

THE
SCRIPPS
RESEARCH
INSTITUTE

Endeavor



In pursuit of the molecular culprits of Type 1 diabetes

Three researchers seek clues to the mysteries of autoimmune disease

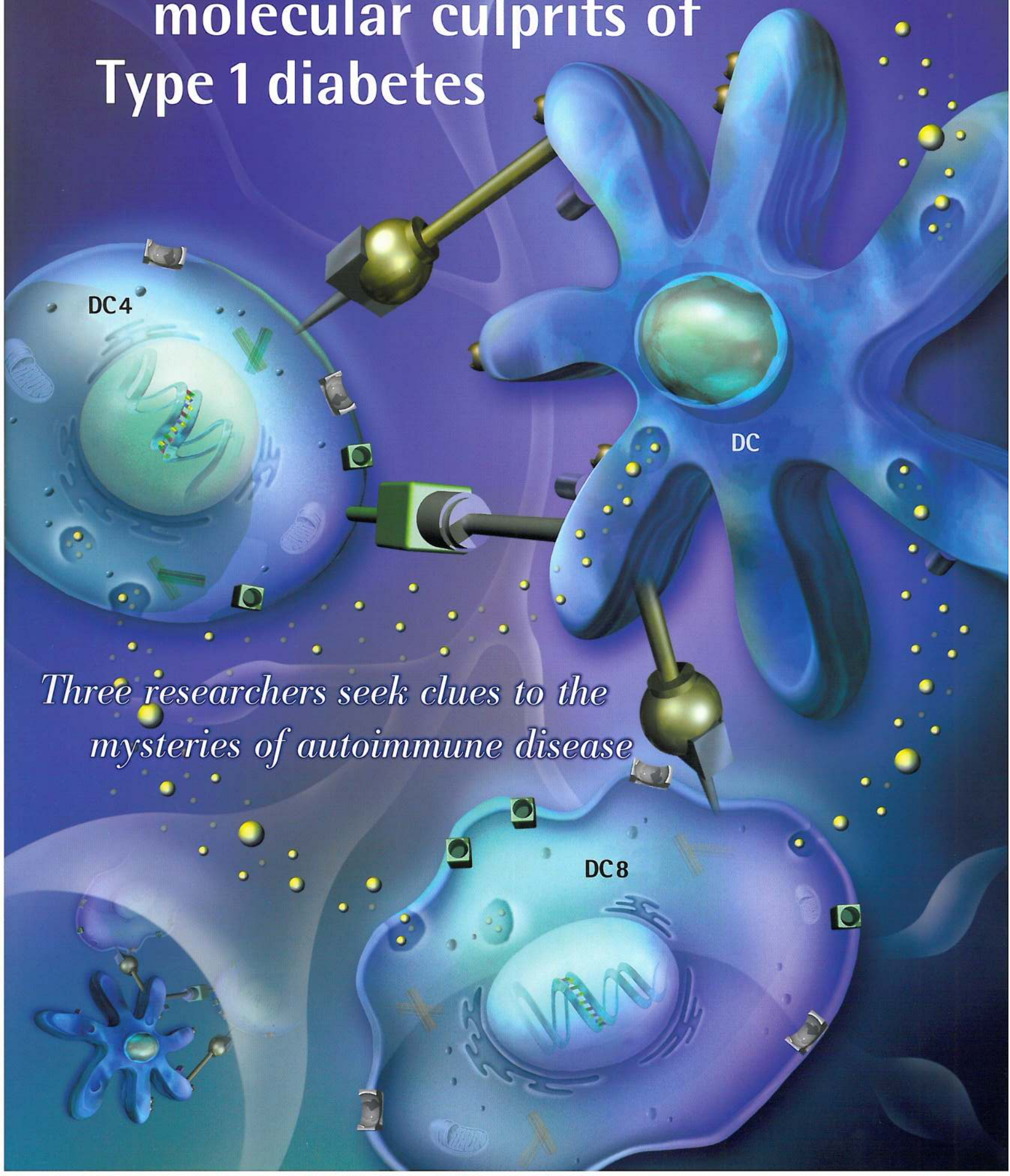
The lure of exploration

Bruce Beutler's quest to understand innate immunity

Renaissance man

Frank Chisari brings his skills to the challenge of hepatitis B and C

in pursuit of the molecular culprits of Type 1 diabetes



*Three researchers seek clues to the
mysteries of autoimmune disease*

.....

**Nearly 40 years have passed since
a young Bob Dylan first sang his famous song,
"The Times They Are A-Changin'."**

.....

This song, through its simple refrain, offered perhaps the single best anthem of the 1960s, a time when, indeed, many changes were afoot. Part protest and part prophesy, "Times" observed the extraordinary events of the early 1960s and anticipated the far-reaching changes that were to come in music, politics, entertainment and science — changes that would reach a crescendo by the end of the decade, define a generation, and reverberate even today.

Biology, for one, has changed in the last four decades. Scientists have made tremendous gains in

In 1995, when three investigators were awarded a multi-year grant sponsored by the National Institutes of Health, they were the only all-woman program project grant at that time.

understanding the molecules and processes of life, while losing the stiff, formal business suits once worn in the laboratory. And biology has changed in subtle ways as well. Today, large scientific projects reach across disciplines and departments to incorporate multiple ideas and contributing investigators, whose ranks increasingly include women as well as men.

In the 1960s, a senior woman research scientist was relatively rare. Today it is not, according to the latest definitive study on the subject, a 2001 report by the National Research Council, *From Scarcity to Visibility: Gender Differences in the Careers of Doctoral Scientists and Engineers*.

The National Research Council reports that the number of women receiving Ph.D.'s in science and

engineering increased 350 percent between 1973 and 1995. Over the same period, the percentage of women employed as full-time academic researchers nearly tripled, from 8 to 23 percent. And in 1995, the report adds, more than 40 percent of new life science Ph.D.'s were awarded to women.

And yet, in 1995, when three investigators at The Scripps Research Institute were awarded a multi-year "program project" grant sponsored by the National Institutes of Health, they were the only all-woman program project grant at that time.

"To have the strength in one department of a sufficient number of senior women is unique," says Linda Sherman, Ph.D., who like her coinvestigators was a young girl when Bob Dylan was singing of changing times.

A PROGRAM WITH THREE PROJECTS

The grant, which was renewed through 2005, funds a program focusing on the basic mechanisms of autoimmunity — diseases involving immune responses to self tissues. It combines the research interests and expertise of the laboratories of Sherman, Nora Sarvetnick, Ph.D., and Sue Webb, Ph.D., in The Scripps Research Institute's Department of Immunology.

The three have independent laboratories and separate grants as well. The program project grant funds studies in all three labs that focus on the specific goal of better understanding how the immune system goes awry in the development of Type 1 diabetes. It allows them to pool their resources and draw on their individual strengths to facilitate progress toward this goal. They publish together, foster collaboration among their post docs, and use several "core" facilities with shared resources.

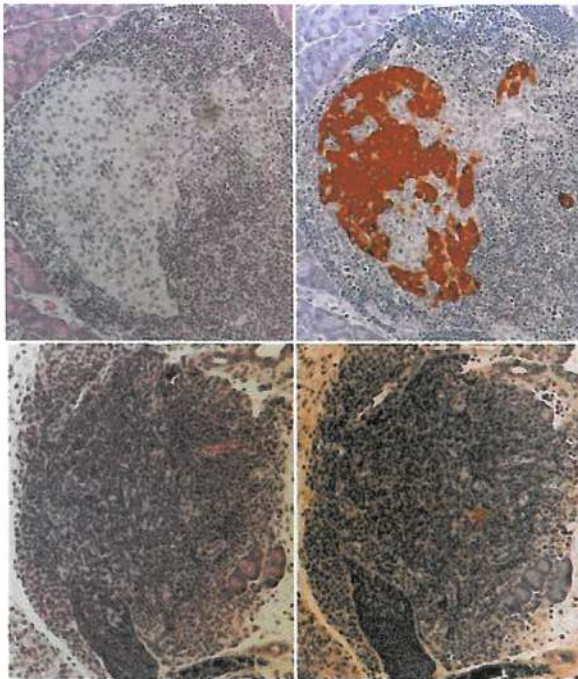
"We collaborate and use each of our expertise to get a bigger picture," says Sherman. That bigger picture

On the Cover:
Investigators
Sue Webb, Ph.D.,
Linda Sherman, Ph.D.,
and Nora Sarvetnick,
Ph.D., collaborate
on Type 1 diabetes
research.

addresses the cellular and molecular causes of autoimmune diseases like Type 1 diabetes, focusing on the role of T lymphocytes.

“[The National Institutes of Health grant] developed out of a mutual interest I had with Linda and Nora on how T-cells are regulated,” says Webb. “It seemed logical that we should get together and see how the regulatory mechanisms we were looking at are compromised in the development of diabetes.”

The two upper panels are consecutive sections of a pancreas showing active inflammation of the islet of Langerhans and insulin-producing beta cells (brown) from a prediabetic model. The lower panels show a similar pancreas after coxsackieviral infection with greater inflammation and loss of the insulin-producing beta cells from a diabetic model.



“In autoimmunity, the balance [between cells and their regulation] has been disturbed,” Webb adds. “If we knew [how to maintain the balance], then we would probably be able to make predictions about how to get it back when it goes off.”

“HORROR AUTOTOXICUS”

Type 1 diabetes is one of around 80 known autoimmune diseases — a collection that includes such diverse and chronic ailments as multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and lupus. Nobel laureate and immunology pioneer Paul Ehrlich coined the term “autoimmune” in 1900, when he recognized the need for the body to avoid making an immune reaction to its own cells. He called this “horror autotoxicus” (fear of self-poisoning).

In these autoimmune diseases, which affect women about three times as often as men, the body’s immune

system attacks the body’s own tissues. In the case of Type 1 (insulin dependent) diabetes, for instance, the insulin-producing beta cells in the so-called islets of Langerhans situated in the pancreas are destroyed by T cells. These cells are the body’s only source of insulin — a protein responsible for regulating blood glucose levels. As the beta cells are destroyed, insulin production becomes limited.

Without insulin, the glucose in the bloodstream increases and is maintained at levels much higher than normal. Over time, this can lead to nerve and kidney damage, impaired eyesight, and an increased risk of developing heart disease, high blood pressure, stroke and vascular degeneration.

The therapy of choice for the disease is to inject insulin, and before the discovery and isolation of insulin in the 1920s, having Type 1 diabetes meant certain death. Though insulin replacement is a rational treatment, Type 1 diabetes is still a chronic disease for which there is no prevention and no cure. About 30,000 Americans develop Type 1 diabetes every year.

Many of these new cases are in children. Type 1 diabetes is one of the most prevalent chronic diseases among children in the United States. Statistics compiled by the National Diabetes Data Group of the National Institute of Diabetes and Digestive and Kidney Diseases and published in the 1995 National Institutes of Health publication *Diabetes in America*, showed that over

Type 1 diabetes is one of the most prevalent chronic diseases among children in the United States.

120,000 children and adolescents — approximately one in every 400 to 500 — have Type 1 diabetes, and every year about 13,000 more children and adolescents develop it.

These are compelling reasons for the researchers to focus on the basic biology of Type 1 diabetes. The greatest hope for preventing and treating the disease is to uncover its underlying molecular causes — the perturbations in key pathways that lead the body’s immune system to attack itself.

“Our goal is to understand the causes of Type 1 diabetes [so that] we might be able to go on and design therapies,” says Sarvetnick.

AUTOREACTIVE T CELLS

The factors that initiate the activation of T cells that go on to destroy the insulin-producing cells in the pancreas are not yet understood. One hypothesis with significant support is that Type 1 diabetes occurs after a person contracts a common virus that infects cells in the pancreas. During the viral infection, the body makes an adaptive immune response, and in most people, this response is specific for the virus — the T cells of those people selectively target and eliminate cells that are infected with the virus, and they recover normally.

In Type 1 diabetes, the killing proceeds out of control. The T cells become autoreactive, vigorously attacking not only the infected islet cells but the healthy ones as well. The T cells eventually destroy all the insulin-producing cells in the body, causing a depletion of insulin in the bloodstream.

However, the precise, detailed mechanisms and molecular interactions that lead to Type 1 diabetes are not clear. Nor is it clear why many more people are infected with the implicated viruses than develop the disease.

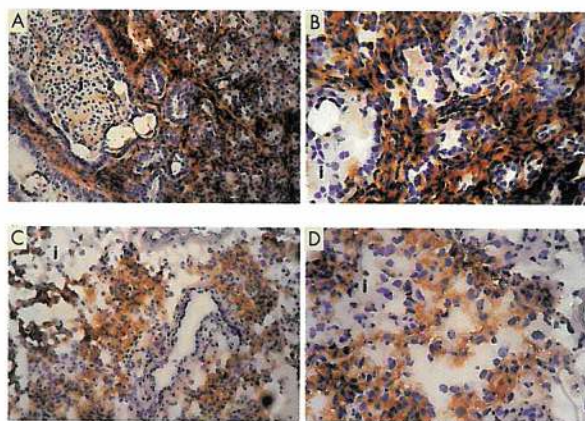
“We’re trying to understand how people who are resistant to this disease counter-regulate these processes,” says Sarvetnick, “and which molecules [and pathways] they work through.”

“The key thing is to discover the pathways and see how we can restore immune tolerance in these potentially devastating pathways,” she adds.

HOW T CELLS ARE REGULATED

Immune responses are normally regulated by a variety of mechanistic “pathways.” These pathways are crucial because it is a breakdown in their proper control that permits T cells to kill healthy insulin-producing cells. Without the breakdown of control, the disease would never develop.

There are two major types of T cells in the body, and Webb’s portion of the program project grant concentrates on how one of these two types, the “helper” T cells, is regulated.



Pancreati after Infection with Coxsackievirus. Panel A is a model with transgenic expression of interferon-gamma in its beta cells of the islets of langerhans. This expression activates macrophages (brown), which protect the tissue from damage. Panel B shows this at a higher magnification. Panel C is a non-transgenic model with normal levels of interferon and macrophages, and less protection from the virus infection. Panel D shows this at a higher magnification.

Helper T cells are often referred to as “CD4+ cells” because of the distinct expression of CD4 molecules on the cell surface. The primary function of these cells is to provide help to various components of the immune system to insure adequate responses to viruses, bacteria, and other microbial pathogens. Helper T cells promote the activity of killer T cells, natural killer cells, and macrophages that destroy the pathogen along with any pathogen-infected host cells.

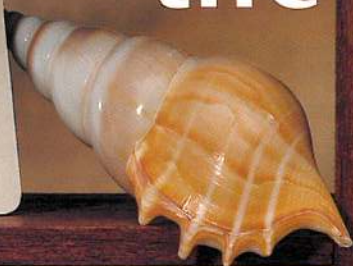
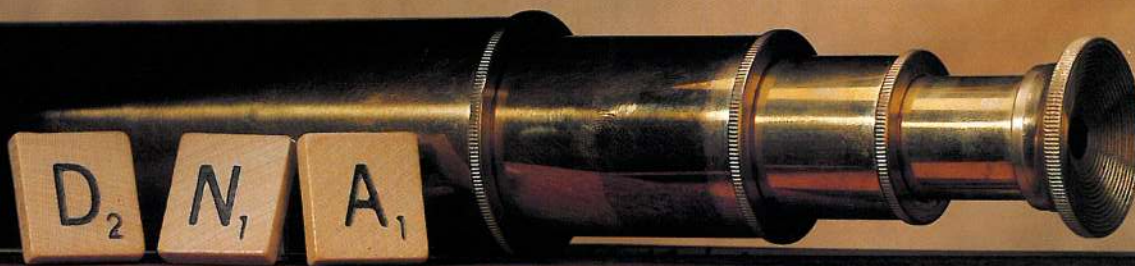
Helper T cells also activate B (bone marrow-derived) cells to produce antibodies, proteins that specifically bind to the pathogen, inhibiting its growth and ability to colonize the body. CD4+ cells activate these various cell types primarily by secreting small

“Our goal is to understand the causes of Type 1 diabetes [so that] we might be able to go on and design therapies,” says Sarvetnick.

chemical messengers, called cytokines, that bind to specific receptors on the target cells.

Before secreting cytokines, however, CD4+ cells must be activated themselves. This requires specific recognition of pieces of the pathogen that have been ingested and displayed on the surface of cells referred to as “antigen presenting cells.” This complicated process involves multiple cell types and a number of interacting cell surface receptors and costimulatory molecules.

This initial recognition of antigen, termed T cell “priming,” must occur under appropriate conditions in



the lure of exploration

*Bruce Beutler's
quest to understand
innate immunity*



.....

**Bruce Beutler knew, almost from the time
he could think rationally about it, that he
was going to be a researcher.**

.....

His father, Ernest Beutler, M.D., currently chairman of The Scripps Research Institute Department of Molecular and Experimental Medicine, and his mother, Bonnie Beutler, a technical writer and avid pianist, raised their children in an atmosphere saturated with science, computers, music, and medicine. “My parents’ interests were transmitted to us in a fragmentary way,” Bruce Beutler says. “Perhaps it was environment, or perhaps Mendelian genetics at work.” Two of Beutler’s three siblings are now physicians, while the third made his career writing software. Beutler and his eldest brother are passionate about classical music (in Bruce Beutler’s case, Bach). Of the four children, Beutler alone decided upon a career in basic science.

As a teenager, Beutler worked in his father’s lab during the summer, and while he liked hiking and birding, his infatuation with research was consuming. From the beginning, he saw solving problems in the laboratory as similar to the adventures of early explorers. Gamblers all, they left the familiar behind and headed out into the unknown, some to triumph, others to obscurity and defeat. But all went just the same, their lives driven by an undefined force.

“In the natural sciences, as in exploration of any kind, discovery is inevitable,” Beutler says. “If Admunsen hadn’t lived, *someone* would have gotten to the South Pole. And if Newton hadn’t lived, we would still understand the laws of motion and gravitation. Nonetheless, there is a thrill to knowing you are the *first* person to do something. And in science, more than other forms of exploration, there’s room for pure invention. It’s possible to be the first to create something that never existed before.”

Like so many of those early explorers, anxious to discover something first, Bruce Beutler became a young man in a hurry.

FROM SAN DIEGO TO CHICAGO TO TEXAS

He completed his undergraduate work at the University of California, San Diego (UCSD) in two years, graduating when he was just eighteen years old: “I was in a rush in those days to get into research.” He immediately headed for Chicago to study medicine, graduating in 1981, and then to the University of Texas (UT), Southwestern Medical Center in Dallas for his internship and residency.

One reason for the rush was Beutler’s sense that great changes were taking place in biology, and he wanted to be part of it. “The molecular cloning revolution was just then starting,” he remembers. “It began while I was an undergraduate at UCSD, and I wanted to become involved quickly.”

He had chosen medical school on the advice of his father who said it would give him a broad scientific education. It did. It also deepened his hunger for the lab, particularly during his internship and residency. “I felt a real need to work on fundamental scientific problems, rather than to follow a routine of treating patients according to pre-established protocols. I missed doing laboratory research, and being in the midst of it.” Although he no longer treats patients, his medical background has become useful: “Learning to diagnose diseases in humans makes it easier to understand what may have gone wrong in a mouse [with] a novel mutation.”

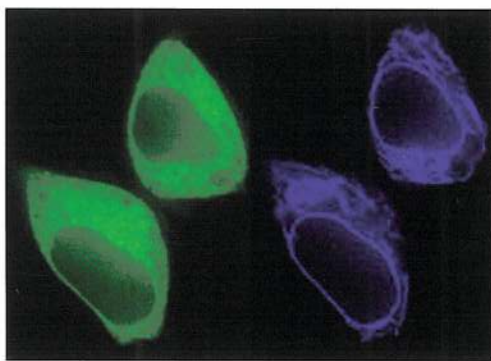
In the middle of his medical training, Beutler managed to marry and start a family. Of his three teenage children, Beutler says — with a slight wistfulness that other parents can especially appreciate — that none have shown any inclination toward a career in science, although the youngest has an interest in computers. “All of them are still young,” he adds with a smile.

In 1983, Beutler moved to New York’s Rockefeller University. His research flourished, and he quickly gained

Investigator
Bruce Beutler, M.D.,
looks for genes that
are important for the
immune system to
function correctly.

Fluorescent tags show the intracellular location of pivotal proteins in the innate immune response to bacterial infection. Toll-like receptor 4, the product of the *LPS* gene, is tagged with a blue label (right), while an adapter molecule, MyD88, which carries signals from *Tlr4*, is tagged with a green label (left).

prominence as the first investigator to isolate mouse tumor necrosis factor, or TNF, a protein hormone originally known for its ability to kill tumor cells, but now understood to be critical to the body's response to infections. It was Beutler who initially recognized the breadth of TNF's actions.



TNF is made in large amounts in response to endotoxin, a molecule that makes up most of the outer membrane of deadly Gram-negative bacterial cells. It was Beutler's discovery that TNF is one of the main causes of the shock syndrome seen during severe infections, a notion once hotly debated, but now universally accepted. Recognizing from the start that TNF is an important cause of inflammation in general, Beutler began to develop TNF inhibitors. One that he developed and patented is now used clinically as the drug Enbrel, among the most effective treatments for rheumatoid arthritis.

After three years in New York, Beutler returned to Dallas, where at UT Southwestern Medical Center, he became an investigator with the prestigious Howard Hughes Medical Institute. He remained in Dallas for fourteen years. It was there that he embarked on the biggest gamble of his career — an expedition into the genome in search of a mutation that was tiny in size but large in its importance to immunology.

WINNER-TAKE-ALL GAME

In 1998, Beutler and his colleague, Scripps Research Institute Assistant Professor Alexander Poltorak, Ph.D., described the cloning of the *Lps* gene (a.k.a. the Toll-like receptor 4 gene or *Tlr4*) in a paper in *Science*. Two years later, Beutler published a more popular and historical account of the quest for the elusive gene in the *Journal of Endotoxin Research*. In it, he wrote: "Positional cloning is a winner-take-all game. Once the target gene is discovered, most of the work that has been done by unsuccessful competitors is for naught. If we were to expend the effort needed to clone *Lps*, we wanted to be the first to find it, and we were aware that many others in this field were challenged by the same scientific problem."

Beutler's account of the cloning of *Lps* is a scientific

adventure story, the laboratory version of the race to the South Pole, complete with triumphs, false leads and moments of personal doubt. For example, when Beutler learned early on that his competitors might be far ahead of him, a competing researcher curtly suggested "with

an implicit sigh of resignation that there would be other genes [for Beutler] to clone."

After five years of extraordinary effort, Beutler and his colleagues finally found their mutation.

Ultimately, the discovery of *Tlr4* accomplished what good exploration always does: It opened the door for still more discovery. As Beutler wrote of their accomplishment, "The new-found identity of *Lps* has enlightened understanding of how we, as vertebrates, sense infection. It has revealed the principal receptors of innate immunity. It has allowed us to search for new approaches to the blockade of inflammation, and also, to search for defects in microbial sensing that might explain immunodeficiency disorders."

THE NEXT EXPEDITION

Finding *Tlr4* was a triumph of "positional" or "forward" genetics. Forward genetics begins with a particular trait, or phenotype, that is caused by a discrete genetic difference between two individuals, and relies upon traditional methods of genetic mapping to place the gene in a particular area in the genome. It makes use of the exceptionally powerful sequencing methods and computational tools that now exist, first to identify candidate genes that are present in the region, and then to locate the mutation itself.

A professor in The Scripps Research Institute Department of Immunology since 2000, Beutler focuses his laboratory's efforts on discovering abnormalities in the immune system caused by mutations, with the ultimate goal of finding genes that are important for the immune system to function correctly: "You start with a phenotype — for example, a [system] that doesn't respond to the presence of endotoxin — and work backwards from there to find out what mutation caused the innate immune system not to respond."

Innate immunity is a form of immune defense all of us are born with, he says: “It doesn’t depend upon antibodies, or prior contact with germs. We all have an innate immune response to bacterial, fungal, and protozoal infections whether we have been exposed to these agents or not. We are hard-wired to defend ourselves.”

Beutler is searching for mutations that disrupt innate immunity.

“The *Tlr4* gene encodes a protein that is the gateway for endotoxin detection and endotoxic shock,” he points out, “while other *Tlr* genes encode proteins that detect other microbial molecules. Collectively these receptors tell us when we’re infected. So each mutation is the beginning of a new quest. And we’ve found some really beautiful mutations.”

But most of the time, they find nothing at all. Their method creates thousands of mutations utterly at random. In that sense, it is exactly like gambling, playing the odds and hoping that they get lucky. From time to time — like beating the house in Las Vegas — they hit the jackpot. Recently, Beutler and his team discovered a new mutation that causes endotoxin resistance, a mutation in a gene that is clearly different from *Tlr4*, or any other known gene required for endotoxin responses.

“I do think that mutations are the key to the understanding of immunity,” he says. “The immune system is so complex that there are probably thousands of ways to disrupt it. The result might be autoimmunity, or an immunodeficiency that could wipe out a whole class of cells. In the long run, once we understand the proteins that are involved in a particular immune function, it should be possible to design drugs that target those proteins, either enhancing or blocking their function. Take a mouse with a severe allergy, for example. Once we understand why the allergy is there, we might be able to design a drug that would prevent it.”

Beutler enjoys the haphazard turns of mutagenesis, largely because “it presents a new puzzle at least once a month.” Prodded by unexpected phenotypes, Beutler and his group delve into areas of biology that they might not otherwise consider.

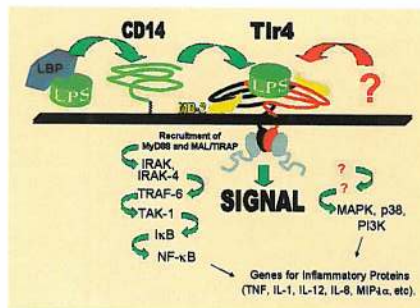
Mutagenesis also compels the researchers to be inventive, for they must design tests that will reveal the presence of a mutation that might otherwise be passed

over. They must also ask questions that are difficult to answer because evolution has created biological systems of vast complexity.

ANOTHER EVOLUTIONARY MYSTERY

In a roundabout way, Bruce Beutler began thinking about precisely such a system: the placenta, a tissue that nourishes the growing embryo and fetus of all advanced mammals, including humans. The riddle of the placenta presents the same sort of exploratory opportunity that *Lps* did — a new chance to leap into the unknown.

“The immunological mystery that the placenta poses was first raised in the 1950s,” he says. “I remember talking about it with my father when I was a teenager, as we discussed many scientific questions. Grafts of foreign tissue are rejected by the immune system, but the placenta is not. Why? It is a fundamental exception in immunology, and an evolutionary puzzle. When the placenta first



evolved some 170 million years ago, the immune system was already well entrenched in vertebrates. It

should have rejected the placenta. But somehow, in this one special case, something happened to defeat adaptive immunity. The development of tolerance to the placenta occurred only once. It did not occur in different species at different times. It may have involved a single, crucial mutation. And it is very likely that we will be able to dissect the phenomenon using mutations, perhaps getting a glimpse into our human past.”

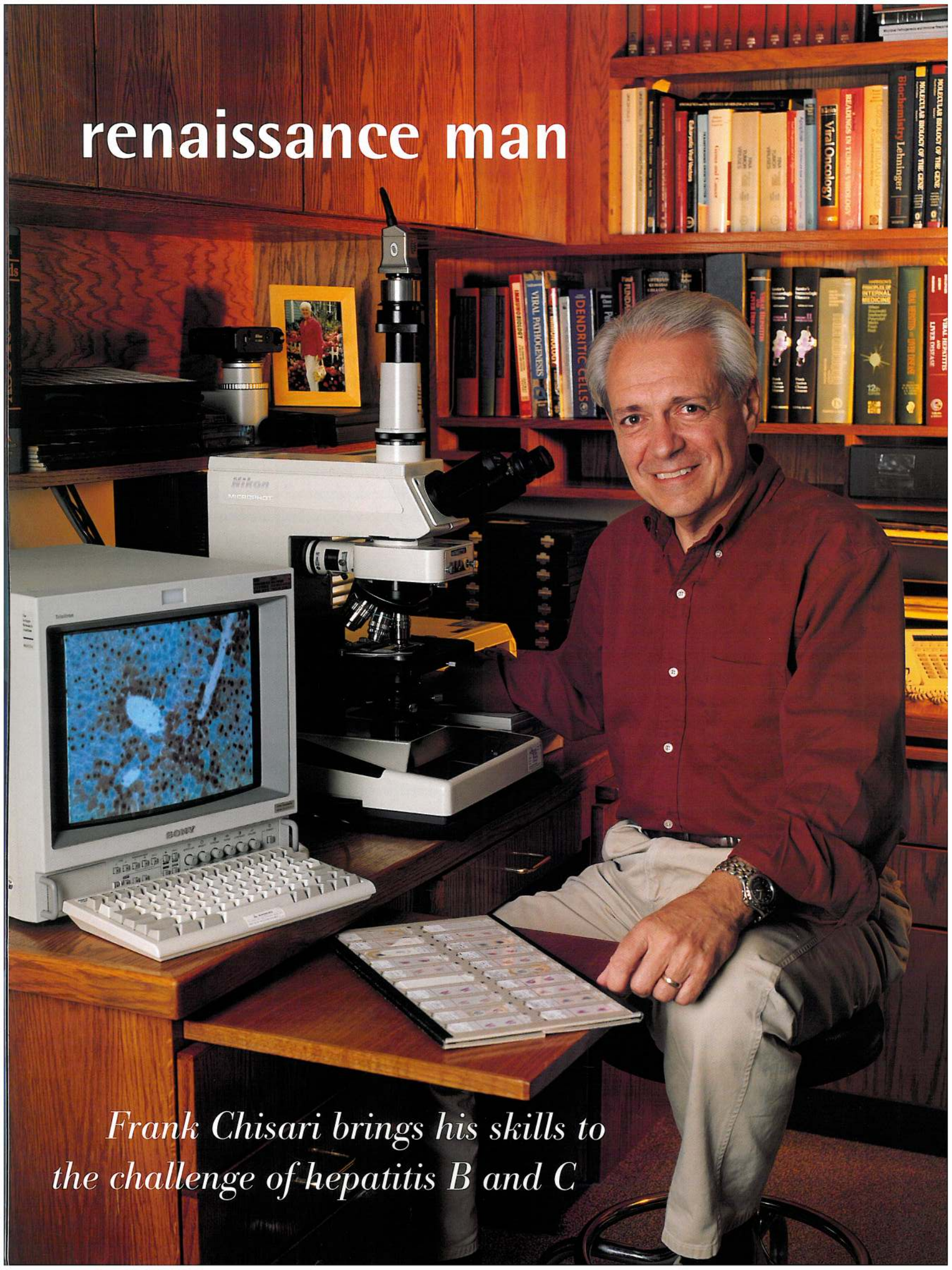
The mutagenesis project is carried out, he says, by a remarkable assembly of postdoctoral associates, students, and technicians: Alison Affleck, Xin Du, Jason Goode, Kasper Hoebe, Navjiwan Mann, Koichi Tabet, Pia Viviani, and Zuping Zhou.

“All in all, the best group of people with whom I have ever worked,” Beutler says. “Without patient and devoted people this type of approach couldn’t succeed. With such people, it can’t fail.”

Spoken like a true explorer. ■

The molecular events that ignite the “fire” of septic shock. The interaction between MyD88 and *Tlr4* is essential for responses to LPS. But other proteins also seem to be involved, indicated by question marks. Beutler and his group are investigating.

renaissance man



Frank Chisari brings his skills to the challenge of hepatitis B and C

.....

He is a man of parts. Born into an expansive Italian family in the Bronx, his name evokes something with roots.

.....

Although everyone pronounces it Chi-sa-ri, with the accent on the second syllable, Frank Chisari knows that the true Italian pronunciation is Key-sa-ri, with the accent on the hard C. In Italian, it means someone who knows how to laugh. It is a name that captures his personality. He laughs easily, enjoys his work and his life. His sense of ease keeps him at it.

It being his nearly thirty-year-old study of the hepatitis B and C viruses. That groundbreaking body of work recently got him elected to the National Academy of Sciences. Chisari is now one of fewer than 2,000 select members across the United States and one of 16 from The Scripps Research Institute — where he serves as a professor in the Department of Molecular and Experimental Medicine and director of the General Clinical Research Center.

“The joy of my work is discovery and learning something new every day,” Chisari says. “It also comes from the hope that what we’re doing will have an impact on these terrible viruses and the hundreds of millions of people infected by them.”

Chisari’s life is uniquely his own — while at the same time a replay of the classic American immigrant story writ large.

Chisari grew up surrounded by a huge extended family on and around the Bronx’s Arthur Avenue, a microcosm of southern Italy transplanted to these American shores. His grandparents emigrated from Sicily at the turn of the century, raised a family of 10 children and began a successful contracting business. Chisari was born in the early 1940s into a thriving community of first and second generation immigrants who loved America but held their Italian culture dear.

Here is how one New York newspaper describes Chisari’s old neighborhood: “Belmont, the ‘Little Italy

of the Bronx,’ evokes memories of old New York: women shopping at outdoor markets along Arthur Avenue, kids lapping up gelati in the summer heat, old men slapping down dominoes in front of Joe’s Deli. [The] area attracted Italian immigrants hired to build the Bronx Zoo in the 1890s. Today it remains quintessentially Italian — and quintessentially Bronx.”

Chisari himself is still something of a transplanted New Yorker. He learned winemaking from his grandfather, a man who had a box car full of zinfandel grapes shipped from California to his cellar in the Bronx each year, and kept his morning catch of live eels in his bathtub so they’d be fresh for dinner. Chisari himself produces

“I wanted my research to be medically focused, so I needed to know how disease affected people.”

about 500 bottles of wine each year in his mini-winery next to the large vegetable garden he tends with his wife behind their house — that is when he isn’t in the lab, or fly-fishing for trout (he doesn’t like eels), his other main hobby.

He was only the second in his family to move away from the old Bronx neighborhood, a difficult decision, but one softened by the culture he has managed to carry with him all the way to Southern California.

MEDICAL INSPIRATION

Inspired by his father’s best friend — an old-fashioned family doctor — Chisari went off to medical school expecting to emerge as a family physician. But, as he says, he got a little distracted along the way.

Part of it was his own curiosity. In med school he

Investigator Frank Chisari, M.D., has been studying hepatitis B and C for nearly 30 years.

Hepatitis B Virus DNA Genome. The concentric circles represent (from inside out) the circular double stranded hepatitis B virus DNA genome, its four major RNA transcripts, and its seven protein translation products. This virus, whose collection of genes is one-millionth the size of the human genome, infects more than 350 million people throughout the world and causes chronic hepatitis, cirrhosis of the liver, and liver cancer. It kills more than one million people in the world every year. A vaccine is available that can prevent hepatitis B infection and all of its complications, including liver cancer.

found that while he enjoyed the challenge of diagnosis, the routine of patient care dulled his interest. In words echoed by so many other researchers, Chisari says, “I enjoyed figuring out what was wrong and I enjoyed helping the patient cope, but I did not enjoy administering the treatment. That was my first realization that I was not going to become a family doctor.”

The second thing was the Vietnam war. Opposed to the conflict, he applied for alternative service in the United States Public Health Service and got stationed at the National Institutes of Health for two years. It was that experience that jump-started his career as a researcher.

He did his postdoctoral work at places like Cornell and the Mayo Clinic, and later spent a year at the Pasteur Institute in Paris. Part of this bouncing around, as he puts it, was to gain experience as a pathologist and internist — “in case I decided to practice medicine down the road.” The other reason was more profound.

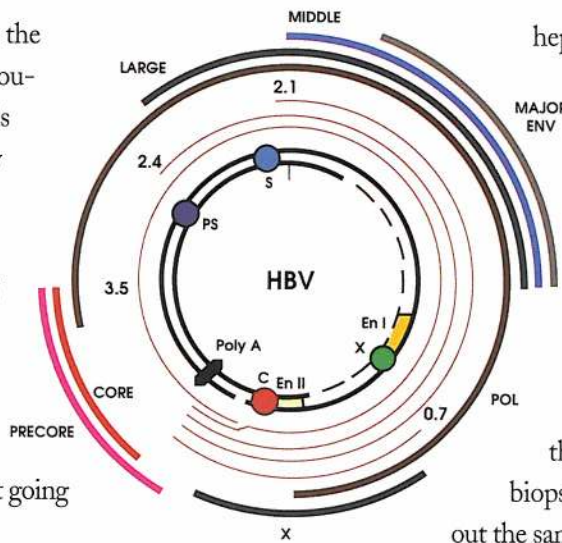
“I wanted my research to be medically focused, so I needed to know how disease affected people,” he says.

THE LONG WAY HOME

Chisari took a circuitous route to his life’s work, going from Washington to La Jolla to Paris and then back to La Jolla.

Chisari’s first real exposure to infectious diseases was at the NIH. But a side project got him into viral hepatitis. Because the hepatitis virus would not grow in culture, NIH investigators were trying to transmit the infection to primates for study. With his training in pathology, Chisari volunteered to examine liver biopsies. That’s when lightning struck.

“One evening, while was I looking at liver biopsies in the microscope, I found what I thought was a clear case of viral hepatitis, lots of inflammation,” Chisari remembers. “When I told the lead investigator, he became very excited, and declared we’d finally transmitted the



hepatitis B virus. I told him we wouldn’t know that until we detected the virus in the tissues. The problem was, neither one of us knew how to do that.”

But there was a pathologist at the then-Scripps Clinic and Research Foundation named Tom Edgington who did know — he had developed an assay to detect the hepatitis B virus in human liver biopsies. Edgington told him to bring out the samples he wanted tested to La Jolla.

So, Chisari gathered up his tissue samples, recruited his wife, and got on a plane to San Diego.

The trip changed everything. Chisari learned how to detect hepatitis virus in primate tissue, and he and his wife fell in love with La Jolla. Edgington soon offered

“In one way, this is my work as a family doctor, amplified a million fold.”

him a fellowship. After completing his work at the National Institutes of Health in 1973, Chisari spent the next several years in La Jolla, California. Struggling to understand not only how the hepatitis virus infected the liver, but how the host responded to the virus, Chisari finally decided that what he needed was a better model.

By 1981, he had become aware of the development of the transgenic mouse — a genetically altered mouse that could mimic a wide variety of disease phenotypes. Chisari’s next idea was simple but far-reaching: If he could insert the hepatitis genome into a mouse, he could have the perfect *in vivo* model to study host-virus interactions. Through a colleague, he managed an invitation to the Pasteur Institute to learn the molecular biology necessary to create his own strain of transgenic mice.

In Paris, he learned enough to produce a transgenic mouse that would model viral hepatitis, the first time that a human pathogen had been introduced by transgenic

technology into a mouse. With this creation, Chisari suddenly found that interest in his laboratory at Scripps blossomed. Over the next 10 years, his staff would expand from three to 30 people. His research would evolve into a full-fledged study of the molecular biology, immunobiology, and pathogenesis of two of the world's most devastating infections.

THE UNKNOWN INFECTION

Hepatitis B and C are part of a small family of viruses that can cause chronic infections. The global hepatitis C epidemic — infecting approximately 200 million people — rivals HIV in terms of public awareness, if not mortality.

One reason that so few are aware of the seriousness of hepatitis B is that there is a highly effective vaccine that can prevent it. In the West, where the vaccine is available and people can afford it, hepatitis B simply is not considered a major threat.

“The other reason,” Chisari says, “is that most of the people who get infected with hepatitis B live in the developing world. Here, we’re basically unaware of the danger. The disease is lower on our radar screen, and that disappoints me because hepatitis B virus infection is devastating other parts of the world where the people are least able to cope with it.”

Hepatitis B is dangerous. More than 350 million people are chronically infected throughout the world and more than a million, many of them children, will die from it each year. Chronic hepatitis B infections are the leading cause of liver cancer.

Chisari’s disappointment grows directly out of his sense of purpose, born in the idealism of the 1960s, and undiminished by time. It helps drive much of his research and, perhaps, helps compensate for the path not taken as the family doctor.

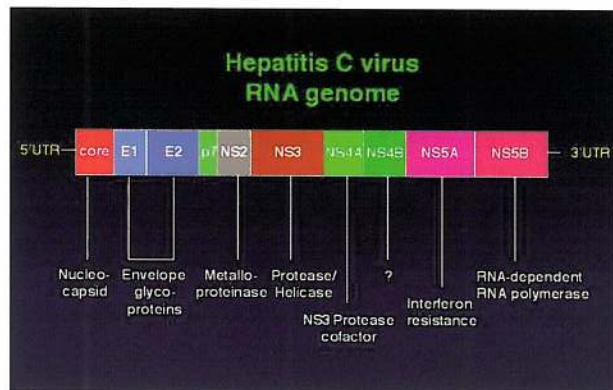
“When I started in medicine, I wanted to have an impact on the lives of patients,” he says. “Maybe the people who’ve been helped by my research are the patients I might have visited. In one way, this is my work as a family doctor, amplified a million fold.”

While the study of hepatitis B remains, to some degree, a problem of funding, public awareness, and logistics, hepatitis C represents the kind of medical

challenge that science faces with HIV. Hepatitis B is a DNA virus that makes few mistakes when it reproduces; consequently, it mutates at a relatively low rate. The hepatitis C virus — an RNA virus — mutates rapidly, enabling it to stay one step ahead of the human immune system. The hepatitis C virus spreads like wildfire in the liver, well before the immune system kicks in. Then the virus mutates so swiftly that the immune system is forced to play catch-up in a race it can never win.

US VERSUS THEM

“We use war analogies for the race between the virus and the immune system,” Chisari says. “The war is carried out by opposing soldiers in the infected tissues. Sometimes the bad soldiers win; sometimes the good soldiers win.



Hepatitis C Virus RNA Genome. The diagram represents the linear single-stranded hepatitis C virus RNA genome and its constituent proteins and functions. This genome is one 350-thousandth the size of the human genome, and infects more than 170 million people throughout the world. Like the hepatitis B virus, the hepatitis C virus also causes chronic hepatitis, cirrhosis of the liver and liver cancer. There is no vaccine available for hepatitis C.

More often than not, there’s a stand-off. In fact, we’ve found that the host can clear the virus without killing the infected cells.”

The idea that the immune system could cure a viral infection without actually destroying infected cells was a breakthrough idea that many of Chisari’s peers rejected at first. Indeed, most scientists believed viral clearance was due only to the destruction of infected cells by cytotoxic T cells. Chisari reasoned that curative mechanisms must also exist or we would self-destruct every time a vital organ like the liver became infected. In a landmark 1995 paper published in the journal *Immunity* Chisari and his colleague, Luca G. Guidotti, established a new paradigm in viral immunology. Using his transgenic mouse model, they demonstrated that the immune system could indeed contribute to viral clearance by stopping viral replication inside the cell without killing it. In a 1999 study published in the journal *Science*, he demonstrated that the same principles were operative during a natural

Chisari cont. from pg. 11

hepatitis B virus infection.

Chisari believes that suppression of viral infections by the immune response rather than complete viral elimination will probably be the long-term outcome for infections like HIV and hepatitis C. The medical challenge will be to boost immunity to a point that if someone becomes infected, the virus won't spread, and the disease will remain in stasis. Patients might have to spend the rest of their lives on medication, but they will survive. Chisari admits that even that optimistic scenario carries risks. What if the immune system is weakened by another infection or by the aging process itself? Will the virus suddenly emerge late in life in a new and more virulent form? No one knows.

THE BIG DEAL

Despite that uncertainty, the difference between today and when Chisari began his research some thirty years ago couldn't be clearer. Back then, no one knew what happened when you got infected with a hepatitis virus.

"Thirty years ago, we knew there was something presumably a virus, in the blood of some people that caused hepatitis," he says. "We knew it was transmitted to others and made them sick too. We didn't know what the agents were or what the process was that caused the infection. While there are still some questions about the details of the infection, we now know a lot of the answers."

He credits the members of his laboratory and colleagues in the scientific community for a large part of that knowledge. While running a thirty-person lab might blunt the satisfaction of being the primary discoverer, it increases the opportunity for discovery, expanding the reach of Chisari's own innate curiosity with the talented help of others.

"This gets me back to the puzzle part," he says. "Being able to figure this out is a joy. The story of the race between the virus and the immune system wasn't known until just a few years ago. Using the models we created, we discovered a brand new concept, a whole new body of knowledge. You might say, 'Hey, what's the big deal?' The virus and the immune system fight it out to see who wins. The big deal is we didn't know how the game was played then. Now we do." ■

Diabetes cont. from pg. 3

order to develop helper activity. Webb is particularly interested in the events that occur during priming of CD4 cells and is trying to determine the constellation of cell surface molecules important in developing T cells that cause diabetes or alternatively regulate or prevent disease.

A PROD PRIOR TO DESTRUCTION

The other major type of T cell in the body, which is also an important player in diabetes, is variously referred to as the "cytotoxic T lymphocyte," the "killer T cell," or because of the molecule it displays on its outer surface, the "CD8 T cell."

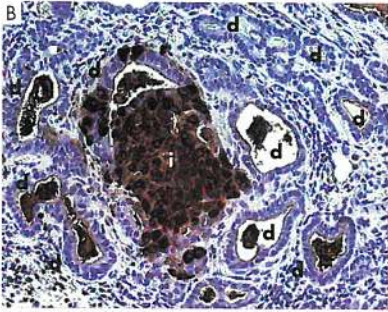
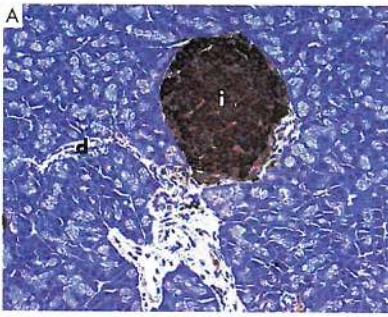
They are the mass murderers of the immune system.

Killer T cells, like all T cells, undergo a complicated maturation process in the thymus when they are raised from precursors. During this maturation, 95 percent of the immature T cells are killed before they are ever released into the bloodstream, based on how they recognize antigen — specifically the "self" antigen that normal cells display. All T cells need to be able to recognize self tissue weakly, which seems to be important for maintaining the proper levels of T cells in the body.

"Having colleagues focused on a single goal makes the work more rewarding, productive, and fun," says Sherman.

T cells that do not have the ability to recognize self antigen at all are selected out, as are the T cells that are too auto-reactive (these would kill perfectly healthy cells displaying the antigen). Ultimately, the thymus produces T cells that have the potential to react strongly with foreign antigen but only weakly with self, including islet cells of the pancreas.

During a normal immune response, T cells are activated by a cell that "presents" them with an antigen. Normally, only those killer T cells that recognize a particular antigen with high affinity (strong recognition) will be activated. And once activated, they will seek out that antigen and kill any cell that displays this antigen on its surface.



A. Insulin expressed in the pancreatic islet (i) of a non-obese diabetes model.
B. Insulin expressed in the pancreatic ducts (d) and islet (i) of a transgenic model in which pancreas regrowth and new islets form from the regenerating ducts throughout adult life. Brown indicates insulin-positive cells.

But in diabetes something changes, and the killer T cells may be activated to attack and kill the insulin-producing islet cells for which they have only low affinity (weak recognition).

Normally killer T cells with weak affinity for pancreatic islet cells would ignore

the uninfected islet cells and kill only the infected ones. But during diabetes, the immune system targets antigen that is displayed on all islet cells, and killer T cells that normally would have only weak affinity for this “self” antigen are enhanced. These killer T cells are “prodded” by helper T cells to kill the islet cells and keep killing them until they are all gone.

Sherman is investigating how the helper T cells interact with these low-affinity killer T cells to make them more reactive. She is defining the rules that govern whether or not T cells see self antigen, how tolerance is established, how it is overcome, and whether there is some way to salvage it.

She has found that up-and-down fluctuations of the levels of certain cytokines — those inflammatory chemicals that cells secrete — prod the killer T cells to become efficient executioners of islet cells, leading to their destruction in the pancreas and to the development of diabetes in the patient.

SPECIFIC CYTOKINE CULPRITS

Sarvetnick’s laboratory is looking at how various cytokines produced by islet cells and by other immune cells during viral infection of the pancreas influence the pathogenic potential of CD8 T cells in diabetes.

Recently, she demonstrated that if islet cells mount a vigorous defense against a viral infection by producing certain cytokines, then the owner of those cells is not

likely to develop Type 1 diabetes. In particular, she showed that islet cells can survive the infection if they are able to detect soluble proteins called Type 1 interferons. She also showed that if they lose the ability to make this response, they disappear from the body upon infection.

“[These cytokines] can affect the half-life of T cells and the antigen presenting cells and change the way that the killer T cells get primed,” Sarvetnick explains.

Sarvetnick’s laboratory has already demonstrated that certain cytokines produced at certain times of infection can lead to the development or inhibition of diabetes in their models. For instance, the molecule interleukin-4 has a potent inhibitory effect on the development of diabetes in pancreas cells expressing the molecule. Another example is if the beta cells produce a chemical called interleukin-10, they have the ability to protect themselves from the virus. But the exact mechanism through which these cytokines enhance the pathogenicity of killer T cells is still unknown, as are the mechanisms through which the regulatory cytokines are themselves regulated.

THE GOAL IS THERAPY

Ultimately, the three scientists would like to understand the problems leading to Type 1 diabetes in order to be able to suggest new strategies for treatment as well as prevention.

One of the great advances that has come in the treatment of Type 1 diabetes in the last 35 years has been the pancreas transplant, which involves replacing the pancreas of a diabetes patient with a healthy organ from a donor. However, this is a major, complicated surgery, limited both by its inherent risk and the low availability of donor organs.

A better solution would be to find a way to provide people who are at risk of developing diabetes with the tools that will enable their pancreatic beta cells to defend themselves during a viral infection. Then Type 1 diabetes would become a preventable disease — the goal of the collaboration.

“Having colleagues focused on a single goal makes the work more rewarding, productive, and fun,” says Sherman. “The collaboration has worked well, and we’re really proud of it.” ■

Adult Stem Cells Used to Control Angiogenesis in the Eye

A team of researchers from The Scripps Research Institute has discovered a way to use adult bone marrow stem cells to form new blood vessels in the eye or to deliver molecules that will prevent the abnormal formation of new vessels.

This technique, which involves injecting the stem cells into the eye, could potentially be used to stimulate vessel growth and address inherited degeneration of the retina in the first instance, and in the second, to treat ocular diseases resulting from abnormal retinal angiogenesis, the aberrant growth of new blood vessels in the eye, which is the leading cause of vision loss in the United States.

"This is very exciting," says Martin Friedlander, M.D., Ph.D., who led the study. "We have shown that the cells can incorporate [stem cells] into the [degenerating] vasculature and make it normal. And when loaded with antiangiogenics, they can selectively wipe out the formation of new blood vessels."

Friedlander, who is associate professor in the Department of Cell Biology and chief of the Retina Service in the Division of Ophthalmology, Department of Surgery at Scripps Clinic, has had a longstanding research program looking at ways of treating eye diseases that result from abnormal angiogenesis.

VISION LOSS AFFECTS MILLIONS

Abnormal angiogenesis is the cause of visual loss in age-related macular degeneration, where new blood vessels grow under the retina, and diabetic retinopathy, where abnormal vessels grow on top of the retina. The end result is much the same in these diseases — the normal structures for the transmission of light to the back of the eye are lost, and vision is catastrophically impeded in many of the tens of millions of Americans who suffer from them.

Adult bone marrow stem cells are "pluripotent" which means they have the potential to develop into a number of different cell types, such as red blood cells, platelets, or lymphocytes. The Friedlander group's basic technique starts with selecting stem cells from the bone marrow that have the capability of becoming endothelial cells, the major cell type lining blood vessels.

Friedlander and his team found that they were able to target activated astrocytes — star-shaped cells that act as a template for vessel formation — with the stem cell *in vivo*. They then tested these stem cells in a mouse model system of ocular disease. In

normal mice, retinal blood vessels form during the first three weeks after birth. In the disease model, the deeper retinal vessels completely degenerate by one month after birth.

The team found that delivery of the stem cells resulted in the proliferation of endothelial cells that formed new blood vessels. This actually rescued and stabilized the retinal vessels when they would otherwise have degenerated.

Following an important collaboration with a group led by TSRI Professor Paul Schimmel, Ph.D., members of Friedlander's group also found that they could shut down the angiogenesis by first transfecting the stem cells with a powerful inhibitor of

.....
*"This is very exciting," says Friedlander.
"We have shown that the cells can incorporate
[stem cells] into the [degenerating]
vasculature and make it normal."*
.....

angiogenesis — a fragment of the human protein tryptophanyl-tRNA synthetase (T2-TrpRS — discovered by the Schimmel laboratory and described in two articles earlier this year).

These transfected stem cells were also guided by the retinal astrocytes to the vasculature in the back of the eye where they expressed the T2-TrpRS protein and prevented the development of new retinal blood vessels without affecting already established blood vessels.

The article "Bone marrow-derived stem cells target retinal astrocytes and can promote or inhibit retinal angiogenesis" is authored by Atushi Otani, Karen Kinder, Karla L. Ewalt, Francella J. Otero, Paul Schimmel, and Martin Friedlander. It appeared in the September 2002 issue of *Nature Medicine* and in the July 29, 2002 advance online publication section of the journal's web site. The research was primarily funded by the National Eye Institute with additional support from The National Cancer Institute, The Skaggs Institute for Chemical Biology, The Robert Mealey Program for the Study of Macular Degenerations, Merck KGaA, and the National Foundation for Cancer Research. ■

Anti-Cancer Nanoparticles: Scientists Design Gene-Tipped Tumor Regressor "Smartbombs"

A group of researchers from The Scripps Research Institute has demonstrated what, in principle, could be a new way of treating cancer and several other diseases where angiogenesis occurs. Angiogenesis, the formation and differentiation of new blood vessels, is a crucial process in cancer, and, when blocked, improves a patient's prognosis.

In cancer-related angiogenesis, tumors develop their own blood supplies by causing cells that line blood vessels to proliferate, forming new vessels and bringing more blood to the tumor. The increased oxygen and nutrients the tumors receive allows them to grow and enable certain "metastatic" cells to leave the tumor, enter the bloodstream, migrate to other tissues of the body, and establish more tumors.

In an article appearing in the journal *Science*, The Scripps Research Institute investigators combined a gene that shuts off angiogenesis with a 50- to 100-nanometer-sized particle that selectively targets the cells that form new blood vessels in cancer tumors. This approach combines gene delivery with specific vascular targeting thereby effectively disrupting the blood supply of tumors without influencing the normal blood vessels or any other tissue.

CUTTING OFF A TUMOR'S SUPPLY ROUTES

This anti-cancer nanoparticle can be likened to a smart bomb that delivers its multiple warhead genetic payload into endothelial cells that proliferate during angiogenesis — which is the medical equivalent of cutting off a tumor's supply routes. Once angiogenesis is stopped, the tumor cells starve, and the tumor is ultimately destroyed.

Anti-angiogenics have been known and studied for many years, but this anti-cancer nanoparticle is a new type of anti-angiogenic. Unlike other, "systemic" angiogenesis blockers, which become diffused throughout the blood stream upon injection, the nanoparticle-targeting vehicle directs itself to areas of the body where the tumors exist and where local vascular cells are expanding to form new blood vessels. The nanoparticle homes in on these cells and drops off multiple copies of a gene that effectively blocks angiogenesis and kills tumors.

"We saw strong regression of large tumors in every system

we looked at," says The Scripps Research Institute Professor David Cheresch, Ph.D., of the Department of Immunology, who led the study.

In the current paper, the investigators first report how they successfully delivered nanoparticles with "reporter" genes — such as those encoding for luciferase or green fluorescent protein, proteins that glow like the tail of a firefly. These reporter genes allowed dramatic demonstrations of the specific targeting of the nanoparticles to tumors. The tumors glowed green under a microscope.

TOWARDS THERAPIES

Cheresch and his colleagues then combined the nanoparticle with the mutant Raf gene and tested whether they could regress tumors *in vivo*, and they found the technique worked. Wherever there were metastatic lesions in the lung or liver, the Raf gene eliminated them.

The next step, says Cheresch, is to develop the technique in a more refined way as a general approach towards cancer therapy. The method might prove efficacious alongside some existing chemotherapy, for instance, to reduce the toxicity of existing anti-cancer drugs.

And, he adds, these nanoparticles may be useful in several other diseases where angiogenesis plays a major role — like heart disease, stroke, rheumatoid arthritis, and certain types of blindness in elderly patients and in patients with diabetes.

In the case of cancer, arthritis, and blinding eye disease this approach will be used as described to destroy newly sprouting vessels. However, following stroke and heart attack, new blood vessel growth is desirable. Therefore, this approach can be used to target pro-angiogenic genes to these sites and in so doing promote the rapid regrowth of blood vessels.

The research article "Tumor Regression by Targeted Gene Delivery to the Neovasculature" is authored by John D. Hood, Mark Bednarski, Ricardo Frausto, Samira Guccione, Ralph A. Reisfeld, Rong Xiang, and David A. Cheresch and appears in the June 28, 2002 issue of the journal *Science*. The research was supported by the National Institutes of Health and by a grant from Merck KGaA. ■

"Warm to the Touch" Gene Found

A group of researchers from The Scripps Research Institute and the Genomics Institute of the Novartis Research Foundation have identified and cloned the first-known gene that makes skin cells able to sense warm temperatures.

In an article appearing in the journal *Science*, a group led by Ardem Patapoutian of The Scripps Research Institute and Stuart Bevan of Novartis describes the protein the gene makes, a type of transient receptor potential (TRP) channel called "TRPV3." This membrane protein opens when it senses a certain temperature and allows ions to pass through and cause an electrical potential that signals the brain.

"This protein may be an important target for drugs," says Patapoutian, "because, like other TRP channels, it may be involved in inflammation and pain-mediation."

Significantly, TRPV3 is the first temperature-sensing molecule identified that becomes activated at warm and hot temperatures, 33 degrees C (91.5 degrees F) and above. And it is the first temperature-sensing channel found in keratinocytes, which are the major type of cell in the skin.

.....
"We have shown for the first time that skin cells are capable of detecting heat through molecules similar to those in heat sensing neurons," says Patapoutian.
.....

Previously, scientists had discovered that humans and other vertebrate animals use specialized neurons located in the spinal column that are connected to the skin and organs through long axons to sense temperature, pressure, and other physical stimuli. Expressed on these axons are the same sort of TRP channels as the one in the current study, and in the last few years scientists have identified them as the "molecular thermometers" that detect hot and cold temperatures in the skin and relay that information back to the brain.

Earlier this year, The Scripps Research Institute and Novartis group identified and cloned the gene — called TRPM8 — that codes for the first-known signaling molecule that helps the



Investigators recently identified the first temperature-sensing molecule that becomes activated at warm and hot temperatures, 91.5 degrees F and above.

body sense cold temperatures and the cooling compound, menthol. That led them in part to the current molecule.

They knew that TRPM8 detects cold. And another set of channels in the spinal cord were known to detect noxious heat. Patapoutian and his team reasoned that one or more molecules like TRPV3 must be able to detect warm temperatures.

"We have shown for the first time that skin cells are capable of detecting heat through molecules similar to those in heat-sensing neurons," says Patapoutian.

At approximately 33 degrees Celsius, TRPV3 becomes activated, opens, and allows an influx of positively-charged ions into the cell — an electrical signal that presumably alerts the brain of the temperature.

It is not known how this signal is communicated to the brain, since keratinocytes, unlike neurons, have no direct link with the central nervous system. Keratinocytes do, however, touch nerve fibers, and it may be through these contacts that the temperatures are communicated — a hypothesis that the team is trying to verify.

The channel's similarity to another temperature-sensing ion channel called VR1 suggests that TRPV3 may be a target for pain therapeutics. VR1 is involved in inflammation and in communicating pain to the brain, and several compounds that block its action are currently under investigation for chronic pain indications.

The research article "A novel heat-sensitive TRP channel expressed in keratinocytes" is authored by Andrea M. Peier, Alison J. Reeve, David A. Andersson, Aziz Moqrich, Taryn J. Earley, Anne C. Hergarden, Gina M. Story, Sian Colley, John B. Hogenesch, Peter McIntyre, Stuart Bevan, and Ardem Patapoutian and appears in the May 16, 2002 online version of *Science*. The research was funded by a grant to TSRI from Novartis. ■

TSRI Researchers Win Prestigious Scientific Awards

Dale Boger, Ph.D.,
Richard and Alice Cramer Professor of Chemistry and member of The Skaggs Institute for Chemical Biology, has won the Paul Janssen Award for Creativity in Organic Synthesis, given on a biannual basis at the Belgian Organic Synthesis Symposium to a chemist under the age of 50 who has made a significant contribution to the field of organic synthesis. Boger is internationally recognized for his work in organic synthesis, medicinal chemistry, heterocyclic chemistry, natural products total synthesis and biological evaluation, synthetic methodology development including combinatorial chemistry, and bioorganic chemistry and has made seminal contributions to the understanding of DNA-drug interactions and small molecule stabilization or disruption of protein – protein interactions involved in signal transduction.

Benjamin Cravatt, Ph.D.,
associate professor in the Department of Cell Biology, member of The Skaggs Institute for Chemical Biology, and The Scripps Research Institute's Kellogg School of Science and Technology class of '97, has been named one of the "TR100," the world's top young innovators according to *Technology Review* magazine for his work "developing tools to illuminate the roles of proteins and enzymes in humans and animals."

Albert Eschenmoser, Ph.D.,
professor in the Department of Chemistry and member of The Skaggs Institute for Chemical Biology, was

awarded the Oparin Medal, the highest recognition of the International Society for the Study of the Origin of Life. The Oparin Medal is given every six years to the scientist deemed to have "had the best sustained scientific research program in the origin of life field." Eschenmoser co-directs a research group at The Skaggs Institute for Chemical Biology that has contributed to the field through investigations into the chemical origins of nucleic acid structure, particularly through work on the thiofuranosyl oligonucleotides (a.k.a. TNAs).

Mark H. Ginsberg, M.D.,
professor in the Department of Cell Biology, has won the 2003 Earl P. Benditt Research Career Award from the North American Vascular Biology Organization for his seminal work on platelet receptor function and integrin biology. According to the organization, "throughout his years at Scripps, Dr. Ginsberg made many important discoveries that have dramatically advanced our thinking of cell – cell interactions and cellular signaling through the family of integrin receptors."

Eric F. Johnson, Ph.D.,
professor in the Department of Molecular and Experimental Medicine, is the recipient of the 2002 Bernard B. Brodie Award in Drug Metabolism, given every other year by the American Society for Pharmacology and Experimental Therapeutics. Johnson received the award for "his pioneering contributions to our understanding of the structure,

function, and regulation of liver cytochrome P450 enzymes."

Richard A. Lerner, M.D.,
Lita Annenberg Hazen Professor of Immunochemistry, Cecil H. and Ida M. Green Chair in Chemistry, president of The Scripps Research Institute, has received the University of California Presidential Medal. The medal is the highest award the university can bestow, established to recognize "extraordinary contributions to the University of California or the community of learning."

Lerner also received an honorary Doctor of Science degree from Northwestern University. Northwestern awards honorary degrees to those judged to have made exceptional contributions to fields valued by the university.

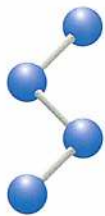
Lerner's 30-year scientific career encompasses a broad scope of activities, ranging from insights into protein structure to identification of a sleep-inducing lipid. His most recent work, and that for which he is perhaps best known, involves groundbreaking discoveries of converting antibodies into enzymes, permitting the catalysis of chemical reactions considered impossible to achieve by classical chemical procedures.

Julius Rebek, Jr., Ph.D.,
director of The Skaggs Institute for Chemical Biology, has won an American Institute of Chemists Chemical Pioneer Award. According to the American Institute of Chemists, "Rebek's lifelong work has led to major innovations in non-covalent molecular forces and pre-biotic mimetics — some of the concepts

he has pioneered are now regarded as starting points in the field."

Stephen W. Santoro, Ph.D.,
research associate in the Department of Chemistry, has been selected as a recipient of a 2002 Burroughs Wellcome Fund Career Award in the Biomedical Sciences. The award provides \$500,000 over five years for young scientists, spanning the period that includes their advanced post-doctoral training and their early years as a faculty member. Santoro, who is a 1999 graduate of The Scripps Research Institute's Kellogg School of Science and Technology, is currently studying the directed evolution of molecules, a Darwinian technique whereby a population of enzymes are modified in myriad ways and then selected for their ability to do something novel.

Ian Wilson, D.Phil.,
professor in the Department of Molecular Biology and member of The Skaggs Institute for Chemical Biology, has been elected to membership of the American Academy of Arts and Sciences. Through Wilson's efforts, breakthroughs have been achieved in several areas of structural biology, immunology, chemistry, biology, and biochemistry, particularly in understanding the chemistry of antibody-antigen recognition, the mechanism of catalytic antibodies, cellular-immune recognition by T cell receptor-MHC interaction, the mechanism of growth hormone-cytokine receptor signaling, and the identification and mechanisms of novel small molecule mimetics of natural hormones.



T H E
S C R I P P S
R E S E A R C H
I N S T I T U T E

NON-PROFIT
U.S. POSTAGE
PAID
PERMIT 751
SAN DIEGO CA

*A publication of
The Scripps Research Institute*

*Office of Communications—TPC20
10550 North Torrey Pines Road
La Jolla, California 92037*

Publisher:

Keith McKeown

Editor:

Mika Ono Benedyk

Writers:

Eric Sauter

Jason Socrates Bardi

Illustration:

Steve M. Lustig

BioDesign Communications Inc.

Design:

Craig Fuller

Sandra Sharp

Greenhaus

Production:

Janet Juliano

Jennifer O'Sullivan

Photography:

Jeff Tippett

Kevin Fung

Printing:

Bordeaux Printers