid manually. As the number of grid spots goes up, so goes the level of tedium.

"What we really want is 100,000 to 1,000,000

molecule images and that just takes too long to do manually," says Carragher. "Then you want to do 10 different conformational states, 20 different labeling studies, and each time it's going to take three to six months. That totals more than the lifetime of a graduate student."

Carragher and Potter, who lead the Automated Molecular Imaging Group, are creating algorithms for automated data collection and analysis, which should simplify the technique of electron microscopy and enable throughput to be increased dramatically.

AUTOMATION FOR EM

Several years ago, Carragher and Potter suggested that automated data collection and analysis could be developed for EM. A similar goal had been accomplished in x-ray crystallography; given the need for structural information in our post-genomics proteomics world, automation would represent significant progress.

They succeeded in developing software for both the collection and the analysis, which they brought to TSRI when they came last year to form the Automated Molecular Imaging Group at TSRI.

Creating the algorithms was not easy. Using the manual technique, a person has to make decisions about where to focus the EM beam and take a picture, looking first at low resolution and then deciding in which areas to collect data at high resolution. For automation to succeed, the computer must do the same thing and use intelligent criteria to search the low-resolution image for appropriate targets.

Carragher and Potter had to write their software to take a low-resolution image, select areas to image in medium resolution, and then analyze that image and strip out targets for high-resolution maps. Then, they had the computers put the data into processing programs and calculate 3-D maps. Recently, they have been testing and refining the programs.

"What we have done over the past year is to show that you can insert a sample in the microscope and calculate a 3-D map fully automatically," says Potter.

In fact, Carragher and Potter constructed one of the best 3-D maps of the tobacco mosaic virus in under two days. By comparison, this would have taken several months of work just a few years ago and perhaps several weeks using conventional methods today.

"We can now go from inserting the virus into the microscope to having a 3-D map in 24 hours," says Milligan, adding that the fear of failure should no longer be a limiting factor for experiments.

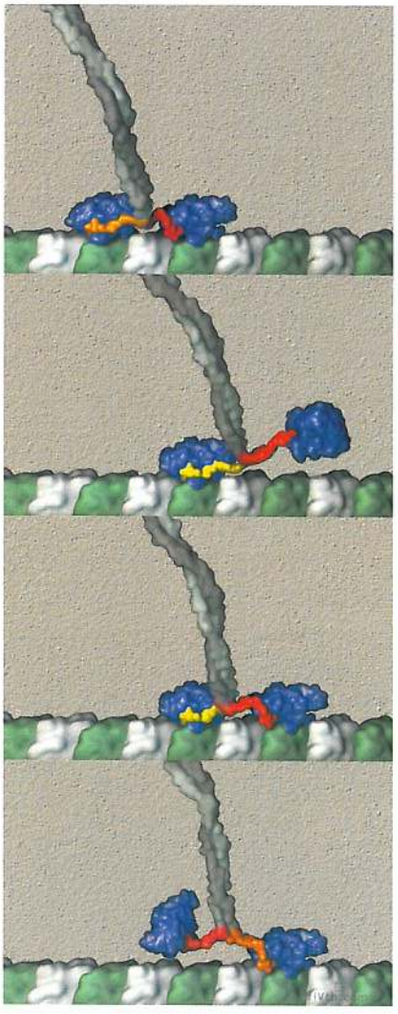
Still, the automation is not fully implemented, so one of the immediate goals of the Automated Molecular Imaging Group is to see their software used for practical applications, something that their coming to TSRI will facilitate.

"At the moment we need to make the technique very efficient and very general, and get it out to the community," says Carragher. "We can do it, and now we want to be able to do it routinely for anybody."

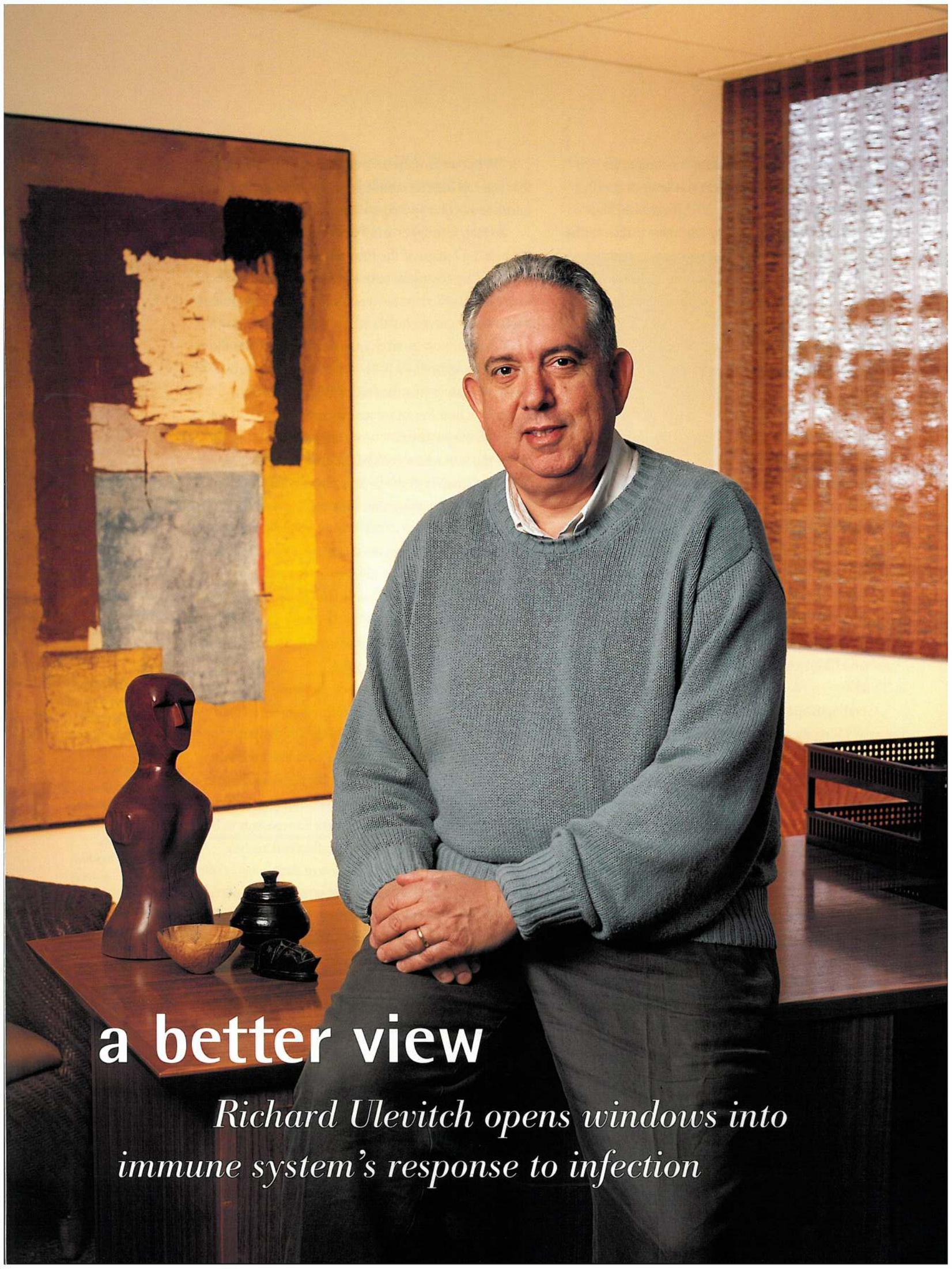
Additional plans include the design of technology that would make EM high-throughput. This includes a robotic specimen handler that Carragher and Potter have been experimenting with that would allow the instruments to be left alone to collect and analyze even larger sets of data.

At present, several people control the microscopes and discuss the images as they collect data. This is what Milligan and the others envisioned when the original plans were drawn. They also anticipated people peering through the glass wall of the control room.

"It's a very easy way to communicate what we are doing," Carragher reports. ■



A sequence of images depicting the conformational changes associated with the heads of a double headed, processive kinesin motor (blue, red, yellow) as it moves between successive binding sites (green) along a microtubule. The images are based on cryo-electron microscopy investigations carried out in Ron Milligan's laboratory together with high resolution structures of the individual proteins from other laboratories. Movies of this sequence, and of a sequence depicting movements in the myosin motor are available at http://www.scripps.edu/milligan/research/movies/. Rendering and graphics by Graham Johnson (http://www.fiVth.com).



a better view

Richard Ulevitch opens windows into immune system's response to infection

Richard Ulevitch, the 58-year-old head of The Scripps Research Institute's Department of Immunology has been around awhile – thirty years, in fact.

How he got here is one of those serendipitous chains of events, the kind Hollywood does so well. A remark here, a suggestion there, and the next thing you know, you're living in Casablanca. Or in this case, La Jolla, California. After receiving his Ph.D. in biochemistry from the University of Pennsylvania in 1971, someone mentioned to Ulevitch that the field of immunology might be a good one to look into for future research possibilities. The interesting thing is he doesn't remember who told him, although he sometimes wishes he did.

...even the mildest intrusion of an endotoxin causes the body's immune system to go on alert, even overreact.

Ulevitch's next move was to the University of Minnesota to begin his postdoctoral training. Soon after, the opportunity to work in the Department of Experimental Pathology at Scripps was presented to him. He was asked to return to Minnesota in 1972 to continue his postdoctoral training. However, this was right after he had met his wife, Susan, and there was no turning back. "Susan was already living in La Jolla when she met me," he says, "and she told me she wasn't leaving." Obviously, neither was he.

They married and raised two children. Today his wife is a licensed clinical social worker. His daughter Annie, now 24, works for the city of New York, and is on her way to law school; their 20-year-old son David, a computer whiz, is a student at Washington University in St. Louis.

But back in 1974, something else happened. Richard Ulevitch discovered endotoxins.

Endotoxins are odd pieces of molecular material. Composed of lipid and sugar chains, the lipopolysaccharide (LPS) molecules make up the cell walls of Gram-negative bacteria. Gram-negative bacteria include *E. coli, Salmonella, Shigella, Pseudomonas, Neisseria, Haemophilus,* and *Meningicocci* — in short, some of the most deadly infectious agents on the planet.

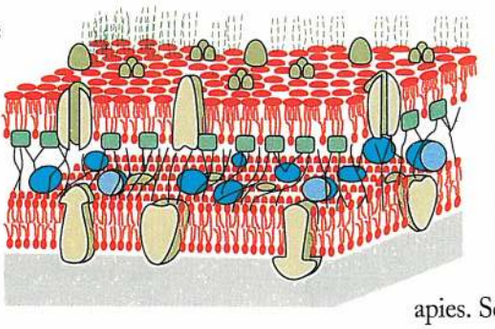
They are notoriously thin-skinned, and small pieces of endotoxin break off easily as they move through the body. When killed or broken, the bacteria release even larger amounts. In and of themselves, endotoxins are benign, but they serve as a warning sign announcing the presence of bacteria. As a result, the immune systems of many organisms — but especially humans — are remarkably sensitive to their presence.

And so endotoxins aren't the problem. The real problem is caused by the reaction of the immune system to them. In that sense, even the mildest intrusion of an endotoxin causes the body's immune system to go on alert, even overreact. An important thing to remember about endotoxins is that they alone can produce a fatal immune reaction or cascade even if the surrounding bacterium is dead.

One of things that led Ulevitch in the direction of endotoxins, or at least encouraged him, was the best selling book, *Lives of a Cell*, by Dr. Lewis Thomas, published the same year that Ulevitch began to develop his own attraction to them. Thomas characterized the body's response to the endotoxins as being "read by our tissues as the very worst of bad news. . . . There is nothing intrinsically poisonous about endotoxin, but it must look awful, or feel awful, when sensed by cells. Cells believe that it signifies the presence of Gram-negative bacteria, and they will stop at nothing to avoid this threat."

Ever since then, finding out exactly how the body handles an influx of endotoxins, and how science might

Richard Ulevitch, Ph.D., Chairman, Department of Immunology.



Schematic depiction of the outer membrane structure of a typical gram-negative bacterium.

modify that reaction has been the driving force behind his work.

While it might seem a small target, for Ulevitch the study of endotoxins opens up the entire immune system to scrutiny.

"These studies," he says, "are a window into the human immune system response to infection, and the mechanisms that control diseases where chronic and often harmful inflammation is present. That's why these infections are so horrible. In order to clear them away, there is an immediate response by the immune system. In some people, there is a complex underlying genetic pattern, as yet not understood, that allows this normally protective response to get out of control, and that can quickly lead to septic shock."

Septic shock starts out as sepsis, a condition that can slip easily into severe sepsis and shock, which means organ failure far from the infection site, most often the lungs, kidneys, and liver. This syndrome may include fever, tachycardia, hypotension and coagulation abnormalities, and is one that cannot be reversed with available treatments. What is most frightening about septic shock is that a substantial number of hospitalized patients develop it, and a great many of those die from it.

One of their findings may one day lead to a new treatment for septic shock.

"It's an insidious disease," Ulevitch says. "It can't always be recognized, and by the time it is, much of the damage has been done. Its progression is difficult if not impossible to reverse. Even after years of research, septic shock continues to be a major cause of morbidity and mortality in intensive care units all around the world."

In the United States, recent estimates suggest that more than 750,000 patients per year are at high risk for developing septic shock. In some patient groups, mortality rates reach 50 percent. The cost to the healthcare system is equally high.

"So, because of the high incidence of septic shock, and the poor prognosis for patients," says Ulevitch, "we have two major long-term goals. First, we're studying the underlying mechanisms of the immune system and how it responds to infection. That understanding may lead to new therapies. Secondly, we're looking to identify new genetic markers that can ultimately be evaluated on an individual basis so we can predict who might be susceptible to septic shock and who isn't." One of their findings may one day lead to a new treatment for septic shock. This finding is the basis of a current clinical trial with a monoclonal antibody, and is sponsored by Icos, a Seattle based biotech company. The antibody selectively blocks the white blood cell receptor CD14, reducing the intensity of the immune system cascade that causes septic shock.

DELINEATING THE UNDERLYING MECHANISM OF DISEASE

The practical aspect of discovering the underlying mechanisms of septic shock goes further than finding a treatment for this single disease, although that remains a critical goal. As Ulevitch suggests, the ultimate target is larger still. The same mechanisms operative in septic shock also contribute to chronic inflammatory disease. Whatever is learned about acute models of infection response can be applied with equal certainty — and equal benefit — to chronic inflammatory disease.

"Currently, there's only one drug that's approved for this condition," according to Ulevitch. "What we're looking for is a way to minimize the body's response to infection without compromising the immune system. The goal is to reduce the body's inflammatory response so that there's a sub-threshold of activity, but one that still allows the bacteria-killing mechanism to work effectively."

Some of his research has a more up-to-the-second application, specifically in the burgeoning area of bioterrorism since treatment of many toxic agents relies on the same host defense mechanisms. In the case of bioterrorism, that means improving a body's non-specific immunity to pathogens by developing molecules that could be added to increase the initial immune response to a vaccine, thus harnessing the protective aspects of

immunity without the potentially dangerous consequences.

All this would seem to be more than enough to keep a researcher busy for years, if not decades. But Richard Ulevitch also has a second job. He is the Chairman of TSRI's Department of Immunology.

"At the beginning, the department was focused on diseases where the immune system was central. Today, our research efforts are much broader."

"I was asked to be chairman about eight years ago," he says, adding quickly that he feels little or no tension between his own research and time spent managing the department. "Most of my time is focused on my own research because of the way TSRI works. As head of the department, my job is to make certain our scientists have the resources they need to do their research. The faculty here is really pretty self-sufficient and the administration is highly supportive. But when they need something, I find a way to get it to them."

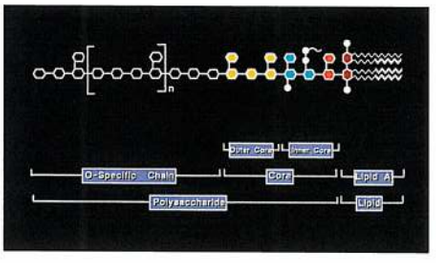
At present, Ulevitch oversees a staff of more than 400 professionals. Among them are about 60 faculty members, and more than 100 postdoctoral fellows. "Our immunology program is recognized worldwide for the breadth of the studies performed here," he says. "That includes efforts to understand the development of the immune system as well as disease-focused efforts in areas such as cancer, autoimmune disorders like diabetes, rheumatoid arthritis, Lupus, infectious disease, and inflammation. At the beginning, the department was focused on diseases where the immune system was central. Today, our research efforts are much broader."

What has been challenging, Ulevitch says, has been to keep one of the largest and most internationally diverse immunology research departments in the world growing and thriving in a world of rapid scientific and cultural change, something he says he's been able to do through a combination of support from both the Institute and its faculty. Ulevitch sees part of that change coming from the expansion of some of the department's work into early clinical development, offering interested scientists the opportunity to see how their research might benefit patients in a more practical way.

"I think there's a place in sophisticated research institutes like TSRI to do internal development on a limited basis to assess the therapeutic potential of certain compounds being studied," he says. "In immunology, for example, we might look at getting monoclonal antibodies into the clinic quickly for some selected diseases — in oncology, for instance. It's an idea that has to evolve and the Institute is well positioned to develop it. I think we have the kind of special infrastructure necessary to make it work effectively."

COMMUNITY INVOLVEMENT

When Ulevitch isn't working on his own research or helping find the right tools to help others with theirs, he can often be found working on a number of community boards in and around La Jolla. One long-standing commitment is with the La Jolla Playhouse, the one-time summer home of film actors like Gregory Peck who would come down from Hollywood to do stock productions during the off months. He became a board member in 1987, and helped chart the future of the playhouse just as it was re-emerging as an important regional theater.



The schematic chemical structure of bacterial endotoxin (lipopolysaccharide) isolated from *Escherichia coli*, a typical gram-negative bacterial species.

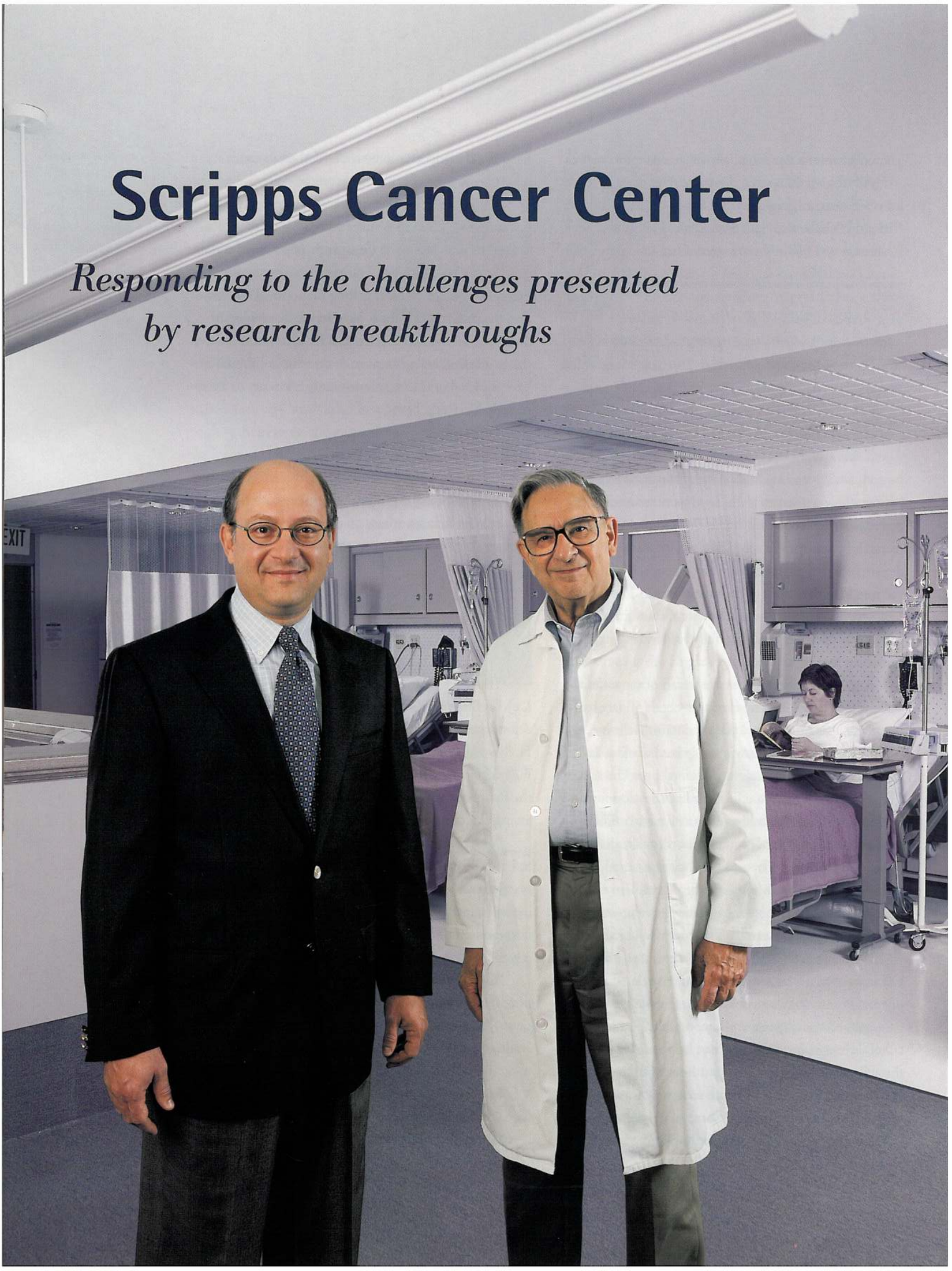
"The playhouse received several grants in the 1980s to basically re-invent itself," he says. "As a result, it's become one of the top two or three regional theaters in the country." The La Jolla Playhouse has produced numerous plays that went on to Broadway including several Tony award-winning musicals.

"One of the reasons I do it is because I think it's important to help your community when you can," he says. "I try to make an impact. I've been on various boards for the last twenty years or so. I wish I had time to do more but I don't."

For that, Richard Ulevitch could point to the person who got him into immunology in the first place. Now if he could only remember his name. ■

Scripps Cancer Center

Responding to the challenges presented by research breakthroughs



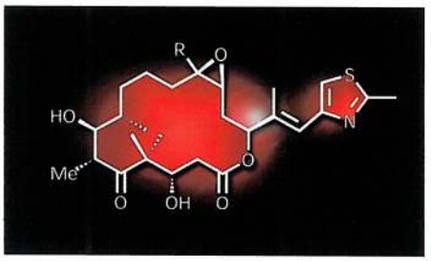
A generation ago all that was known about the cause of cancer was that cells had lost their ability to regulate growth: there was no understanding of why.

Today scientists understand at least part of that "why?" A gene that is normally regulated — turned on then off in response to an external stimulus — is turned on and remains on all the time, resulting in the unchecked cell growth we call cancer. New tools now enable scientists to look at gene expression so they can penetrate directly to the heart of the problem. This enhanced understanding of how cancer strikes and how it can be treated has resulted in a revolution in cancer care.

The Scripps Cancer Center (SCC), under the direction of Alan Saven, M.D., Head, Division of Hematology and Oncology at Scripps Clinic, was launched in 1999 to respond to the challenges presented by research breakthroughs. The Center aims to facilitate collaboration between TSRI and the five constituent hospitals of the Scripps system. TSRI's Chairman of the Department of Molecular and Experimental Medicine, Ernest Beutler, M.D., heads its Board of Governors with the objective of initiating a fast track from bench to bedside. Achieving this goal will begin with the discovery in TSRI's laboratories of new, potentially effective drugs and therapies, moving through their testing in controlled clinical conditions, and finally putting them into the hands of practicing physicians. Since there will never be a single treatment for a disease as complex and varied as cancer, this process will be repeated over and over again as new discoveries are made and tested.

COMPOUNDS FOR TARGETED THERAPIES

Designer drugs and targeted drug delivery are key to the success of new treatments. A well-publicized recent example is Gleevec, developed by Novartis for the treatment of chronic myeloid leukemia. TSRI has developed many molecules in its laboratories that potentially can be used in targeted therapy. Scientists in the laboratory of K.C. Nicolaou, Ph.D., Chairman, Department of Chemistry, for example, can synthesize the most complicated organic molecules that are selectively toxic to tumors but not to the surrounding tissue. Their development has followed the same principles as were used in the case of Gleevec, and they will hopefully have clinical applications for targeted drug delivery. The health care delivery side of the SCC is ideally placed to take these drugs through clinical trials to implementation, completing the journey from bench to bedside. The SCC hopes to harness the biological and chemical expertise at TSRI, and capture the results in studies at the General Clinical Research Center at Green Hospital en route to full implementation throughout the Scripps system. Scripps physicians have an enormous patient reservoir, treating about one-third of all cancer patients in the San Diego area.



Molecular structure of epothilone B, a molecule synthesized in Dr. K.C. Nicolaou's laboratory which has the potential of becoming a new anticancer drug.

Dr. Beutler describes 2-CdA development as a "scientifically beautiful story, insightful into the way medical research works."

Because it is a not-for-profit organization, Scripps Cancer Center evaluates new therapies based on benefit, not on the number of cases. As a result it will test drugs that treat less common forms of cancer, drugs that would likely not be selected by large pharmaceutical companies whose focus is on blockbuster drugs for common

Left to Right: Alan Saven, M.D., Head, Division of Hematology and Oncology, Director, Scripps Cancer Center. Ernest Beutler, M.D., Chairman, Department of Molecular and Experimental Medicine, Chairman, Scripps Cancer Center Board of Governors.

diseases. One of Scripps' great success stories was the development of the drug 2-CdA as a remarkably effective cure for a rare form of cancer, hairy cell leukemia, a disease that strikes only about 600 patients each year in the United States. Dr. Beutler describes 2-CdA development as "a scientifically beautiful story, insightful into the way medical research works." TSRI scientists continue to develop new cancer-fighting molecules that will follow the path blazed by 2-CdA development.

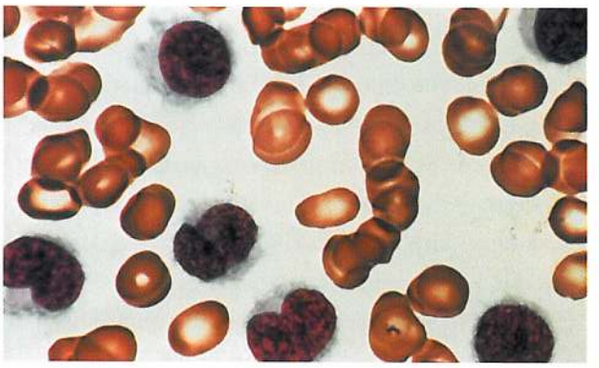
One approach to fighting cancer is being pursued in the laboratory of David Cheresh, Ph.D., Professor, Department of Immunology. The original concept upon which all this work is built is very simple. All solid tumors depend upon the growth of new blood vessels. This process, called angiogenesis, occurs in adults only in a few special circumstances. As tumors begin to grow they secrete chemicals that promote formation of new blood vessels, enabling a tumor to acquire the nutrients necessary for its growth and survival. Importantly, these tumor-associated blood vessels also serve as a conduit for escaping tumor cells that enter the bloodstream and seed in distant organs. If the blood supply to the tumors can be blocked, it might be possible to starve the tumor and reduce its chance of spreading throughout the body.

Numerous attempts have been made over the years to cut crucial supply lines and, in effect, to starve tumors to death. Most efforts failed because of the complicated biology of blood vessel growth. In 1994, Cheresh and his colleagues discovered a single biochemical switch that triggers the growth of blood vessels. More importantly, they found two proteins that were able to turn off the switch, depriving tumors of their blood supply. What is particularly exciting about this treatment is that, unlike more traditional cancer therapies, it does not damage normal tissue. Instead, the proteins interfere with a step that is important only in the creation of new blood vessels. Existing arteries, veins, and capillaries are unaffected.

This discovery will provide the basis for creating drugs to help overcome the threat of drug resistance.

A wide variety of solid tumors are targeted for treatment using these anti-angiogenesis proteins, including malignant melanomas and cancers of the prostate, lung, breast, colon, pancreas, and brain.

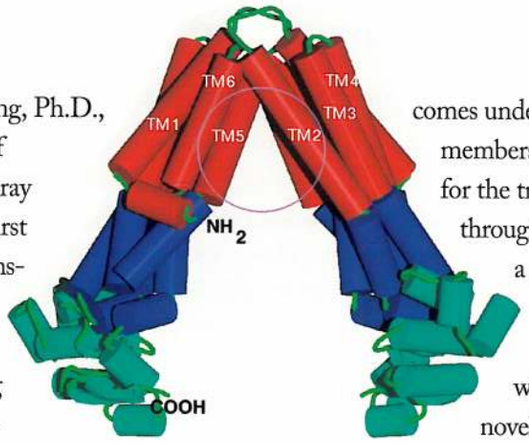
A very different approach is taken by Ralph Reisfeld, Ph.D., Professor, Department of Immunology, and his colleagues, who are developing vaccines that stimulate the immune system to kill cancer self-antigens before they become established. Two separate tracks are being followed in the effort to stimulate the immune system to reject tumors and to battle metastases successfully. The first, passive therapy, works indirectly by targeting antibodies to find the tumor cells and then activating the body's other defenses against them. In the second, active therapy, effector cells are asked to kill tumor cells directly. T cells, if properly activated, can be very effective killers. Since the tumors have fooled the immune system into believing that they are not foreign but part of the self, the trick is to overcome the T cells' natural tolerance towards self antigens, to put them on alert status and to prompt them to attack. Overcoming this natural reluctance of the T cells to attack could become the basis for a successful vaccine.



The peripheral blood smear reveals hairy cells with typical frayed blue cytoplasm, indicative of the circumferential cytoplasmic projections, and ovoid nuclei (Wright's stain, x450).

TACKLING THE PROBLEM OF DRUG RESISTANCE

New strains of disease resistant to proven treatments are constantly developing, defeating the ability of medical practitioners to deal with them effectively. Thousands of proteins in the outer walls or membranes of cells help the cells interact with the outside world. Some act as defensive pumps, shuttling antibiotics out of bacterial cells or chemotherapy drugs out of cancer cells. With the help of these pumps, also called transporters, many cancers and bacterial infections are becoming invincible.



The x-ray structure of the multidrug resistance transporter homolog MsbA from *Escherichia coli*. The transporter was solved to 4.5 angstrom resolution in the laboratory of Geoffrey Chang, Ph.D. MsbA is organized as a homodimer with each subunit containing six transmembrane α-helices and a nucleotide-binding domain. The view shown is looking into the opening of the chamber (circled), which catalyzes the "flip-flop" of substrates from the inner to the outer membrane leaflet.

In September 2001, Geoffrey Chang, Ph.D., Assistant Professor, Department of Molecular Biology, produced an x-ray crystal structure that provides the first detailed glimpse of a membrane transporter protein. This discovery will provide the basis for creating drugs to help overcome the threat of drug resistance. A long-range goal is the development of a new class of drugs that patients would take with chemotherapeutic agents to prevent the latter from being denied access to cancer cells where they can do the work for which they were designed. Effectively plugging the pumps would make many of the diseases more vulnerable to the medications they now brush aside.

IMPROVING TRANSPLANTATION

On the clinical side, James Mason, M.D., Director, Blood and Marrow Transplantation and Associate Director of the Scripps Cancer Center, is working at the cutting edge of research making blood and marrow transplant procedures safer and better. Instead of transplanting bone marrow itself, peripheral blood stem cells derived from bone marrow are used. Autologous transplants use the patient's own peripheral blood stem cells, which are "donated" and frozen or cryo-preserved for future use. Chemotherapy, alone or in conjunction with radiation therapy, is then used to destroy the affected cancer cells. In this process other cells are also damaged. The previously donated cells are now transfused back into the patient in a rescue attempt. When cells from the bone marrow or peripheral blood of a donor are used, as opposed to autologous cells, the procedure is called an allogeneic transplant.

Blood and marrow transplants are appropriate for treating a wide variety of cancers, including acute and chronic leukemia, non-Hodgkins lymphoma, Hodgkins disease, multiple myeloma, and certain solid tumors such as testicular cancer in relapse.

To foster communication and cooperation among TSRI and the five Scripps hospitals, a common Scientific Protocol Research Committee and an Internal Review Board (IRB) have been established. Every major action affecting the cancer programs of the separate units now comes under the scrutiny of the IRB. Its members determine which new protocols for the treatment of cancer are adopted throughout the system. In addition, a clinical research network has been established so that cancer patients in the Scripps system will have immediate access to novel and innovative compounds through their local oncologists.

As Saven says: "The emphasis of the Scripps Cancer Center is to promote bench-to-bedside research, harnessing the basic research accomplishments of TSRI and the excellence in Scripps clinical cancer care."

Fortunately, the U.S. federal government continues to supply important grant funds for defined basic scientific research projects. Private donors have also been found to provide major funding not only for the institutional structures that support the overall research enterprise, but also as a way to fill gaps not covered by government grant funds. Nevertheless, although Scripps has been blessed with generous donors in the past, the demand for funding always outruns the supply.

At the other end of the drug development chain, clinical research is woefully underfunded. Government research funds are available to pay for some trials but the amount is never enough. Who then will fund the trials of drugs to treat rare cancers, the area in which the Scripps Cancer Center has a unique role to play? An enormous need and opportunity exists for private donors to support these clinical trials.

...a clinical research network has been established so that cancer patients in the Scripps system will have immediate access to novel and innovative compounds through their local oncologists.

The Center is applying for National Cancer Institute funding through a planning grant, with the long-term hope of the SCC becoming a comprehensive cancer center. ■

Kellogg School of Science and Technology

TSRI Names Graduate College in Honor of Janet and W. Keith Kellogg II

In honor of their extraordinary contributions to science and education, The Scripps Research Institute named its graduate college the Kellogg School of Science and Technology for philanthropists Janet R. ("Jean") Kellogg and W. Keith Kellogg II.

"The Kelloggs have been great benefactors of TSRI for many years and their commitment to education is exceptional," says TSRI President Richard Lerner. "We are grateful for their extraordinary generosity and for their enthusiasm for the discoveries taking place at TSRI."

For many years, the Kelloggs have been among the country's most devoted philanthropists, giving generously through their own estate and through a foundation established in memory of Mr. Kellogg's parents, Helen and John Kellogg, the son of cereal magnate W.K. Kellogg. Their support of the Kellogg School of Science and Technology at TSRI brings together two objectives in the Kelloggs' giving — support for science and support for education.

The Kelloggs have been long-standing patrons of education, giving generously to several institutions of higher education in California and in the Chicago area, where they lived for many years. Most notably, the Kellogg Graduate School of Management at Northwestern University was named in their honor.

The Kelloggs' commitment to science is evident in their having established an endowed chair in chemistry and having made a significant contribution towards the Arnold and Mabel Beckman Center for Chemical Sciences at TSRI. They also funded the Continuing Care Unit at Scripps Memorial Hospital-Encinitas and the Kellogg Cancer Center in Evanston, Illinois.

"We are very pleased to have a name so synonymous with education associated with our institute, which is committed to offering the highest quality graduate education and to making seminal discoveries in science," says Jeffery Kelly, vice president for academic affairs and dean of graduate studies at TSRI.

In less than 15 years, TSRI has built its Ph.D. program into one of the most respected graduate programs in the country.

The 13-year-old Macromolecular and Cellular Structure and Chemistry (MCSC) Program was recently ranked ninth overall in the biological sciences and the 10-year-old Program in Chemistry ranked sixth overall in chemistry in the April 15, 2002 edition of *U.S. News & World Report*. TSRI's Ph.D. chemistry program was also ranked second in the nation in organic chemistry.

"[The Kelloggs'] support of our graduate program ensures state-of-the-art education for this country's finest young minds," says Carlos Barbas, Ph.D., who holds the Janet and W. Keith Kellogg II Chair in Molecular Biology. "The impact of this gift will be felt for generations as these scientists mature and contribute to our society the fruits of their graduate education."

In special recognition, TSRI conferred honorary doctorates of science on the Kelloggs at this year's commencement ceremony on May 17. ■

Promoting Wound Repair

One of the First Known Biological Roles for Mysterious γδ T Cells Discovered

Researchers at The Scripps Research Institute have identified a major role in promoting wound repair played by a mysterious type of immune cell that resides mainly in the skin and gut – the γδ T cell (pronounced "gamma-delta").

"Very little has been known about the function of these cells until now," says TSRI investigator Wendy Havran, Ph.D., who led the effort that detected this novel function of γδ T cells.

The findings, published in the journal *Science*, should be important for scientists who are interested in treating diseases that arise from epithelial cell disorders, like asthma, psoriasis, cancers, and inflammatory bowel disease.

Havran, who is an Associate Professor in the Department of Immunology, has been studying γδ T cells for several years. Various biological roles for the cells had been postulated by scientists, and many researchers had sought to determine how they might be involved in diseases. Until now these studies only deepened the mystery of the γδ T cell.

A CELL OF KNOWN ORIGIN BUT UNKNOWN FUNCTION

What had been learned of γδ T cells in the nearly two decades since their initial discovery was that they arise early in fetal development in the thymus. From there, they migrate to epithelial tissues – the thin outer layer of cells that makes up the outermost layers of skin and lines organs like the intestines and lungs.

Unlike the canonical T cells of immunology – the white blood cells – most γδ T cells do not circulate through the bloodstream. Instead, they are the major T cell component of the skin, lung, and intestine, where they take up residence

Two TSRI Scientists Elected Members of the National Academy of Sciences

Two professors from The Scripps Research Institute — Drs. Francis V. Chisari and Chi-Huey Wong — were elected to membership in the National Academy of Sciences in recognition of "their distinguished and continuing achievements in original research."

The election was held April 30, 2002 during the 139th annual meeting of the Academy. Election to membership in the Academy is considered one of the highest honors that can be accorded a U.S. scientist or engineer. Those elected today bring the total number of active members to 1,907. The number of National Academy of Sciences members at TSRI now totals 14.

Francis V. Chisari, M.D., Professor, Department of Molecular and Experimental Medicine, and Director, General Clinical Research Center, is known for his work on hepatitis B and C virus infections and carcinogenesis. He is widely recognized for a series of discoveries that defined the immunological basis for HBV clearance, persistence and disease; demonstrated that the immune response can terminate HBV replication without killing infected cells; established the basis of hepatocarcinogenesis during chronic HBV infection; and laid the foundation for the development of therapeutic vaccines to cure chronic hepatitis, the leading cause of liver cancer throughout the world.

Chisari, born in New York, NY, received his B.A. from Fordham University and graduated in 1968 from the Cornell University Medical College. He completed postdoctoral training at Cornell, Dartmouth, NIH, the Mayo Clinic and the Pasteur Institute. Chisari has been on the faculty at Scripps since 1973, and serves as Adjunct Professor in the Department of Pathology, University of California School of Medicine. He is the recipient of numerous prestigious awards and honors, including the 1999 Rous-Whipple Award and the Ernst Jung Prize for Medicine, and is the author of more than 200 research articles.

Chi-Huey Wong, Ph.D., Professor, The Skaggs Institute for Chemical Biology, and Ernest W. Hahn Professor and Chair in Chemistry, has developed methods that have made possible the synthesis of classes of compounds — especially those related to carbohydrates — important in biology and medicine and that have pointed the way to "green" methodologies for uses in large scale chemistry. He has developed a number of enzymatic and chemical-enzymatic methods for the synthesis of carbohydrates, as well as contributions to the synthesis of novel peptides, glycopeptides and glycoproteins. Wong's work in the area of RNA recognition and carbohydrate-selectin interaction has led, in part, to the development of compounds to combat the problem of antibiotic resistance. Other research may lead the way to the development of new anti-inflammatory and anticancer agents.

Wong received a B.S. in chemistry and biochemical science as well as a master's degree in biochemical science from National Taiwan University. In 1982, he received a Ph.D. from Massachusetts Institute of Technology and completed postdoctoral studies there. He then joined the chemistry faculty at Texas A&M University until he was named to his faculty appointments at The Scripps Research Institute in 1989. Wong is the recipient of many awards and honors and was named one of the 100 most cited chemists in the world from 1981-1999, comprising less than one half of one percent of all publishing researchers. ■

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and monitor the neighboring epithelial cells for damage and disease.

Though γδ T cells are the first T cells the thymus produces, this organ nearly shuts off production of them later in development. Throughout life, the body maintains its population of γδ T cells "on-site," allowing them to divide as needed.

In the epidermis where the γδ T cells are concentrated – numbering half a thousand cells per square centimeter – they have a spiny, stretched-out, finger-like shape that contacts as many skin cells as possible.

Unlike other T cells in the body, which display a wide diversity of receptors that recognize a wide diversity of antigens – the molecular components of various pathogenic invaders – the γδ T cells in the skin seem to have little, if any, diversity and display a uniform receptor and recognize only a single antigen.

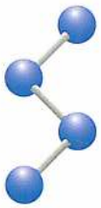
"When wounds heal, the epithelial cells in the skin have to proliferate and fill in the wounds," says Havran.

The study showed that when skin is cut or damaged, keratinocytes, a type of epithelial cell common in the epidermis, release the antigen that is recognized by the γδ T cells, which then become activated. Once activated, the γδ T cells begin making a growth factor that binds to keratinocytes and other epithelial cells, helping them proliferate and leading to the closure of the wound.

The activated γδ T cells undergo a morphological change and become little round factories, concentrating their energy on producing the growth factors and repairing the wound. They also proliferate, multiplying to increase the response to the wound.

"When γδ T cells are missing, you see a delay in wound repair," says Havran, adding that the body still has other mechanisms to facilitate wound repair that eventually heal the wound.

The research article "A Role for Skin γδ T cells in Wound Repair" was authored by Julie Jameson, Karen Ugarte, Nicole Chen, Pia Yachi, Elaine Fuchs, Richard Boismenu, and Wendy L. Havran and appeared in the April 26, 2002 issue of *Science*. The research was funded by the National Institutes of Health and the Leukemia and Lymphoma Society. ■



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