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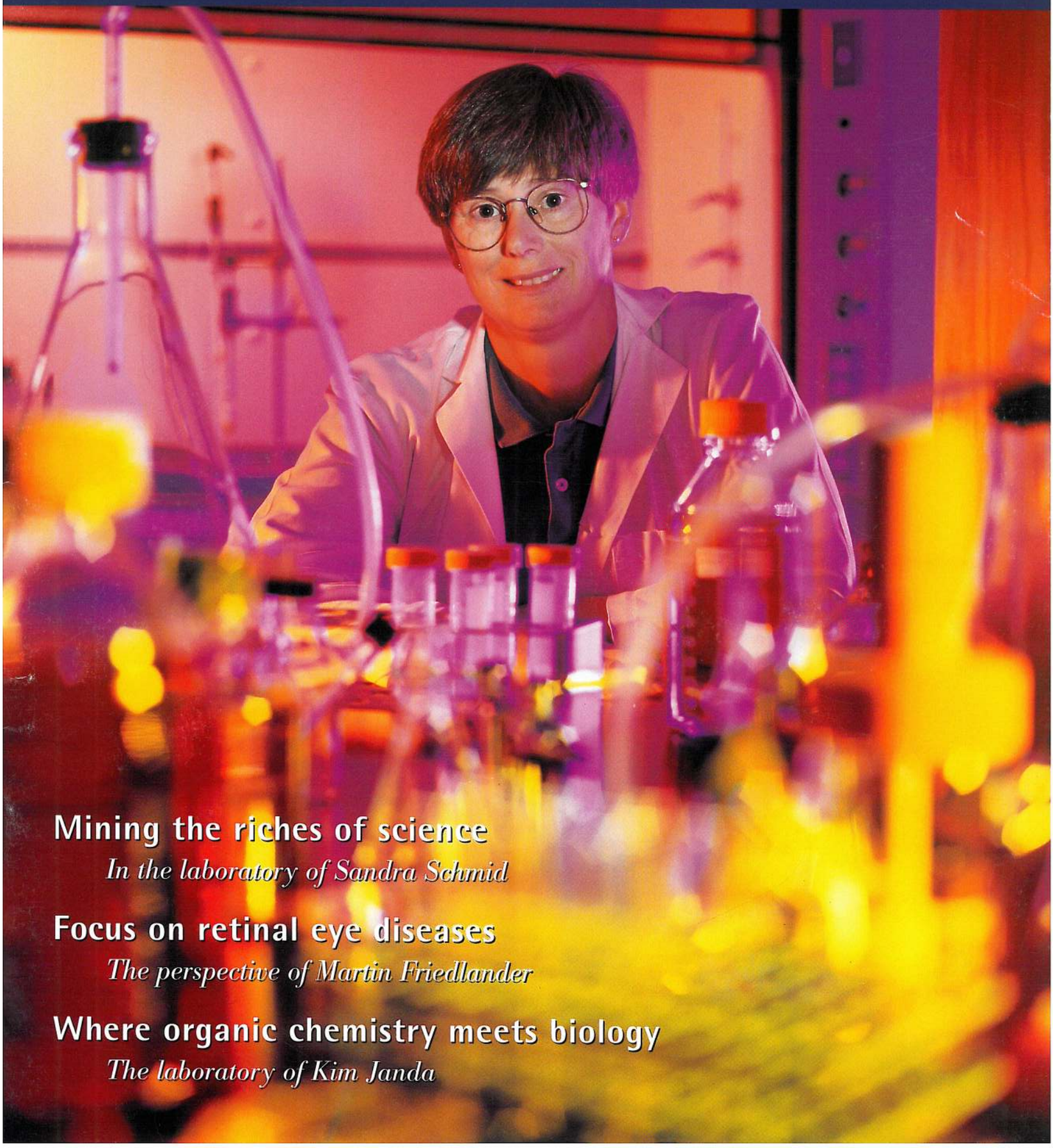
THE SCRIPPS RESEARCH INSTITUTE

Endeavor



Mining the riches of science

In the laboratory of Sandra Schmid

Focus on retinal eye diseases

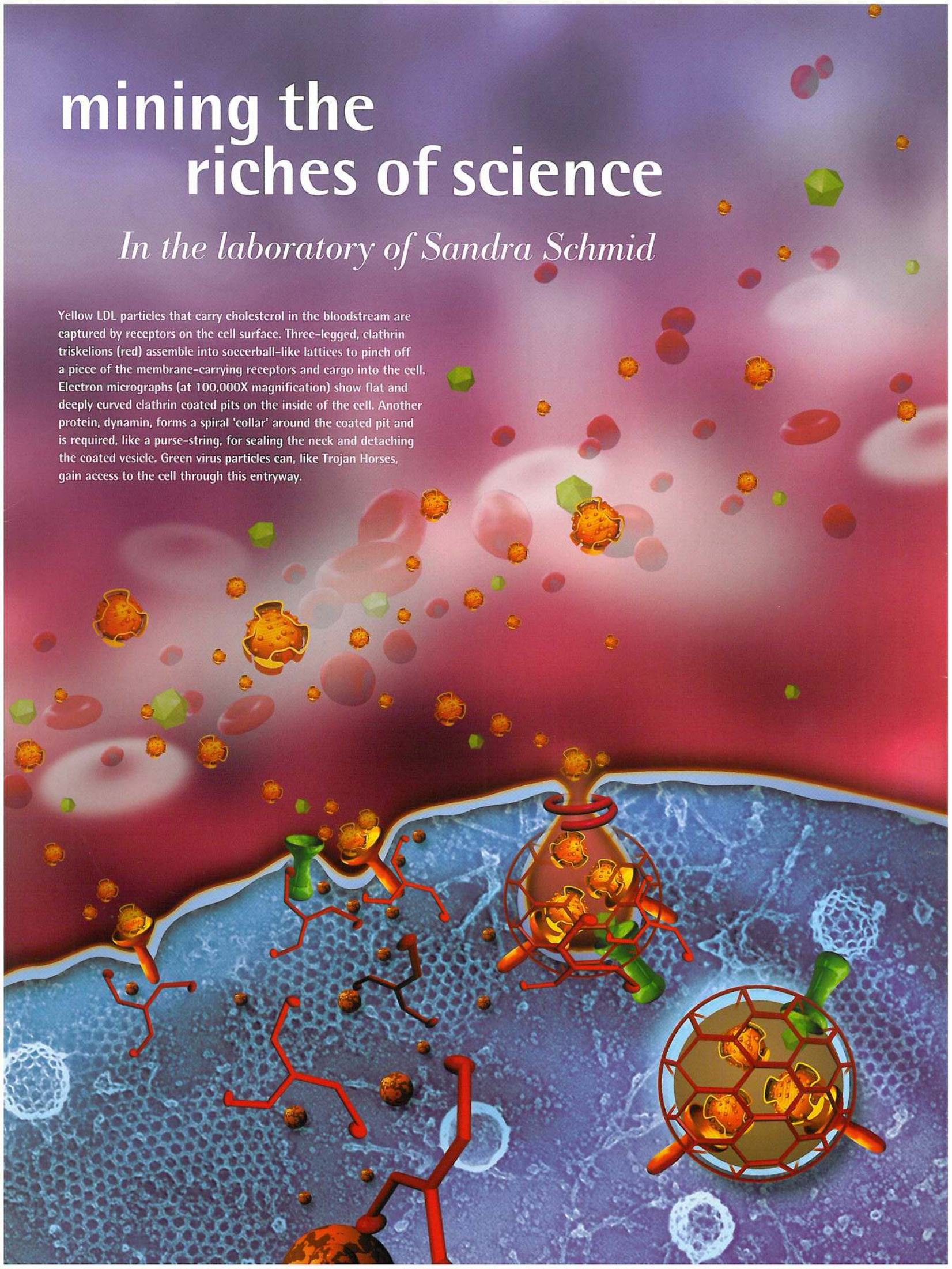
The perspective of Martin Friedlander

Where organic chemistry meets biology

The laboratory of Kim Janda

mining the riches of science

In the laboratory of Sandra Schmid



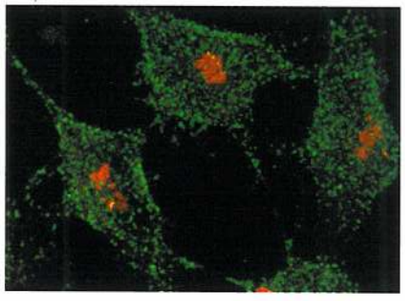
Yellow LDL particles that carry cholesterol in the bloodstream are captured by receptors on the cell surface. Three-legged, clathrin triskelions (red) assemble into soccerball-like lattices to pinch off a piece of the membrane-carrying receptors and cargo into the cell. Electron micrographs (at 100,000X magnification) show flat and deeply curved clathrin coated pits on the inside of the cell. Another protein, dynamin, forms a spiral 'collar' around the coated pit and is required, like a purse-string, for sealing the neck and detaching the coated vesicle. Green virus particles can, like Trojan Horses, gain access to the cell through this entryway.

For Sandra L. Schmid, Ph.D., Associate Professor in the Department of Cell Biology, there are different types of scientists and she likens all of them to miners. This is not as unusual an analogy as it might seem.

William Haseltine, one of the founders and the CEO of Genome Sciences, was recently quoted as saying, "If you were to think of scientists as coal miners of the mind, you'd have it about right."

In Sandra Schmid's mind, first come the wildcatters, individual explorers who set out to discover scientifically rich deposits and then move on, content to let someone else do the heavy lifting while they head off over the next hill. Like the rest of the scientific community, they know that you get the Nobel Prize not for digging but for those single, startling discoveries that make the front page of *The New York Times*.

After that come the strip miners, scientists who tackle broad areas of science but who go only so deep, who define themselves by sweep, not depth. Then there are the deep pit miners, the ones who, as they say in the current parlance, like to drill down. That description with its connotations of determination and practicality fits Sandra Schmid perfectly.



"I consider myself to be a deep pit miner," she says. "As an undergraduate at the University of British Columbia (Schmid is Canadian) I developed an interest in how proteins are transported in small packages or vesicles into, out of and across cells. I staked my claim as a graduate student in biochemistry at Stanford University focusing on one class of transport vesicles. My laboratory at Scripps continues to dig for a deeper understanding of how these vesicles form and fill with cargo. Our mining continues to produce insights of significant value." As any good miner knows, the deeper you dig the more likely you are to find diamonds.

DIGGING IN AT TSRI

Schmid joined the faculty of The Scripps Research Institute 11 years ago. She was recruited immediately after completing her postdoctoral training in cell biology at Yale, which was supported sequentially by two of the most prestigious awards for young investigators; a Helen Hay Whitney Fellowship and a Lucille P. Markey Scholarship. The latter also helped finance her first five years as an independent assistant professor.

She might have been a freshman at TSRI but she knew precisely where she wanted to dig, had known since she was a graduate student: She wanted to study endocytosis, a process that lies at the heart of human cell metabolism.

EYING THE PROCESS

Basically, endocytosis (or receptor-mediated endocytosis) is an uptake mechanism that allows cells to ingest various substances including nutrients, growth factors, even viruses and toxins. Small pieces of membrane from the cell surface are pulled inward by a protein "coat" that assembles into a lattice-like structure forming a depression, called a "coated pit," that protrudes, almost like a reverse blister, into the interior of the cell. Receptors that attract nutrients and growth factors are concentrated in coated pits as they continue to deepen. Finally, the neck of the basket is pinched off releasing a small "coated vesicle," first described as a "vesicle in a basket," that carries its cargo into the cell.

The process is trickier than it sounds, because the environment outside of our cells — the bloodstream,

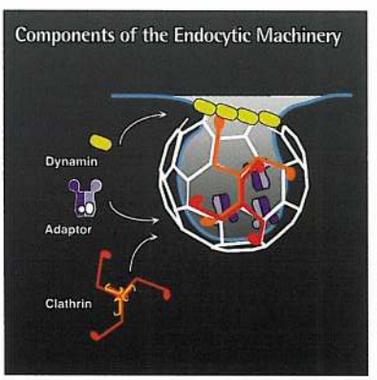
The diagram to the left is an immunofluorescence micrograph. The green dots correspond to the hundreds of coated pits on the plasma membrane; the red shape is the trans-Golgi network inside the cell.

On The Cover: Sandra Schmid, Ph.D., Associate Professor, Department of Cell Biology.

really — is vastly different from the one inside our cells. The bloodstream is similar to seawater, high in free-floating sodium and calcium. But within our cells, there is little sodium and hardly any calcium to speak of. For our cells to survive, these two environments must be kept separate, even though they exchange chemical information on a regular basis. How they do that exactly is still something of a mystery; think of it this way. The cell is a balloon. Now select a small section of the balloon, fill it with a nutrient, inject it into the center of the balloon but don't break the balloon and don't leave a hole.

Morever, cells don't let strangers into their basket party, at least not on purpose. Like any well-run establishment, they have an entrance policy and they discriminate — only those molecules with specific tickets can get into the club (or the basket) and when it gets full, the door closes and the basket takes off. The protein molecules that end up in these baskets are thousands of times more concentrated within the basket than anywhere else in the body.

Occasionally, though, the doorman gets handed a stolen ticket and the wrong kind of customers — viruses and toxins — get inside. The surfaces of both substances are littered with proteins. Using the proteins as masks, they attach themselves to those molecules with the appropriate receptors and are accidentally carried into the cell. If that sounds vaguely sinister, Schmid has a theory: Viruses have been studying cell biology for hundreds of millions of years, we've only been doing it for a century. They're way ahead of us.



Schematic diagram of the coated vesicle upon which the Schmid lab's attention is focused.

DIGGING FOR GOLD

Thanks to Schmid and the work of her laboratory fellows, we're starting to catch up. "I've been studying endocytosis for almost twenty years," she said, and her efforts have produced some rich ores. As a graduate student she determined how clathrin, the major coat protein, assembles into baskets and purified a cell protein that releases clathrin from coated vesicles after they have formed. "The coat has to be recycled and the vesicle has to be naked to deliver its contents to the endosome, a repository and sorting depot for incoming cargo." As a postdoctoral fellow, Schmid developed new methods to isolate endosomes and defined them biochemically. Her laboratory at TSRI has developed the technology to recreate each of the steps leading to endocytosis in the test tube, allowing them to identify the cellular machinery that carries them out and to reveal how it works.

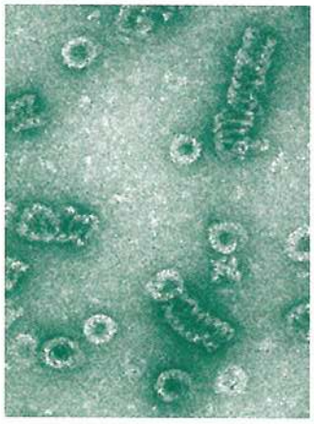
The practical possibilities of controlling cellular uptake through dynamin seem phenomenal. Once understood completely, it might be possible to block the uptake of viruses and toxins into the cell.

In addition to the coat proteins, clathrin and adaptors, that form the lattice of the basket, Schmid and her colleagues discovered that another rather large protein, dynamin, plays a key role in releasing the baskets or vesicles from the cell membrane. For endocytosis to work correctly, it obviously requires a mechanism that can separate the vesicle membranes from that of the cell without breaking the surface of either. Dynamin's chemical structure allows it to assemble itself into rings and spirals. During endocytosis, dynamin molecules form a ring around the top of the basket, like a purse-string to seal off the neck. In other words, the budding vesicle's coat has a collar. Schmid discovered that dynamin could be manipulated to control the rate at which vesicles pinch off. With that discovery, they soon created mutant forms of dynamin that could either speed up or bring the entire process of endocytosis to a complete stop.

At this point, she says, they have discovered the master regulator molecule and are learning the hierarchy of interactions in what is a remarkably complex machine. It is, she points out, as though they had gathered together all the parts needed to build an automobile engine but aren't quite certain how they work together. Their ability to reassemble this cellular machinery in the test tube will eventually allow them to piece together the entire puzzle.

An important next phase is to understand precisely how the transference between cell surface and the cell interior is made. The most acceptable candidate is the thin bilayer of lipids or fat that covers the surface of each cell.

"There has to be some kind of rearrangement of this lipid bilayer," she said. "We think the mechanism will end up looking something like the airlocks on a space ship in that at least one lipid layer is always closed."



Negative stained EM images of dynamin assembled into rings and helical stacks of rings.

Indeed, Schmid's laboratory has recently shown that a rare lipid species is required both to initiate coat assembly and to release the vesicle. They are currently digging to discover how this lipid is made and what it does.

The practical possibilities of controlling cellular uptake through dynamin seem phenomenal. Once understood completely, it might be possible to block the uptake of viruses and toxins into the cell. Speeding up endocytosis helps to turn off signalling receptors that trigger uncontrolled cell growth, as occurs in cancer. Alternatively, after a procedure such as angioplasty, it might be possible to slow down the regeneration of smooth muscle cells in the arterial wall by clearing signalling receptors from the cell surface.

"There are a number of ways we think this process might eventually have some practical value," she says. "We're studying a basic mechanism and the better we understand it, the better we can intercede with viruses and toxins or to selectively target cancer cells with specific cytotoxic drugs. It is an essential process but one that can lead to so many applications."

AN EMINENTLY PRACTICAL PERSON

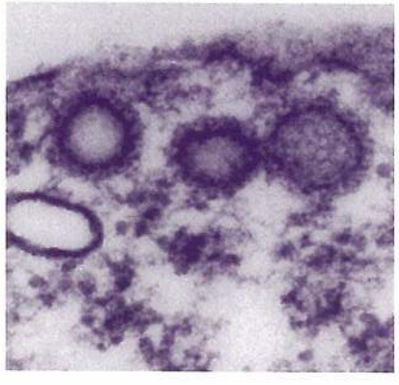
TSRI encourages this kind of practical thinking. In terms of scientific mining, it has always been a stubbornly independent operation.

"People here think about novel therapeutics and new ideas and you get sucked up into that excitement," she points out. "I think in practical terms — so I can explain to my mom and dad and my children what it is that I do. So when I'm digging in the dark, I try to shine my light in the corners."

A great many of the young women on her staff who were attracted to the laboratory for the scientific opportunities it presented, found her a role model — an eminently practical woman who has managed to have both a family and a career without short-changing either. She makes it clear that there is no serious reason that being a good mother and having a competitive career in science are incompatible goals. The secret, she claims, is not to spread yourself too thin — either personally or scientifically — and to have a very clear understanding of your priorities when you start out.

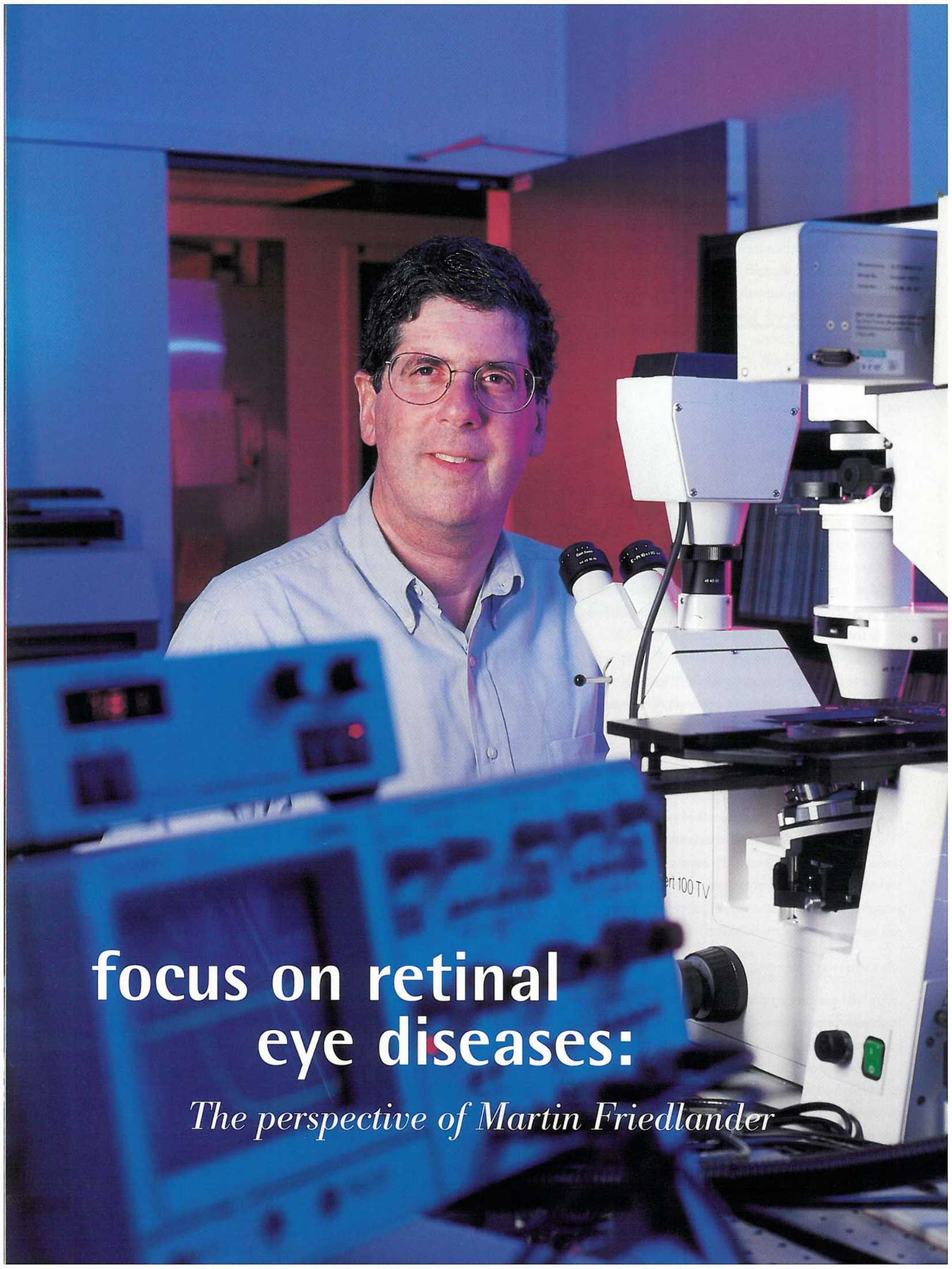
With her husband — William Balch, Ph.D., Professor, Department of Cell Biology, who also works at TSRI — they run a staggered shift. Her husband goes to work early and leaves his laboratory at five so that he's home in time to cook dinner and have it ready when she gets home around seven. "My kids complain, however, when we only talk science at dinner."

"There are two things that are important to me, family and science. What drops off the end are leisure activities that don't include my family. For example, I can't tell you what's playing at the symphony or the local multiplex. I haven't seen a movie in years that wasn't a Disney movie. By the same token, my research is very rewarding and I'm proud of the scientific reputation I have built, both at TSRI and in the international community."



Thin-section electron micrograph images of clathrin coated pits that accumulate in cells expressing mutant dynamin molecules.

Schmid's accomplishments have been recognized by a Career Recognition Award from the American Society for Cell Biology and she was named an Established Investigator of the American Heart Association. She is founding co-editor of a new journal on intracellular transport, named Traffic, that will be based at TSRI. Finally, she says, "I am most proud of the quality of postdoctoral fellows who want to train and work in my lab. Their contributions are immeasurable." ■



focus on retinal eye diseases:

The perspective of Martin Friedlander

Until recently, physicians have had little to offer patients with age-related macular degeneration (ARMD) and diabetic retinopathy, the leading causes of visual loss in people over and under the ages of 65, respectively.

Now, thanks to a recent convergence of advances in the field of basic vascular cell biology and clinical medicine, several new therapeutic approaches to these diseases are being evaluated.

Both of these vision threatening eye diseases are characterized by the development of abnormal blood vessel growth in the eye, a process known as angiogenesis. In the case of ARMD, new blood vessels grow under the retina, while diabetic retinopathy is caused by the growth of abnormal vessels on top of the retina. The effect is much the same; the vessels interfere with normal structures or the transmission of light to the back of the eye, impeding vision.

Friedlander's focus is on how integrins and MMPs function during ocular angiogenesis.

Martin Friedlander, M.D., Ph.D., Associate Professor, Department of Cell Biology, and a retina specialist in the Division of Ophthalmology at Scripps Clinic, is conducting key research aimed both at understanding these disease processes and at developing treatments for them.

"The proliferation of new blood vessels is a common feature in many ocular diseases including not only age-related macular degeneration and proliferative diabetic retinopathy but also rubeotic glaucoma, interstitial keratitis and retinopathy of prematurity. It also is a leading factor contributing to corneal graft failure. If we can selectively target new vessels involved in these diseases while leaving old vessels alone, then we would have a way to shut down these angiogenic processes," said Friedlander.

FROM ONCOLOGY TO OPHTHALMOLOGY

Many forms of cancer also depend on the development of new blood vessels to survive and grow. Thanks to work done in the field of oncology, several anti-angiogenic compounds are now in clinical trials. These include compounds targeting a variety of growth factors including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).

As in the oncology field, VEGF is one of several targets for reducing angiogenesis in ocular disease. Recent studies indicate that VEGF may play an important role in stimulating angiogenesis in diabetic eye disease. Clinical studies with anti-VEGF antibodies and other VEGF-blocking molecules are now underway to evaluate the potential of this approach for treatment of diabetic retinopathy, he noted.

But there is more to the story than VEGF. For many years, TSRI researcher David Cheresh, Ph.D., has been studying another aspect of angiogenesis involving a class of molecules called integrins. About eight years ago, he discovered that one particular integrin, $\alpha_v\beta_3$ was activated on newly sprouting blood vessels and that the same integrin is expressed on new blood vessels feeding tumors. Even more exciting, he and his colleagues at Merck KGaA were able to create other molecules to block $\alpha_v\beta_3$ and shut down tumor growth. The two scientists met shortly after Friedlander arrived at TSRI in 1993, having moved his lab from UCLA.

"I had been interested in the potential of antiangiogenesis for treating eye diseases for many years. We knew that abnormal growth of new blood vessels played a major role in these blinding diseases. The problem was, we didn't have a rational approach to treating angiogenesis. At a dinner for new faculty, Richard Lerner brought my attention to an upcoming journal article by David Cheresh on the integrin research. This research showed me that they knew something about the

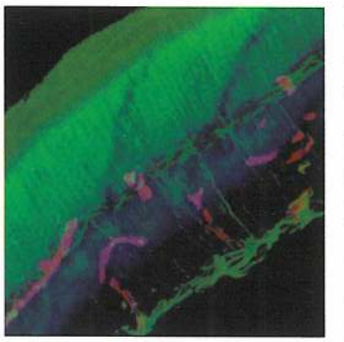
ARMD

- Leading cause of visual loss in Americans over 65 years old.
- Could triple in incidence in the next 20 years, as the population ages.
- Affects as many as 15 million Americans over the age of 65.
- As many as 15% of those will experience vision loss as a result of new vessel growth in the eye.
- Currently no cure or effective treatment.

DIABETES RETINOPATHY

- Leading cause of visual loss in Americans less than 65 years of age.
- There are 16 million diabetics in the US of whom 40,000 per year develop ocular complications.

Martin Friedlander, M.D., Ph.D., Associate Professor, Department of Cell Biology.



Histological section of adult mouse retina stained immunofluorescently to show cell nuclei (blue), blood vessels (red) and astroglial filaments (green). These micrographs reveal the relationships between blood supply and the complex layers of the retina.

mechanism of angiogenesis, providing the basis for a rational therapeutic approach, something I had been looking for for years," Friedlander recalled.

The two have been collaborating ever since. Friedlander's focus is on how integrins function during cytokine-driven angiogenesis processes. In his early work, he confirmed that the $\alpha_v\beta_3$ integrin was indeed expressed on new vessels growing in the eye.

He also found that he could shut down new vessel growth in animal eye models by using an antibody antagonist of $\alpha_v\beta_3$ integrins developed in the Cheresh lab. The surprising finding was that this antibody did not shut down VEGF-driven angiogenesis. An antibody to a distinct but related integrin, $\alpha_v\beta_5$, did shut down the VEGF-, but not FGF-driven angiogenesis. Furthermore, a peptide antagonist of both integrins shut down both types of angiogenesis. From this work emerged the concept of at least two distinct cytokine-driven, integrin-mediated pathways of angiogenesis.

Subsequent research correlating data from human disease specimens with the animal model results revealed that different integrins were activated depending on where in the eye the new vessels were growing. In some cases VEGF was involved, while in other cases FGF was a more important factor. The researchers showed that patients with ARMD, who have new vessels growing under the retina, expressed mostly $\alpha_v\beta_3$. Patients with diabetic retinopathy, in contrast, activated two integrins, $\alpha_v\beta_3$ and $\alpha_v\beta_5$.

"This has profound implications for understanding both the cause of these diseases and potential treatment approaches. The findings suggest that targeting VEGF alone would not produce any significant benefits for ARMD patients, whereas it may be very effective for treating diabetic retinopathy. Clinical trials are underway in oncology using humanized antibodies to $\alpha_v\beta_3$ integrin. Studies with retinal tissue from patients with ARMD indicate that the antibodies may have a significant effect on angiogenesis. Clinical trials in ARMD are planned with this approach," he said.

Funding for Friedlander's work is provided by the National Eye Institute, National Institute of Health; the Robert Mealey Program for the Study of Macular Degenerations; Merck KGaA; and CibaVision/GTI/Novartis.

MATRIX METALLOPROTEINASES

Matrix metalloproteinases (MMPs) are enzymes involved in regulating the extracellular matrix, the glue-like structure that holds our bodies together. They are involved in many cellular processes including angiogenesis. Friedlander's lab is examining the relationship between integrin signaling and the extracellular matrix, looking for a way to block MMPs involved in angiogenesis selectively, without interfering with other vital processes.

"These MMPs are all over the body. If you throw in an antagonist you will affect many systems in the body. In fact, one MMP antagonist was pulled from the market several years ago after patients developed serious side effects," he said.

The researchers may have found a more specific MMP. Recent research showed that actively growing endothelial cells have a way of localizing a specific MMP, called MMP2, to the tips of new vessels. The research showed that MMP2 can be degraded into another molecule called PEX (the carboxy-terminal, non-catalytic domain of MMP2). PEX in turn can bind to the $\alpha_v\beta_3$ integrin, providing another way to shut down angiogenesis.

"This demonstrates a wonderful trait of nature. It appears that nature evolved a mechanism for using molecules for one purpose, and then recycle and use them to shut down the very same process," he noted.

OLD DRUGS, NEW USES

The antiangiogenic properties of the class of drugs known as corticosteroids have been known for many years. However, the severe side effects that accompany long-term use of these drugs have limited their use in treating eye disease. A new potent angiostatic steroid, anecortave acetate, that is devoid of the glucocorticoid activity that causes the side effects, may be the answer. Phase II clinical trials of this agent (sponsored by Alcon Laboratories) for treating ARMD are now well along; Friedlander is one of 15 principal investigators nationwide.

"I'm very excited about this trial. We have worked with this compound in the laboratory and have been impressed with the results in animal models," he said.

He is also a principal investigator at one of 30 centers worldwide participating in a clinical study (sponsored by Novartis) of another drug that was not originally developed for treatment of eye disease, called octreatide (Sandostatin LAR).

TOPOGENESIS

During medical school, and then as a junior faculty member, Friedlander worked in the laboratory of Gunter Blobel, M.D., Ph.D. Blobel, who won the 1999 Nobel Prize in Physiology or Medicine, described the general principles underlying the sorting and targeting of proteins to particular cell compartments. He determined that the protein itself carries the information that specifies its proper destination in the cell. These cellular zip codes are known as topogenic signals.

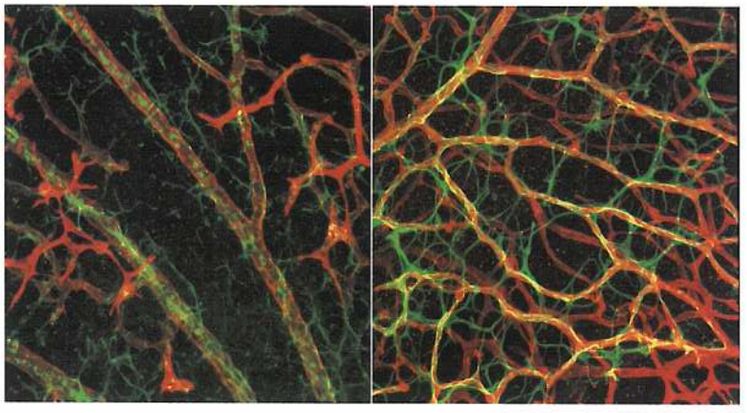
Friedlander participated in that early research first describing the presence of internal topogenic signals in polytopic membrane proteins like rhodopsin. He continues to apply the principles discovered in the Blobel lab to his current research. Part of his research group continues to study the role that topogenic signals play in targeting visually important polytopic membrane proteins to their proper places in normal and diseased eyes. He has studied the role of topogenic signals in the function of rhodopsin, a protein essential for sight. He is also studying the role that topogenesis plays in sodium and calcium exchange in photoreceptors. It appears that when these two proteins are mutated and display the wrong cellular 'zip code', this can result in degenerative changes in the eye of the type seen in certain inherited and acquired retinal and macular degenerations.

SPECIAL DELIVERY

An issue that continues to elude researchers developing treatments for eye diseases like ARMD and diabetic retinopathy is how to get the drugs to the intended destination. While molecular biology continues to provide sophisticated molecules with therapeutic potential, the technology to deliver these drugs lags behind. Noting that the drug companies "just aren't moving fast enough," Friedlander joined this effort and has accepted the challenge of developing practical drug delivery devices in his lab.

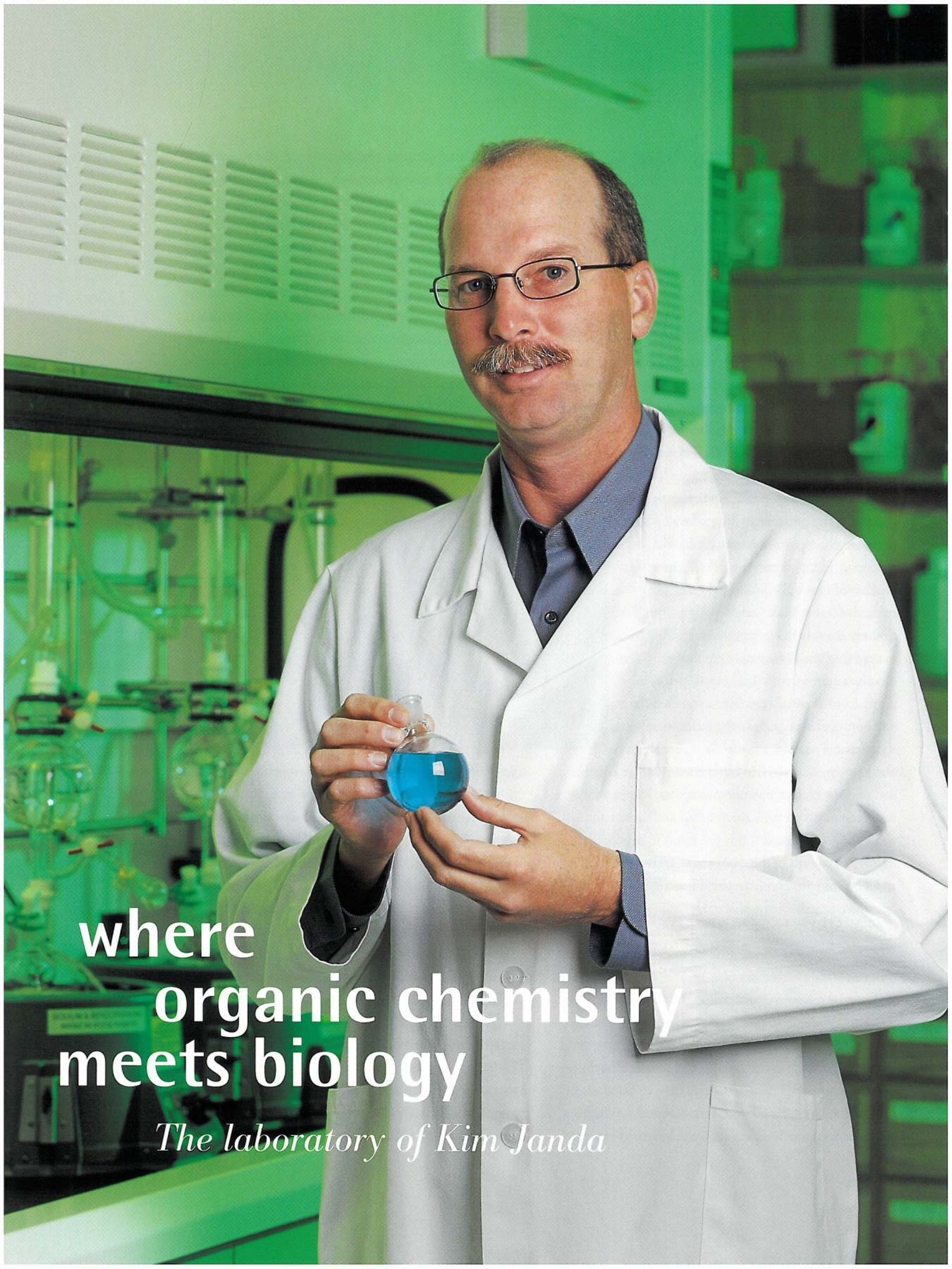
"My lab is interested in basic science. But we are also interested in clinical applications. So we are collaborating with a bioengineering group at Brown University to develop bio-erodable polymers — tiny microspheres in which to incorporate some of these novel compounds. It is helpful that the eye is a self-contained system. We would like to be able to inject a treatment behind the eye and then have it be released slowly over time. The idea would be to inhibit the progression of disease by injecting only a couple of times per year," he explained.

Cell-based delivery is another option his lab is exploring. In collaboration with Drs. Glen Nemerow and Peter Ghazal, associate professors in the Department of Immunology, the Ocular Gene Therapy Program at TSRI investigates ways to incorporate useful compounds directly into the cells involved. One approach involves using genetic engineering to introduce a gene into cells that will then produce a protein. Another approach they are looking at involves putting genetically engineered cells into a semipermeable membrane, and putting that membrane inside an inert container. This type of implant would allow slow release of a medicine or protein, while minimizing the risk of triggering an immune response. Still another approach involves using the outer coating of the eyeball, known as the sclera, as a kind of sponge. It may be possible to inject the sclera with a therapeutic compound and then let that compound seep into the eye over time.



Comparative fluorescence micrographs of the retinal vasculature in the mouse at 9 days (left) and 14 days (right) after birth. The vessels are stained red and astroglial fibers are in green. Note the striking increase in complexity with increasing age. These images were prepared from optical sections of whole retinas taken with the laser scanning confocal microscope.

"I cannot imagine a better place in the world to combine basic science and clinical research than The Scripps Research Institute. Now we can combine a major focus on visual cell biology with the clinical facilities to offer our patients the latest available therapeutic options," he said. ■



where organic chemistry meets biology

The laboratory of Kim Janda

Although he never planned it that way, Kim D. Janda, Ph.D., Professor, Department of Chemistry and The Skaggs Institute for Chemical Biology, has gotten more than his 15 minutes of fame. Much more.

His groundbreaking work in the area of immunopharmacotherapy — specifically, an antibody that appears capable of neutralizing the effects of cocaine and the development of a chemical warfare detection kit — put him in the spotlight twice in the last year.

In all fairness, the chemical warfare detection kit attracted attention in part because Janda wouldn't disclose the source of his funding to the media much beyond a tantalizing spy novel response: it came from an unnamed government agency, he said.

"Someone at this unnamed government agency asked us about a detection kit," Janda explains, "and said he would fund the project. We came up with the methodology, an on-site color kit. Basically, all chemical warfare agents are nerve gases — sarin, soman and VX. All three decompose to a common element known as MPA (methylphosphonic acid) and our test detects MPA."

Janda and a colleague created a monoclonal antibody that could recognize MPA molecules after they'd been marked with a special chemical solution. It worked quickly and easily: If the antibodies recognized the decomposed remnants of sarin, the mixture changed color.

"The agency paid us to develop the technology but never did anything more with it," he adds. "This was before the Sudanese bombing, so they could have used our methodology there."

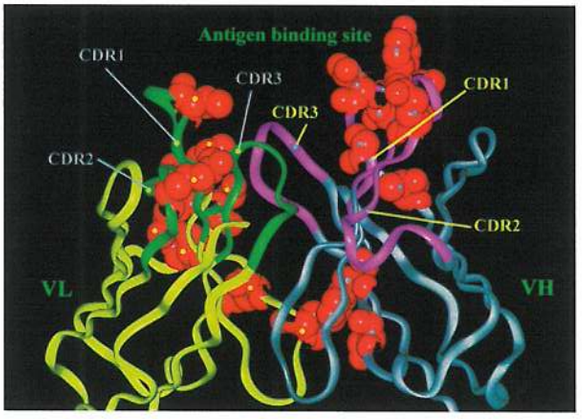
BREAKING AN ADDICTION

The cocaine antibody was a much different and much more significant discovery, both in terms of its science and its potential usefulness. It made the national news, appearing on both cable and network television and in all the major newspapers. That wasn't what impressed Janda, a man who takes his work seriously but admits to taking himself less so.

"I knew we'd made it when we got on the *Tonight Show* and *Politically Incorrect*," he jokes.

Janda, who received his Ph.D. in chemistry from the University of Arizona in 1984 and came directly to TSRI after that, clearly understands that cocaine addiction — more psychological than physical but still difficult to treat — is a serious problem in the United States. The National Institute on Drug Abuse and Alcoholism estimates that more than 2 million people need treatment for their dependence on cocaine. After that, the statistics turn even grimmer: Approximately 900,000 Americans start treatment but at least three-quarters of those return to using the drug.

"The media used the word vaccine to describe the antibody but that's a bit broad," he explains. "It's what we call active immunization because the antibodies



Humanized anitbody that is being used as a passive immunity medication to blunt cocaine abuse and relapse during protracted abstinence.

are produced within the body. We created a specific polyclonal antibody immune response that attaches itself to the cocaine molecule and prevents it from reaching the brain. It's like painting a bull's eye on cocaine so the immune system can recognize and remove it — the same way the immune system removes all foreign substances in the body. In layman's terms, a bunch of little antibody PacMen go around gobbling it up. It has to do it very rapidly because cocaine has a very short half-life in the body — around twenty minutes or less."

Janda points out that they have created another version of the cocaine antibody that is so prolific it can actually draw the cocaine molecules out of the brain. This is the passive version because these cocaine-binding antibodies are first produced in the lab and then injected.

Kim Janda, Ph.D., Professor, Department of Chemistry and The Skaggs Institute.

The antibody acts like a giant sponge, soaking up the cocaine. Janda believes that the antibody's unique ability to rapidly neutralize large quantities of cocaine within the body could be extremely useful in emergency rooms where physicians must deal with critical overdose situations. Using a two-antibody therapy (passive and active), he adds, totally obliterates cocaine from the system.

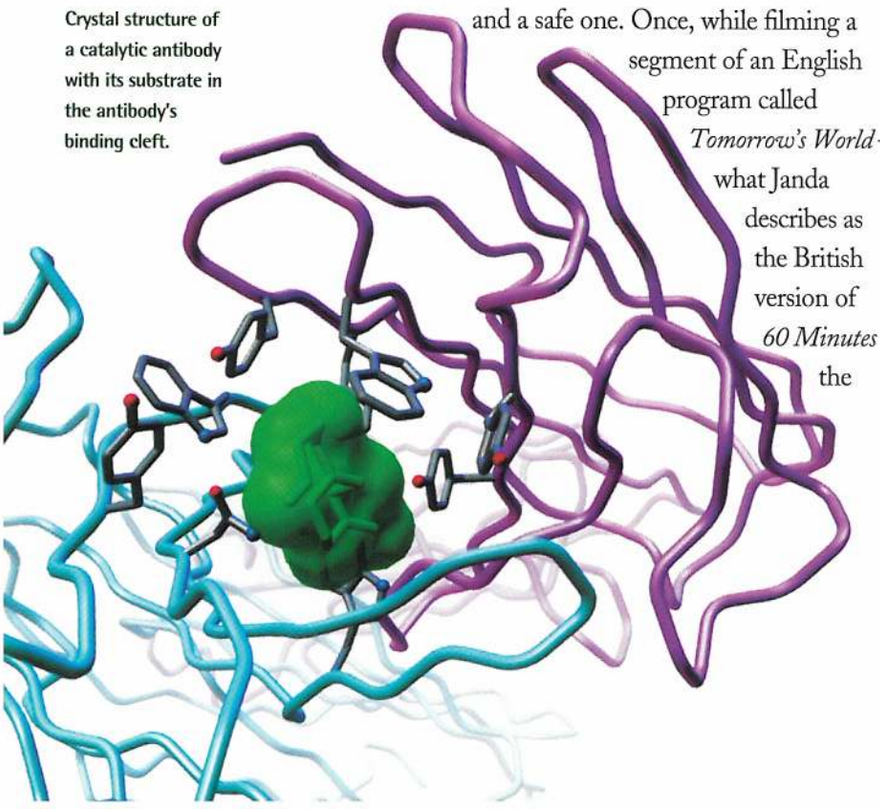
While the effects of the active immunization antibodies now last for several months before a booster shot becomes necessary, Janda and his colleagues are working to create passive antibodies that will also last longer — up to a month. With long lasting antibodies in place to continually block the drug's high, there is much smaller chance of a relapse, at least in theory.

THE HUMAN EQUATION

When Janda announced the possibility of human clinical trials later in the year, the public reaction to the story intensified substantially, adding a highly uncomfortable element to the whole media experience. His laboratory has been inundated with hundreds of emails, phone calls and letters from families, spouses and loved ones begging for his attention.

Janda emphasizes that the people who write him or try to make contact are desperate for help and see his work as their last chance. He can't help them but he understands their desperation. "I read some of the emails and they make very sad reading," he adds.

He also believes the antibody is a worthwhile treatment and a safe one. Once, while filming a segment of an English program called *Tomorrow's World* — what Janda describes as the British version of *60 Minutes* — the interviewer asked him if he would be willing to give his vaccine to children. Yes, Janda said, he would — it might help prevent the problem from ever getting started.



Crystal structure of a catalytic antibody with its substrate in the antibody's binding cleft.

Even though Janda claims to enjoy interviews, it's clear that his recent media experience goes far beyond the normal life of a scientist.

"This is so much different than my regular work," he said. "My bread and butter is catalytic antibodies."

WHERE ORGANIC CHEMISTRY MEETS BIOLOGY

Janda's undergraduate work was in clinical chemistry, learning the techniques of a modern medical laboratory. However, his graduate work was in organic chemistry, the creation of molecules. His goal after graduate school was to find somewhere he could blend his knowledge of organic chemistry with biology. TSRI turned out to be the exact place he needed. Dr. Richard Lerner, currently president of the Institute, had just become head of the Department of Molecular Biology and was looking for young chemists to work on the idea of creating catalytic antibodies. Janda was one of the first chemists hired. It was a good match from the very start.

"I think the real advantage of Scripps is that there are no hard lines drawn for what you want to do," Janda says. "Doing good science is everything here, so you can cross over to any area you want. In a lot of places there are the old classical dividing lines between disciplines. Here there are a lot of undefined areas — and the opportunities that go with them."

Janda describes the work of his lab as moving into areas that are interesting. For him, interesting cuts a fairly wide swath.

"In our lab we do everything from hardcore organic chemistry to molecular cloning techniques and polymers to immunopharmacotherapy and cancer," he says. "Several years ago we did some work with early HIV protease inhibitors, so our work with cocaine antibodies — immunopharmacotherapy — while important, is not our primary focus."

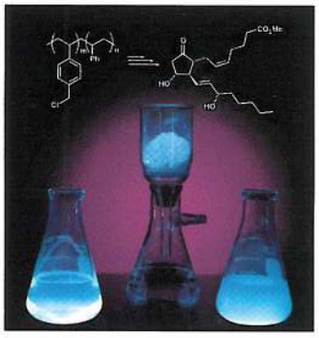
CATALYTIC ANTIBODY RESEARCH

The laboratory is focused on four major areas: catalytic antibodies, combinatorial chemistry, enzyme inhibition and immunopharmacotherapy. By using tools

from other disciplines such as molecular biology, immunology, enzymology, and neuropharmacology, Janda and his colleagues work quite comfortably at the nexus of chemistry and biology.

At the moment, the best spot for that is, as he says, catalytic antibodies. The role of a catalyst in any chemical reaction is to accelerate that reaction. In the past, immunization — the induced production of antibodies by the immune system to prevent a disease — has relied exclusively on inert antigens — basically dead substances such as the discarded protein shells of viruses. At TSRI, Janda's laboratory developed antigens that mimic part of a chemical reaction, allowing them to create catalytic antibodies that accelerate that reaction.

Add to that, the laboratory's development of a system that allows for the direct selection of a specific antibody function by using chemical selection from existing libraries of existing antibodies and the enormous potential of his work appears obvious.



Clearly part of that great potential is the laboratory's recent development of human antibodies capable of recognizing specific markers on certain tumor cells called glycopeptides. Although they are very rare, these antibodies are produced by cancer patients and are present in their bloodstream. By taking blood samples from these cancer patients, Janda and his colleagues have been able to reproduce these rare human antibodies that not only recognize tumors but also, in fact, seek them out.

"If we can produce these human antibodies in large enough quantities," Janda says, "we could attach them to specific drugs that destroy these tumors. It's a rifle shot approach to cancer therapy, one that should be significantly more effective than the traditional chemotherapeutic approach."

Although he claims he's not interested in producing compounds with commercial potential, he believes that his methodologies will help others produce them. What commercial aspirations he has he exercises by helping create new biotechnology start-up companies.

NEW BIOTECHNOLOGY COMPANIES

The first was CombiChem, a five-year-old California company involved in combinatorial chemistry. By accelerating the discovery process of leading drug candidates, CombiChem helps move viable lead candidates into the R&D pipeline more rapidly and with a greater chance of success. It was Janda's involvement with the development of the cocaine antibody that led to the founding of another start-up, Drug Abuse Sciences.

But like the sudden publicity surrounding the announcement of the cocaine antibody, starting a company was never his main goal. In truth, he seems almost to have stumbled onto the whole idea of medical commerce and appears bemused by the fact. But things have a way of moving in self-fulfilling circles.

Take his golf game, for instance.

FORE!

"I picked it up early and kept at it," he said. More than keep at it, he excelled at it, playing tournament games before he was six years old, winning numerous competitions in the state of Ohio. He played well into his college years, becoming one of the school's most prominent scholar-athletes.

He still plays but not often, perhaps once a month. He shoots between mid- to low-70s with no handicap. A good score recognized by anyone who knows the game, just as anyone familiar with the game would quickly recognize the name of chair Janda occupies at Scripps: The Ely R. Callaway Chair in Chemistry.

"Callaway Golf funds my chair in chemistry and it had something to do with my playing ability," Janda says. "Ely Callaway was interested in funding a chair at Scripps, so Richard Lerner said he knew an outstanding scientist who was also a scratch golfer. It more or less happened after that."

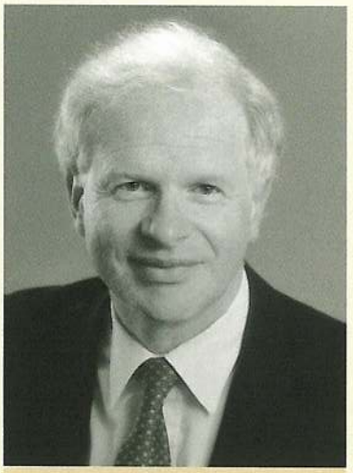
In the midst of all this serendipity, what holds Janda is the work. Most days — most weekends, too — you'll find him in the lab. Science, he says, knows no calendar and it remains at the center of his life.

"One of my mentors used to tell me that when chemistry isn't fun anymore, it's time to get out," he says. "Coming to work to me is still fun. There are a lot of things out there to find and discover. I'm still looking." ■

A soluble polymer matrix that fluoresces under the stimulation of ultraviolet light. The use of these soluble polymer matrices allows for the synthesis of prostaglandin libraries of molecules. Prostaglandins constitute the most physiological potent nonprotein molecules found in mammals.

Tamas Bartfai Named to Head Harold L. Dorris Neurological Research Center

Noted neuroscientist Tamas Bartfai, Ph.D., has been named director of the newly established Harold L. Dorris Neurological Research Center at The Scripps Research Institute. In addition, he will hold the Harold L. Dorris Chair in Neuroscience. The center was formed with a $10 million commitment from Helen L. Dorris of San Diego.



Tamas Bartfai, Ph.D., Director, Harold L. Dorris Neurological Research Center

Bartfai is former head of central nervous system research at Hoffman-La Roche, in Basel, Switzerland. Most of his professional career was spent in academia at Stockholm University, most recently as Chairman, Department of Neurochemistry and Neurotoxicity. Born in Budapest, Hungary, he received his undergraduate education there at Eotvos Lorand University and a Ph.D. in biochemistry at Stockholm University. He has served as a visiting scientist at Hadassah-Hebrew University Medical School, Jerusalem; Yale University Medical School; and the Neuropsychiatric Institute at University of California, Los Angeles. Bartfai holds adjunct appointments at The Rockefeller University and Stanford University.

His work has implications for such diseases as depression, Alzheimer's disease, schizophrenia and sleep disorders.

According to William H. Beers, Ph.D., TSRI Senior Vice President, "We look forward to the leadership that Dr. Bartfai will bring to this newly created research center at TSRI. He is internationally recognized for his accomplishments in the neurosciences and his broad range of interests across a number of disciplines within the field."

Bartfai's work has been directed toward several scientific topics during his 27-year career in physiological chemistry. Most notably, he has made contributions in the fields of the molecular/biochemical basis of cognition, and the molecular/biochemical basis of fever. His work has implications for such diseases as depression, Alzheimer's disease, schizophrenia and sleep disorders. Involved in the development of psychopharmaceutical agents for the last 20 years, he developed Zimelidine, the first selective serotonin reuptake inhibitor (SSRI) and two anti-psychotic agents used in the treatment of schizophrenia.

Recently, he elucidated the molecular mechanism of a new kind of antidepressant, substance P antagonist, which modifies a previously untapped neurochemical system. This finding may lead to the development of new and more effective drug targets against depression, as well as anxiety disorders and schizophrenia. His work on the design, synthesis and biochemical and pharmacological application of the first galanin antagonists was essential for the elucidation of the biological effects of galanin in depression, cognition and pain, and led to the three galanin receptors becoming the target of more than 20 projects in the pharmaceutical industry.

The author of some 260 scientific publications, Bartfai is the recipient of numerous prestigious research awards, including the Eotvos Prize in Chemistry, the Svedberg Prize and the Eriksson Prize. In addition, he has been named a Senior Fullbright Fellow as well as a Fellow of The Neuroscience Institute.

The new center will bring a dedicated effort to providing education and conducting research into neurological disorders, including schizophrenia and Alzheimer's disease, as well as advancing knowledge of the process of aging of the brain. Newly recruited scientists will join in an interdisciplinary focus on the brain, expanding ongoing research currently conducted in TSRI's Departments of Neurobiology, Neuropharmacology, Chemistry and Molecular Biology.

According to TSRI President, Richard A. Lerner, M.D., "This most generous commitment from Helen Dorris, the largest that TSRI has received for furthering research in the neurosciences, comes at a particularly opportune time as scientists here are poised to reap the enormous benefits from the nearly concluded mapping of the human genome. We at TSRI expect the Center to foster rapid advances in the fundamental understanding of the brain." ■

K.C. Nicolaou Wins International Aspirin Prize for Solidarity Through Chemistry

K.C. Nicolaou, Ph.D., Chairman, Department of Chemistry, Professor, The Skaggs Institute for Chemical Biology, and Professor, Department of Chemistry, University of California, San Diego, has been awarded the first International Aspirin Prize for Solidarity Through Chemistry by Quimica Farmaceutica Bayer, S.A. (Barcelona). The worldwide, biennial prize has been established to mark the centenary of the synthesis of a pure and stable form of acetylsalicylic acid, the active ingredient of aspirin in 1897 and the registration of Aspirin as a trademark in 1899 by Bayer.

Nicolaou was presented the award at the Chemical Institute of Sarria, Ramon Llull University, Barcelona, Spain, for his work on the total synthesis and chemical biology of natural products. He is perhaps most widely recognized for his work on taxol, and also has performed the total syntheses of the medically important natural products amphotericin B, calicheamicin, rapamycin, brevetoxins A and B, and vancomycin. His recent contributions to combinatorial chemistry and chemical biology further broaden the impact of his work on biology and medicine.

Nicolaou received a bachelor's degree in chemistry from the University of London and a Ph.D. from University College, London, in 1972. He completed postdoctoral appointments at Columbia University and Harvard University. In 1976 he joined the faculty of the Department of Chemistry at University of Pennsylvania and was named the Rhodes-Thompson Professor of Chemistry in 1988. He was appointed Darlene Shiley Professor of Chemistry and Chairman, Department of Chemistry, at The Scripps Research Institute in 1989.

A member of the National Academy of Sciences and a Fellow of the American Academy of Arts and Sciences, he is the recipient of many national and international awards, including the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry, the Janssen Prize for Creativity in Organic Synthesis, the Rhone-Poulenc Silver Medal from the Royal Society of Chemistry, the Ernest Guenther Award in the Chemistry of Natural Products, the Chemical Pioneer Award from the American Institute of Chemists, the American Chemical Society New York Section's Nichols Medal, the Linus Pauling Medal of the American Chemical Society, the 1997 Distinguished Scientist Award from the San Diego Section, American Chemical Society, and the Gustavus John Esselen Award for Chemistry in the Public Interest by the Northeastern Section, American Chemical Society. The author of more than 450 scientific publications, Nicolaou also has been recognized with several honorary doctoral degrees. ■

Paul Schimmel Receives Prestigious Honors

Paul R. Schimmel, Ph.D., Professor, Department of Molecular Biology and The Skaggs Institute for Chemical Biology, has been named a recipient of the Biophysical Society's Emily M. Gray Award, for his "significant contributions to teaching and education in biophysics." He shares the award with Charles Cantor, Ph.D., of Sequenom, Inc. The Biophysical Society is a professional, scientific society established to encourage development and dissemination of knowledge in biophysics. In addition, he recently was elected to membership in the American Philosophical Society at its Annual General Meeting in Philadelphia. Founded by Benjamin Franklin in 1743, the society is the oldest learned society in the United States devoted to the advancement of scientific and scholarly inquiry.

Schimmel's major research interests have concentrated on the decoding of genetic information, with an emphasis on the rules of the universal genetic code, work that has placed him "squarely in the middle of the origin of life question," according to a colleague. His laboratory uncovered an operational RNA code for amino acids which related specific sequences/structures in small RNA oligonucleotides to specific aminoacylations. He and his coworkers were also among the first to establish the modular design of aminoacyl tRNA synthetases. He later showed how this design relates to the operational RNA code and its relationship to the genetic code.

Prior to his appointment to TSRI's faculty in 1997, Schimmel was the John D. and Catherine T. MacArthur Professor of Biochemistry and Biophysics at Massachusetts Institute of Technology. A member of the National Academy of Sciences, he is the author or co-author of many scientific papers and of a widely used three-volume textbook on biophysical chemistry. He was a recipient of the Alfred P. Sloan Fellowship, the American Chemical Society's Pfizer Award in Enzyme Chemistry, and was elected to membership in the American Academy of Arts and Sciences. He has been active in many scientific and academic organizations and committees, including service as Chairman of the Division of Biological Chemistry of the American Chemical Society and as an editorial board member of ten different scientific journals. Having a longstanding interest in the applications of basic biomedical research to human health, Schimmel holds several patents and is a co-founder of four biotechnology companies. These companies are developing new therapies for human diseases and disorders. He is a graduate of Ohio Wesleyan University and holds a Ph.D. from Massachusetts Institute of Technology. ■

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