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VOLUME TEN / NUMBER ONE

THE SCRIPPS RESEARCH INSTITUTE

# ENDEAVOR

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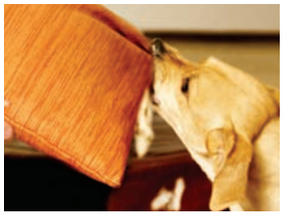
VOLUME **TEN** / NUMBER **ONE** **SPRING 2007**

FEATURES:









ALSO:



*ENDEAVOR* IS A PUBLICATION OF THE SCRIPPS RESEARCH INSTITUTE

This issue of *Endeavor* magazine features a few of the Scripps Research investigators who are working to better understand aging—and how we might be able to slow the process and increase the quality of life in our later years.

# *At the Forefront*

*Combination Therapy Obliterates New Vessel Growth in Tumors and Retinopathy*

Using a new and dramatically effective treatment approach, scientists for the first time achieved complete inhibition of new blood vessel growth in animal models of a highly vascular brain tumor and of neovascular eye diseases with little or no effect on normal tissue vasculature.

"Our study shows that combining anti-angiogenic agents that target multiple angiogenic pathways can significantly increase the effectiveness of such a therapeutic approach," said Martin Friedlander, M.D., Ph.D., a Scripps Research scientist and retina specialist at Scripps Clinic who led the study. "Such combination angiostatic therapy provides a whole new range of treatment options for patients with neovascular diseases, where complete inhibition of new blood vessel growth is the desired result."

**REFERENCE**: *PNAS*, 104(3), 967-972 (January 16, 2007).

*Chemical Pathway Causes Mice to Overeat and Gain Weight*

Researchers who are studying how body temperature and energy metabolism are regulated have discovered that an inflammation-related pathway appears to play a critical role in the onset of obesity. Further study of the pathway could lead to better understanding of the physiological foundation of obesity in humans and even the discovery of new treatments for the condition.

The team, led by Scripps Research neuroscientists Manuel Sanchez-Alavez, Ph.D. and Tamas Bartfai, Ph.D., discovered that mice genetically altered to lack a molecule known as the EP3 receptor tend to be more active during their normal sleep cycle and to eat more. In the study, this led to weight increases of up to 30 percent relative to mice with the receptors.

**REFERENCE**: *PNAS*, 104(8), 3009-3014 (February 20, 2007).

*Study Reveals Structural Dynamics of Single Prion Molecules*

Using a combination of novel technologies, scientists at Scripps Research and the Whitehead Institute for Biomedical Research have revealed for the first time a dynamic molecular portrait of individual unfolded yeast prions that form the compound amyloid, a fibrous protein aggregate associated with neurodegenerative diseases such as Alzheimer's disease and variant Creutzfeldt-Jacob disease—the human version of mad cow disease.

"By focusing on single unfolded prions, we were able to define the dynamics of two distinct regions or domains that determine conversion dynamics," said molecular biologist Ashok A. Deniz, who led the study. "Our research techniques can now be used to probe the structures of other amyloidogenic proteins. This could prove important in understanding the basic biology of amyloid formation, as well as in designing strategies against misfolding diseases."

**REFERENCE**: *PNAS*, 104(8), 2649-2654 (February 20, 2007).

*Novel Insights into Tumor Suppression*

Scientists have discovered a surprising new function of a well-known signaling pathway that, when activated, can inhibit tumor development. The research focused on an anti-tumor defense response called senescence, or cellular aging—which can occur prematurely to combat the development of cancer. Conducted in cell culture and animal models, the study identified one essential element of this anti-tumor response, p38-regulated/activated protein kinase (PRAK).

"In uncovering this basic mechanism, we've advanced our knowledge of how cancers develop," said Scripps Research scientist Peiqing Sun, Ph.D., who led the study with Jiahuai Han, Ph.D., also at Scripps Research. "More importantly, we have identified a pathway in normal cells that, when activated, can inhibit tumor development. This lays the groundwork for new cancer therapy—for future drug development to artificially activate this pathway in cancer cells."

**REFERENCE**: *Cell*, 128, 295-308 (January 26, 2007).

*New Mechanism Activates Pain-Sensing Channel*

A Scripps Research team has identified a mechanism that enables certain compounds to activate a pain-sensing protein. The findings could lead to the development of potential new therapies for managing acute and chronic pain.

The researchers found that TRPA1, a protein that helps transmit pain signals, is a direct sensor of reactive chemicals. "While many noxious and pungent compounds were known to activate this pain receptor, we discovered that they do so by directly and irreversibly binding to the cysteine amino acids of this protein," said cell biologist Ardem Patapoutian, Ph.D., whose lab conducted the study in collaboration with the Cravatt and Schultz groups. "Our study shows that TRPA1 activation is directly linked to chemical insult."

**REFERENCE**: *Nature*, 445, 541-545 (January 21, 2007)

*"It is amazing how little we know about temperature regulation given how important it is in our physiology."*

*BRUNO CONTI, PH.D.*

# *Resetting the Dial*



BRUNO CONTI GIVES LIFE EXPECTANCY A NEW TWIST

Bruno Conti, Ph.D., attracted a lot of attention recently when his paper came out in the journal *Science*. Suddenly, journalists were calling from around the world. Could his team have revealed a possible fountain of youth? And what was this about a link to obesity?

"The media coverage was exciting," says Conti, who still seems slightly bemused by the avalanche of calls and emails. "But I also felt the responsibility to convey the science in an accurate way. People wanted to know how to live longer, but we are basic scientists investigating a specific phenomenon, for now in mice. While this was an important step forward from many aging studies, it is still premature for a 'temperature-based' life-extension approach in humans."

Yet the findings are intriguing, both due to the elegance of the experiments and their larger implications.

In the breakthrough paper, published November 3, 2006, the team reported that a modest but prolonged reduction in the core body temperature of mice extended their life expectancy by up to 20 percent. This is the first time that changes in body temperature had ever been shown to affect lifespan in warm-blooded animals.

"For years, calorie restriction was the *only* way known to prolong lifespan in warm-blooded animals," says Conti, who is an associate professor at The Scripps Research Institute. "But the degree of calorie restriction needed to extend lifespan (25 to 40 percent) is not easy to achieve, even in mice. It's not a very practical way to extend lifespan—and not very fun."

In contrast, in Conti and colleagues' study, mice lived longer while eating as much as they wanted.

## AN INGENIOUS SCHEME

The idea for the study came in the year 2000, shortly after Conti had been recruited to Scripps Research by Professor Tamas Bartfai, Ph.D., director of the Harold Dorris Neurological Research Institute. Both scientists shared an interest in neuro-immunology, a discipline studying the interaction between the immune and the nervous systems including the action of pro-inflammatory cytokines on temperature regulation during infection—fever.

"It is amazing how little we know about temperature regulation given how important it is in our physiology," says Conti. "The fact that homeotherms [warm-blooded animals], including mice and humans, have a constant body temperature has allowed them to colonize the entire planet. However, a good amount of energy has to be used to maintain this temperature constant."

Conti and Bartfai began thinking about the relationship between body temperature and lifespan. Scientists knew that cold-blooded animals, such as roundworms (*C. elegans*) and fruitflies (*Drosophila*),



lived longer at colder temperatures. In warm-blooded animals, calorie-restriction resulted in longer lifespan and lower core body temperature. But was calorie restriction itself responsible for this longer lifespan, with reduced body temperature simply a consequence? Or was the reduction of core body temperature a key contributor to the beneficial effects seen with calorie restriction?

"We started to wonder if it was possible to generate a mouse with a reduced temperature to look at this question directly," says Conti. "We said, 'Why not? But how?' Luckily for us, the Ellison Medical Foundation and Ms. Helen Dorris were willing to fund such a high-risk project."

Thanks to the expertise of their colleagues at Scripps Research, particularly of Manuel Sanchez-Alavez, M.D., Ph.D., the scientists hit on an ingenious scheme. Just as holding a match near the thermostat in a room can fool a house's temperature-regulating system into "thinking" that the entire room is hotter so the air conditioning turns on, the scientists decided to try to trick the brain's thermostat by producing heat nearby.

## FOOLING THE THERMOSTAT

To do so, the scientists targeted the preoptic area, a brain structure in the hypothalamus that is known to regulate the body's temperature. As luck would have it, a Scripps Research colleague Luis de Lecea (now at Stanford University) had cloned a neuropeptide called hypocretin, which was expressed in a subset of cells (and only in that subset) in a nearby part of the brain, the lateral hypothalamus—a mere 0.8 millimeters from the preoptic area. The scientists decided to use the hypocretin neurons as the site of heat generation to influence the nearby thermostat.

To generate heat, the team looked to a class of proteins called uncouplers (UCPs). These proteins sit on inner membrane of mitochondria, where the proton gradient derived from the metabolism of food is coupled to the production of high-energy phosphate molecules called adenosine tri-phosphate (ATP), the source of cellular energy. UCPs can "uncouple" this process allowing part of the proton gradient to leak through the membrane thereby generating heat instead of ATP. Drawing on the techniques of molecular biology, the scientists planned to express an uncoupler, UCP-2, in hypocretin neurons. This would act as the lit match next to the brain's thermostat.

"The idea was cool—so cool I thought it would never work," says Conti. "But we tried it anyway."

And, in fact, it worked beautifully, resulting in a continuous reduction of core body temperature of 0.3 to 0.5 degrees Celsius during the mice's waking hours.

The scientists were then able to measure the effect of lowered core body temperature on lifespan. They found that the mice with lowered core body temperature had a longer median lifespan than those that didn't—about 20 percent for females and 12 percent for males.

Interestingly, the scientists also found that male mice with lower body temperatures became slightly fatter, with about 10 percent more body weight than their normal littermates; the females showed no significant difference in weight.

*"Our findings caught a lot of interest but, as I came to realize, could be easily misconceived… It is not good to live in a refrigerator. It is not necessary to avoid using the heat in your apartment."*

*BRUNO CONTI, PH.D.*



## FROSTBITE WON'T HELP

So it was that after more than five years of painstaking attention to every detail in the study to ensure its scientific rigor, Conti found himself thrust into a different role, fielding questions about his research from the media and responding to inquiries from the public about just what they could do to live longer.

"Our findings caught a lot of interest but, as I came to realize, could be easily misconceived," notes Conti. "It's easy to misinterpret the concept of core body temperature—the temperature of those parts of the body where the vital organs reside, namely the trunk and the head. This is where the temperature is maintained constant in warm-blooded animals. In contrast, the temperature of the skin or the extremities is referred to as 'peripheral' and is subject to considerable variation."

So, when someone asked Conti if it was good to forget about a heavy coat in the winter to stay cooler, he had to say "no." "Your body would keep your temperature the same," he explains. "It is not good to live in a refrigerator. It is not necessary to avoid using the heat in your apartment." And when someone else was excited about her prospect for a long life because she had cold hands, Conti had to correct her. "I don't want to disappoint anybody," he says, "but this is peripheral body temperature."

Interestingly enough, true core body temperature is rarely properly measured in humans. Even though temperature is taken every time one goes to the doctor's office, this is only an indication of the core body temperature, not an exact measurement. Conti also notes that the kind of variation the scientists measured in the lifespan study, often less than half a degree Celsius, is rarely considered noteworthy, even in medical settings, although sleep physiologists might take heed.

There was one more potential misinterpretation Conti was eager to head off. "Our study indicates that there is a pathway that regulates longevity that is independent of calorie restriction," he says, "but eating healthy is still a good way to live longer."

Darn, still no excuse to eat lots of cookies.

## ATTRACTED TO THE BLACK BOX

Conti's interest in science dates back to his childhood in a small village in Northern Italy, Olginate, where, surrounded by the countryside and nearby Lake Como, he developed an abiding fascination with the natural world. After attending a science-oriented high school, he headed for the University of Milan, at first torn between the fields of physics and biology.

"I chose biology because the phenomenology seemed a little more unpredictable [than physics] and that was fascinating to me," he says. "After I started, it was clear I had made the right choice because I really enjoyed it."

Following a path dictated by his intellectual curiosity, at the University of Milan Conti conducted thesis work in yeast microbiology. He then moved to New York Medical College, where he pursued research on antibody engineering and investigations on the role of macrophages in HIV. Conti was then offered a postdoctoral position in molecular neurobiology at Cornell University.

→ *Continued on p.15*

*"The quality of life of an individual with severe osteoarthritis is often greatly impaired. As a scientist, I'd like to contribute to changing this situation for patients."*

*MARTIN LOTZ, M.D.*



# *The Problem with Wear and Tear*

MARTIN LOTZ EXAMINES OSTEOARTHRITIS

Even in comparison with other diseases of aging, osteoarthritis has a remarkably broad impact. Currently affecting about 15 to 20 million Americans, osteoarthritis is expected to increase by 50 percent over the next two decades, and there are no effective treatments.

"All existing therapies are only palliative, but even the COX 2 inhibitors most often prescribed for inflammation and pain associated with osteoarthritis can have gastrointestinal or cardiac side effects, or can even cause death," says Martin Lotz, M.D., a professor in the Department of Molecular and Experimental Medicine at The Scripps Research Institute. "Nothing is available that can slow down or stop the progressive degeneration of cartilage that characterizes the disease."

Internationally known for his investigations of osteoarthritis, Lotz is searching for diagnostic tools and therapies to treat cartilage degeneration.

"The quality of life of an individual with severe osteoarthritis is often greatly impaired," Lotz says. "As a scientist, I'd like to contribute to changing this situation for patients."

## THE NEED FOR A CUSHION

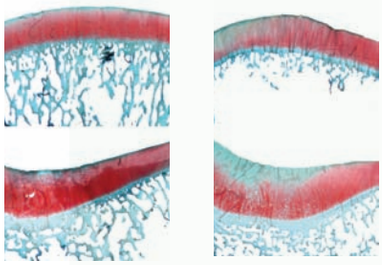
Osteoarthritis, also known as degenerative arthritis, is a disease that begins in and affects joint cartilage, the major weight-bearing "cushion" in joints. The disease results from a combination of wear and tear on cartilage and underlying age-related changes that cause cartilage to deteriorate. Osteoarthritis commonly affects the hands, spine, and large weight-bearing joints, such as the hips and knees.

Those at highest risk for osteoarthritis are people who are obese, who have a genetic predisposition for the disease, or who have suffered acute or cumulative joint trauma. Many people, however, have none of these risk factors and develop the disease simply as a function of age. "Osteoarthritis can result when mutations occur in the most prevalent collagen found in cartilage—type 2 collagen—but this genetic form of osteoarthritis represents a small percentage of the overall patient population," Lotz says.

Symptoms of osteoarthritis vary greatly from patient to patient. Some people are debilitated by their symptoms while others experience few problems, despite joint degeneration that is apparent on x-rays. Symptoms also can be intermittent.

This heterogeneity—the fact that osteoarthritis can be mild and sporadic in some or severe enough in others that a joint replacement is required—has contributed to the difficulty in finding suitable drugs and treatments.

"There is no single 'type' of osteoarthritis patient," Lotz says. "In a way, it's like treating cancer, a disease that also presents itself in many forms and for which no single treatment is effective in all cases." →



Cartilage of a 17-year-old (left) compared with that of a 56-year-old.



## GLASS-LIKE NO MORE

Composed of about 85 percent water, cartilage holds the key to healthy joints. In addition to water, the most significant component of cartilage is type 2 collagen. This form of collagen acts almost like a rubber band—held in an extended position by proteoglycans—proteins and sugars also found in cartilage. When weight is placed on joints, collagens and proteoglycans allow cartilage to absorb weight and be compressed; when weight is removed, they allow cartilage to bounce back. This behavior gives cartilage its characteristic ability to deform under a mechanical load and to resume its shape when the load is gone—in short, to cushion joints. In addition to type 2 collagen and proteoglycans, cartilage also contains chondrocytes—cells that produce cartilage.

Normally, the surfaces of cartilage are perfectly smooth, almost glass-like, enabling joints to move without friction. "In a healthy joint, the mechanics of that frictionless surface is so perfect that it far exceeds anything we can construct," Lotz says.

Once a joint surface starts to break down, however, the story changes. The frictionless state disappears, and over time, cartilage may become eroded down to the underlying bone. As cartilage wears down, the body sets off an inflammatory response to the breakdown products and the person begins to experience joint swelling and dysfunction, stiffness, and pain upon movement.

## UNDERSTANDING THE DOWNWARD SPIRAL

One of the fundamental questions Lotz hopes to answer is why in some people joints age normally, while in others cartilage begins the downward spiral toward disease.

"We know that all of our organs age, and that our joints also age, but we don't know how age triggers cartilage deterioration," Lotz says. "Most confounding in osteoarthritis is why some fortunate people live their entire lives without ever getting the disease. They may experience normal joint aging, but without the pain or stiffness that seriously impedes quality of life."

Getting to the bottom of what constitutes normal joint aging, as opposed to joint aging in osteoarthritis, is a key quest for Lotz.

His research has shown that cell death—known as apoptosis—of cartilage is a major factor in the onset of osteoarthritis and that those who experience a higher level of cell death are more likely to have a greater degree of cartilage deterioration.

"For all its complexity, cartilage is actually a fairly simple structure," Lotz says. It only contains a single cell type—chondrocytes—responsible for maintaining the tissue. As more and more cartilage cells die off, fewer remain to resynthesize and turn over type 2 collagen and proteoglycans, and the cartilage loses its biomechanical function.

The best example of cell death linked to cartilage loss occurs after joint trauma, according to Lotz, because osteoarthritis often sets in after a joint injury, when cartilage cells die. Lotz's lab has a pre-clinical study under way that is testing a number of cell death inhibiting drugs to assess their effectiveness in preventing the onset of osteoarthritis after joint trauma.

Another aspect of Lotz's work is the study of n-acetylglucosamine—a modified form of the popular glucosamine, often used as a supplement to treat osteoarthritis. Glucosamine stimulates cartilage cells to produce proteoglycans and collagen. Lotz and Alexander Shikhman, M.D., Ph.D., a researcher in his group, discovered and patented n-acetylglucosamine for local injection into injured joints, with the objective of preserving cartilage integrity and preventing cells from deteriorating or dying. Clinical trials are now in progress with osteoarthritis patients to test the safety and efficacy of this therapy.

Studying the role of stem cells as a possible future therapy for tissue repair in osteoarthritis is another area in which Lotz sees promise.

*"Most confounding in osteoarthritis is why some fortunate people live their entire lives without ever getting the disease. They may experience normal joint aging, but without the pain or stiffness that seriously impedes quality of life."*

*MARTIN LOTZ, M.D.*

"Strangely enough, in osteoarthritis, stem cells actually contribute to cartilage degeneration by becoming involved in the inflammatory aspect of the disease," he says. "We are looking for opportunities to use drugs—growth factors—to re-direct stem cells toward repairing cartilage defects."

This work involves transplanting stem cells into injured tissue in a way that promotes differentiation into chondrocytes, the cells that produce cartilage. Lotz and his group are working to identify markers that define the chondrocyte stem cells in bone marrow and other tissues that may be isolated and used for therapeutic purposes.

## DRIVING WITH MISALIGNED TIRES

A native of Heidelberg, Germany, Lotz obtained his medical degree from the University of Heidelberg in 1981 and practiced internal medicine in Germany before coming to Scripps Research in 1983. In 1990, he went to the University of California, San Diego, where he practiced rheumatology; in 1997, Lotz returned to Scripps Research to start the Division of Arthritis Research.

Although he started out studying rheumatoid arthritis, Lotz soon switched to osteoarthritis, a disease he had seen as a physician adversely affect many of his patients. Although rheumatoid arthritis, an immune disorder, is a much rarer disease, more treatments are available. "It is fascinating to me to try to get to the bottom of the one disease—osteoarthritis—where there is such an enormous discrepancy between the number of people suffering and the complete lack of anything available. I want to help them in a meaningful way by slowing down or halting the disease."

"The end-stage of osteoarthritis is inevitable decline," he says. "First, there is joint pain, which makes it hard for someone to walk or easily move around. That lack of mobility often causes weight gain and with that comes cardiovascular side effects. Usually, a joint replacement is the only thing that will restore mobility. Although today's joint replacements usually do their job well, our goal is to find therapies to intervene before a joint replacement becomes necessary."

Lotz is a strong proponent of making lifestyle changes to try to stave off the onset of age-related osteoarthritis. Once an avid marathon runner—he estimates that he has run around the world about one and a half times—Lotz gave up that form of exercise years ago in favor of yoga.

"As I learned more about osteoarthritis, I started thinking about exercises that give the same cardiovascular benefit as running without the risk of joint injury," he says. "I'm not a big advocate of excessive running for most people."

He feels running is risky unless one has a "runner's body" that can withstand the incessant pounding. "There must be a good, natural alignment of the pelvis with the lower extremities, otherwise it's like a car driving on misaligned tires—inevitably, certain areas of the tires will start to wear out unevenly."

Although Lotz says that further study is necessary to determine yoga's effectiveness in staving off osteoarthritis, he believes that from a purely biomechanical standpoint it comes out ahead of most other forms of exercise because there is no impact or trauma to the joints, yet all of the joints, from head to toe, are engaged. One of the interesting aspects of joint mechanics is that while excessive stress on specific areas can injure joints, an even amount of pressure across the entire joint stimulates the healthy maintenance of cartilage.

Lotz has practiced yoga about three times a week for the last 15 years. "This is my way of doing what I can to keep osteoarthritis at bay," he says. "I would advise everyone—adults, as well as teenagers—to think about the possibility of trying to prevent joint disease long before it happens."

ANNA SOBKOWSKI

AS MANY AS 4.5 MILLION AMERICANS ARE CURRENTLY AFFLICTED WITH ALZHEIMER'S, ACCORDING TO THE NATIONAL INSTITUTES OF HEALTH—ABOUT FIVE PERCENT OF MEN AND WOMEN AGES 65 TO 74, AND NEARLY HALF OF THOSE AGE 85 AND OLDER.

*"I'm still walking about an inch off the ground. I never thought I'd be able to do this kind of research in academia. I thought I would either have to stay in academia and forget drug development, or leave academia and forget about steering my own ship. Here I can do both."*

*MALCOLM LEISSRING, PH.D.*

# *Unclogging the Drain*



MALCOLM LEISSRING EXPLORES NEW APPROACHES TO ALZHEIMER'S DISEASE

For many of us, the prospect of old age wouldn't seem nearly as frightening if medicine could offer effective treatments for Alzheimer's disease, a brain disorder that gradually destroys a person's memory and ability to learn, reason, make judgments, communicate, and carry out daily activities.

As many as 4.5 million Americans are currently afflicted with Alzheimer's, according to the National Institutes of Health—about five percent of men and women ages 65 to 74, and nearly half of those age 85 and older. The disease can be devastating not only for these individuals, but also for their families.

The physical hallmarks of Alzheimer's disease, first identified by German physician Alois Alzheimer in 1906, are changes in the brain—clumps, called amyloid plaques, and tangled bundles of fibers, called neurofibrillary tangles. Subsequently, these abnormal structures were linked to a sticky protein produced in the brain called beta-amyloid.

Malcolm Leissring, Ph.D., the leader of a neurobiology group at Scripps Florida, is one scientist devoting his efforts to finding new treatments for Alzheimer's disease. The launch of his research program excited many people in the Palm Beach County area, and even inspired one family to create a new organization to raise funds for Alzheimer's research at Scripps Florida. Leissring works closely with members of the group to help donors and caregivers understand Alzheimer's, and his work aimed at fighting it. Such interaction with the people directly affected by a disease may not be common for a research scientist, but Leissring is not a common researcher.

## UNDERSTANDING A SCOURGE

When Malcolm Leissring first began investigating Alzheimer's disease in the 1990s, most research was focused on developing treatments that would decrease production of beta-amyloid in the brain. But a few researchers were beginning to take a different approach. Could the breakdown of beta-amyloid, long ignored as a focus for treatment development, be as important as its production—or even more so?

Today, the bulk of Leissring's work focuses on the destruction of beta-amyloid, more specifically, on the enzymes responsible for the process and compounds that control it.

Scientists now recognize that the accumulation of beta-amyloid clumps that inhibit brain function and cause Alzheimer's fundamentally results from an imbalance between the production and breakdown of beta-amyloid. Leissring uses the analogy of a kitchen sink, where the faucet is beta-amyloid production and the drain is the protein's destruction. A faucet pumping out water faster than the drain can work leads to an overflow, but so does a clogged drain.

Alzheimer's patients afflicted by early-onset forms of the disease, a small fraction of the total, all have genetic mutations that lead to an overactive beta-amyloid faucet. →

*"When someone you love has Alzheimer's, there is nothing you can do for them. There are no medicines, no treatments, you can't legislate against it. There's nothing you can do, so research becomes a very important issue."*

*PATTY DOHERTY*
*Founder of The Unforgettable Fund*



But plaque formation in the typical Alzheimer's patient is more likely due to problems with the beta-amyloid drainage system, regulated by a group of enzymes that cut the protein into pieces. This, of course, has led to great interest in these enzymes, with the hope of identifying treatments that might enhance the process. This line of research is especially enticing because the large number of enzymes involved in beta-amyloid destruction offers far more targets for drug treatments than the relative few responsible for beta-amyloid production.

One of the most significant beta-amyloid destructors is a protein called insulin-degrading enzyme, or IDE. While working as a postdoctoral fellow at Harvard Medical School, Leissring led a seminal study showing that the beta-amyloid plaques present in a mouse model of Alzheimer's were dramatically reduced by a relatively small increase in IDE. A much larger increase in another enzyme, neprilysin, was found to completely prevent all Alzheimer's-like symptoms, including plaque formation, inflammation, and premature death.

This work helped convince Leissring and other researchers that gaining control of IDE and other enzymes that break down beta-amyloid was a promising path.

## SO YOU WANT TO BE A ROCK STAR

That Leissring has pursued Alzheimer's research, or any other branch of science, might well come as a surprise to those who knew him in high school. He left high school at age 15—by taking a test, not flunking—with the intention of pursuing his dream of a career as a musician—a heavy metal guitarist, to be precise. "My goal in life was to become a rock star," he says. But things didn't go as smoothly as he had hoped.

His first step was to go to a community college in his hometown of Santa Rosa, California. He signed up for a music recording class that required he also take an electronics course. To his surprise, he aced electronics and nearly flunked recording.

The experience convinced him he was more inclined toward academics, so he went to the University of California, Berkeley to study psychology as an undergraduate. There, he was surprised to learn that most drugs in use today were discovered more or less by accident. However, based on progress in our understanding of the brain, Leissring became excited by the possibility that drugs could one day be developed by rational design, instead of blind chance.

But Leissring didn't give up playing guitar entirely, and in fact has been in a string of heavy metal bands, something it is safe to say few biomedical researchers can claim. He laments that his bands—with names like Wrath, Intense, and Tragus—have suffered for lack of a good lead singer. Ironically, it was this very problem that began his close connection with the victims of Alzheimer's in Palm Beach County.

## AN UNFORGETTABLE EVENT

Soon after Leissring's arrival in Florida, a *Palm Beach Post* reporter wrote a profile on him that highlighted not only his research but also his musical pursuits. The article mentioned that, having left his band behind in the cold when he left Harvard, he was in need of a new singer.



A local graphic artist named Patty Doherty contacted the reporter to have a message passed to Leissring. "I said, tell him I'll sing lead vocals for him, whatever he needs we'll find it, just get back in the lab and get to work."

The fact that, by her own admission, Doherty is decidedly not a singer is perhaps worth noting as an indicator of how anxious people in the community have been to support Scripps Florida and see research there move forward. At the time, her father was in the late stages of Alzheimer's. Doherty didn't become a singer, but the note did lead to her meeting with Leissring and taking him to visit her father, an event that profoundly impacted Leissring. "For the first time, I saw how depressingly horrible this disease really is," he says.

When her father died in early 2006, Doherty's family and friends decided to set up a non-profit organization called The Unforgettable Fund that would raise funds to support Alzheimer's research by Leissring and others at Scripps Florida. To date, the group has raised more than $20,000. By operating exclusively on the Internet, the fund costs very little to run, and also provides a place for donors to leave memories for their loved ones, to share experiences, and to learn more about Alzheimer's.

"When someone you love has Alzheimer's, there is nothing you can do for them," Doherty says. "There are no medicines, no treatments, you can't legislate against it. There's nothing you can do, so research becomes a very important issue. I can't go into the laboratory and watch test tubes or light Bunsen burners, but I can raise money."

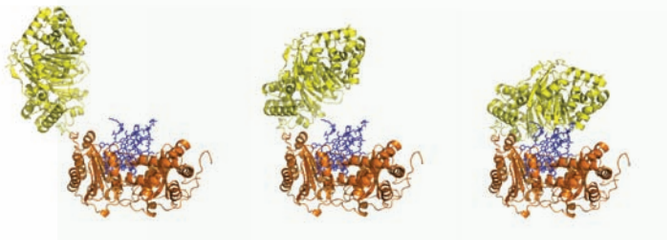
Fittingly enough, Leissring has said that in Florida, people like Doherty have made him feel like a rock star, because the community is so excited about Scripps Florida's arrival and the enormous potential it holds for translating basic science into new therapies.

"Here in Palm Beach County, advancing Alzheimer's research has become a real team effort between my lab and diverse members of the community. I don't think I would have found this anywhere else," says Leissring. "People down here feel genuinely empowered by the chance to help out, and I am grateful to them for their magnanimity."

## MULTIPLYING OPPORTUNITIES

In between applying for new grants and conducting experiments, Leissring finds time to keep caregivers and donors informed about his work and other advances in the field through postings on The Unforgettable Fund website at http://www.theunforgettablefund.com.

A case in point was a 2006 paper in the journal *Nature* that described the structure of IDE, and about which Leissring and one of his mentors wrote a commentary. The study, led by Wei-Jen Tang at the University of Chicago, found that IDE is shaped something like a clam shell, with two bowl-shaped halves hinged at one end and held shut much of the time at the other end by a loose chemical bond that acts as a latch. IDE can only attack and destroy beta-amyloid molecules when the latch is released, allowing the two halves of the molecule to open. The Tang team showed that a mutated version of IDE with a broken latch was some 4,000 percent more active than normal. →



Insulin-degrading enzyme in action. The structure of IDE resembles "Pac-man," with two bowl-shaped halves (yellow and orange) connected by a flexible hinge. This cartoon shows IDE chomping on a molecule of insulin (blue).



These findings have created great excitement in the field because they open multiple new paths for developing Alzheimer's treatments. While mutating IDE genes in humans is beyond the bounds of current medicine, researchers such as Leissring can look for drugs that target IDE components, such as the latch. Leissring's group has already made some progress towards that goal, identifying compounds that increase IDE's activity by about 400 percent, albeit not very potently. In the near future, Leissring's group will screen hundreds of thousands of compounds hoping to identify even better potential treatments.

Another recent and promising development in the field was the discovery that beta-amyloid, while produced primarily in the brain, is capable of moving back and forth between the brain and the bloodstream. This means that treatments administered in the blood could still achieve the goal of reducing beta-amyloid levels in the brain. With a grant from the National Institutes of Health (NIH), the Leissring group is exploring this possibility by injecting mice with blood cells modified to continually produce excess IDE or other enzymes capable of destroying beta-amyloid. If this approach is successful—and early signs suggest that it is—Leissring says that Alzheimer's patients could one day go in for therapy akin to kidney dialysis to reduce their beta-amyloid levels. "Drugs that shut down the faucet of beta-amyloid production must enter the brain, which can be difficult and also dangerous," says Leissring, "but drugs or other treatments that unclog the drain may not have to."

Although it may seem counterintuitive, Leissring's group has also intentionally designed a group of compounds that *inhibit* IDE to better understand its activity. "As a basic scientist, sometimes you want to make a disease worse to understand it better." Interestingly, reducing IDE levels might offer an effective treatment for diabetes by increasing insulin levels. Although there could be complications if beta-amyloid levels also rise, Leissring has discovered that certain compounds can alter IDE's ability to destroy insulin without affecting other substrates like beta-amyloid. Leissring is currently applying for a patent on the inhibitors he developed, and hopes that a private company will eventually explore their potential to combat diabetes and other problems.

## A DREAM COME TRUE

Leissring said he remains amazed that he has the opportunity to actually design drugs that may ultimately be able to help people, just as he dreamed of doing at Berkeley.

"I'm still walking about an inch off the ground," he says. "I never thought I'd be able to do this kind of research in academia. I thought I would either have to stay in academia and forget drug development, or leave academia and forget about steering my own ship. Here I can do both."

The approach of unclogging the drain holds enormous potential, but realizing that potential requires funding, which has recently sunk to historical lows. For Doherty, whose family paid both the emotional and financial costs of Alzheimer's, and countless others like them, progress and new treatments can't come soon enough. "I don't think anybody really has described correctly or accurately how bad Alzheimer's is," says Doherty. "We cannot afford to not cure this disease."

MARK SCHROPE

*"[Calorie restriction] is not a very practical way to extend lifespan—and not very fun."*

*BRUNO CONTI, PH.D.*

# *Resetting the Dial*



*(continued from page 05)*

"At the time, neurobiology was like a black box to me," he says. "I knew very little."

Despite this fact—well, Conti admits, because of it—he accepted the position. At Cornell, he discovered that his broad background in molecular biology and immunology gave him a unique perspective on the topics at hand. He ended up cloning a pro-inflammatory molecule now known as interleukin 18, which is produced in immune cells during infection and which Conti also found produced in adrenal glands during stress and in the brain.

"From that point on, I became really interested in neuro-immunology," he says.

He realized that because this molecule was produced during stress, it provided an avenue to investigate the relationship between mental state and susceptibility to diseases, in other words, how the central nervous system modulates immune function. That, in turn, opened questions that could be framed the other way around—how the immune system affects brain functions. Conti began studying the presence and the possible roles of interleukin 18 in the brain.

It was at this point that Bartfai—known in the field for work on a similar molecule, interleukin 1ß—invited Conti to Scripps Research to join its Harold Dorris Neurological Research Institute. Bartfai is happy about the decision.

"Bruno has the best scientific curiosity and self-criticism," Barfai says. "He also has an extremely friendly, collaborative manner—you can always fight over science but it never gets beyond that. I wish more of my colleagues were like him, but cloning is forbidden..."

## UNANSWERED QUESTIONS

In Southern California, Conti again finds himself surrounded by the natural world, which he enjoys through activities such as hiking and sailing. He has also recreated another part of his childhood—Italian food, which he eats and cooks with great enthusiasm. "I love pasta, of course," he says. "I also make risotto and I prepare gnocchi from scratch."

Conti, who seems to have an endless supply of energy, also bubbles with excitement about the future of his research. He plans to further explore the mechanisms of interleukin 18, which he now believes may play roles in both obesity and atherosclerosis. He is also planning to address the many questions raised by the recent *Science* paper.

Sparking Conti's curiosity are issues of how lowered core body temperature extends lifespan and healthspan—what are the mechanisms at work? In addition, why did core body temperature drop during the mice's waking hours, but not during their sleep cycle? Why did the female mice with lowered core body temperature live longer than their male counterparts? And how did these male mice come to gain weight?

"Another thing we want to do is to combine calorie restriction with lowered core body temperature," he says. "If we restrict the calories of these animals with lower body temperature, would they live even longer?"

Happily, many mysteries remain for Conti to solve.

MIKA ONO BENEDYK

# Giving Opportunity

## ULRICH MUELLER AND THE FUTURE OF DEAFNESS RESEARCH

*The Scripps Research Institute is currently raising funds to create an endowed Chair of Hearing Loss and Deafness Research to support the future of deafness research at the institute and to explore issues of importance to deaf and hard-of-hearing people.*

Professor Ulrich Mueller, Ph.D., a member of the Institute of Childhood and Neglected Diseases, is one of the researchers at The Scripps Research Institute who is investigating the underlying causes and potential treatments of hearing loss. In fact, his passion is deafness.

"Deafness is so prevalent in humans, yet no pharmaceutical company is doing anything about it," Mueller says. "Also, of all the senses—vision, smell, and taste—it is the least well known. Because of these factors, I feel I can make a real impact on health care through my research."

Deafness is the most common form of sensory impairment in the human population, affecting over 30 million Americans and their families. More than half of all people over 75, and 80 percent of those over age 80, suffer some form of hearing loss. On the other end of the age spectrum, one in a thousand children are born with a hearing impairment.

"Hearing loss leads to a significant decline in the quality of life and often to a sense of isolation," says Mueller. "To develop therapeutic strategies against hearing loss, it is critical that we understand how sound signals are processed by the ear and nervous system, and how such processing is perturbed in disease."

### *Opportunity for Interaction*

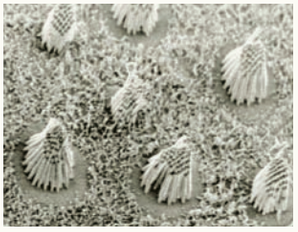
Mueller—whose interest is in how the nervous system works, both from the perspective of basic science and possible treatment strategies—came to Scripps Research four years ago from the Friedrich Miescher Institute in Basel, Switzerland. Prior to his stint there, he received his Master's from the University of Cologne in Germany, earned a Ph.D. from Princeton University, and completed postdoctoral work at the University of California, San Francisco.

"I came to Scripps Research because of the opportunity for interaction with top biologists and chemists, both at the institute and other institutions in La Jolla," he says.

Much of his lab's attention has focused on the genes that cause Usher Syndrome. And about four in 10,000 babies born in the United States have Usher syndrome, a devastating genetic disease that causes deafness and blindness. Mueller's studies have shown this type of deafness is caused by defects in hair cells, which are situated in the inner ear and function as sensors for sound.

"Surprisingly, our recent findings show that one of the genes that is affected in Usher Syndrome is also linked to deafness from birth and age-related hearing loss," said Mueller. "We're targeting this one gene to deal with each of these diseases."

An endowment gift to establish a faculty chair at The Scripps Research Institute is one of the most meaningful and lasting gifts available to a donor. The benefits of an endowment gift will be enjoyed and acknowledged by generations to come.



Left: a scanning electron micrograph of several hair cells important for hearing. (*Courtesy of Amanda Littlewood-Evans*)

## Professor Ulrich Mueller's passion is research on deafness.

*A Big Task Ahead*

Mueller and others in the deafness research field have a big task ahead of them. Of the more than 400 genetic loci in the human genome that have been linked to deafness, only about 100 have been assigned to specific genes. According to Mueller, identifying relevant genes is critical for the development of diagnostic and therapeutic strategies.

"We're trying to get all this under control," said Mueller. "In my lab, we carry out positional cloning strategies to identify genes that are linked to deafness. We have recently linked several genes to different forms of hearing impairment, including age-related hearing loss. This should open up new therapeutics.

"We're also looking at ways to delay the deafness process. If we can eventually double the amount of time over a lifetime that it normally takes a person to go deaf, we won't need to develop a cure, since most people don't live until 130."

Mueller has seen much progress in the field, and he's hopeful for the future. "Deafness research is on the brink of some momentous breakthroughs," he says. "Over the past decade, the field has gained momentum and we are now in a position to develop and test new therapeutic strategies that may lead within the next decade to advances in slowing age-related hearing loss, or even providing cures for some forms of deafness."

*If you are interested in endowing the Chair of Hearing Loss and Deafness Research to facilitate groundbreaking research by ensuring a stable funding source for deafness research at Scripps Research, please contact Wendy Scott Keeney, vice president of development, (858) 784-7083 or wkeeney@scripps.edu.*



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