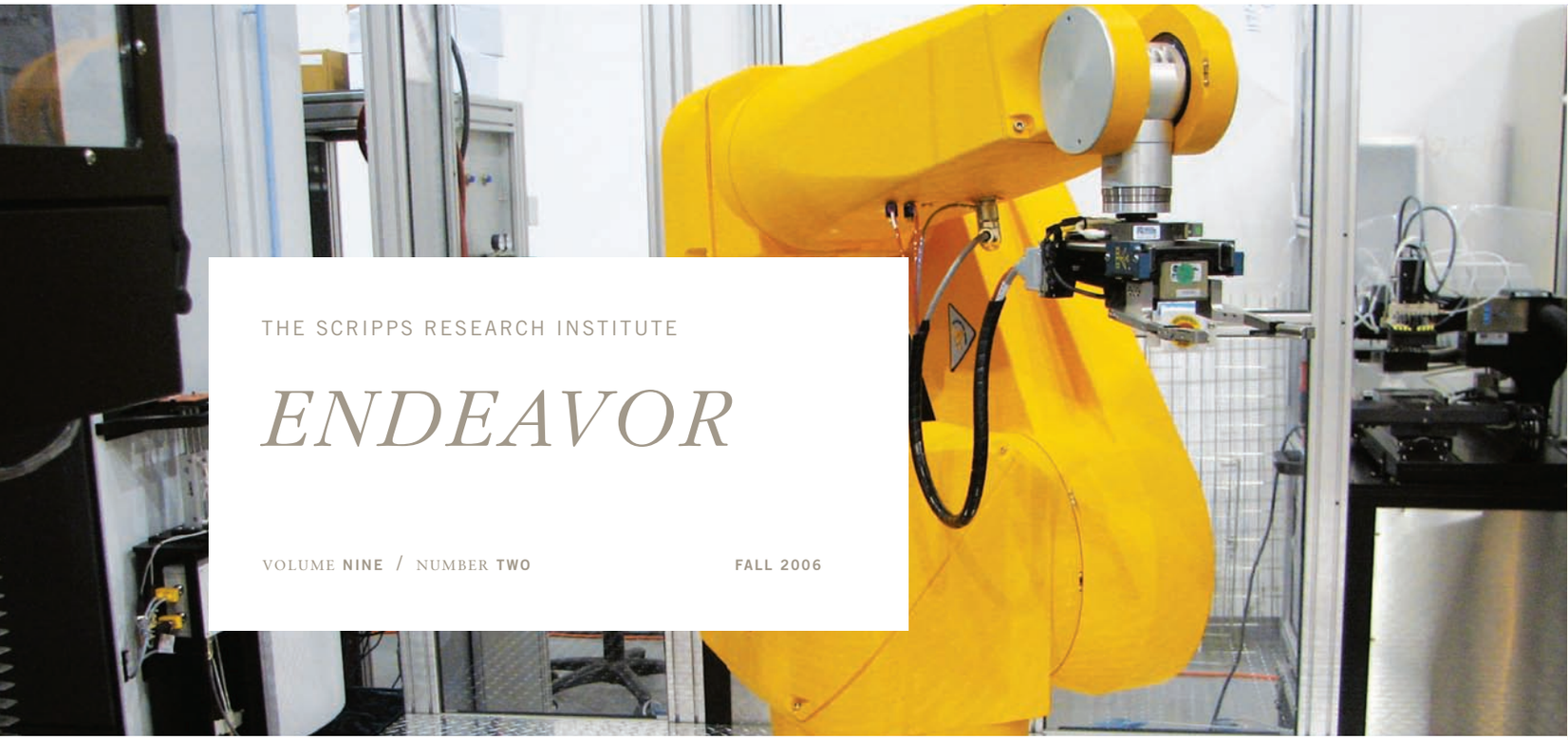
FALL 2006

VOLUME NINE / NUMBER TWO

THE SCRIPPS RESEARCH INSTITUTE

ENDEAVOR



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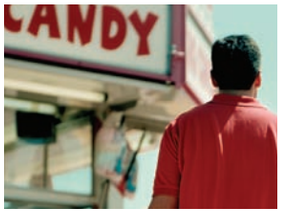
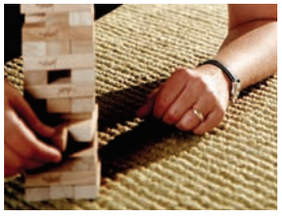
ENDEAVOR

VOLUME **NINE** / NUMBER **TWO** **FALL 2006**

FEATURES:





ALSO:

ENDEAVOR IS A PUBLICATION OF THE SCRIPPS RESEARCH INSTITUTE

This issue of *Endeavor* magazine features Scripps Research investigators working to understand obesity—an increasingly common condition that now puts almost one third of all Americans at increased risk of developing diabetes, heart disease, stroke, and some types of cancer.

At the Forefront

Minor Mutations in "Bird Flu" Virus Increase Chances of Human Infection

Scientists at The Scripps Research Institute, the Centers for Disease Control, and the Armed Forces Institute of Pathology have identified what the researchers described as a possible pathway for a particularly virulent strain of the avian flu virus, H5N1, "to gain a foothold in the human population."

The H5N1 avian influenza virus, commonly known as "bird flu," is a highly contagious and deadly disease in poultry. So far, its spread to humans has been limited, with 177 documented severe infections, and nearly 100 deaths in Asia, according to the World Health Organization.

Using a recently developed microarray technology—hundreds of microscopic assay sites on a single small surface—the study, led by Scripps Research Professor Ian Wilson, D. Phil., showed that relatively small mutations can result in switching the binding site preference of the avian virus from receptors in the intestinal tract of birds to the respiratory tract of humans.

REFERENCE: *Science,* 312, 404-410 (April 21, 2006).

Lack of a Key Enzyme Increases Resistance to Sepsis

Scientists at Scripps Research, The La Jolla Institute of Allergy and Immunology, and Merck Research Laboratories have uncovered a "fundamentally new role" for an enzyme that, when present *in vivo* in certain forms, impedes the immune response to bacterial infection.

According to the new study, the presence of caspase-12, which appears to modulate inflammation and innate immunity in humans, increases the body's vulnerability to bacterial infection and septic shock, while a deficiency confers strong resistance to sepsis. This new discovery suggests potential treatments for sepsis and other inflammatory and immune disorders.

"It's known that the presence of caspase-12 as a full-length protein occurs in a small percentage of people of African descent," said Richard Ulevitch, Ph.D., chair of the Scripps Research Immunology Department. "As a result, some of these individuals are far more susceptible to severe sepsis and have a significantly increased risk of dying from it."

REFERENCE: *Nature,* 440, 1064-1068 (April 20, 2006).

New Class of Enzyme Inhibitors Blocks Replication of SARS Virus

Scientists have discovered a class of compounds that blocks the SARS virus from replicating, a finding that may open the door to new drug targets against the deadly disease. The study was conducted by researchers from Scripps Research; the Genomics Research Center; Academia Sinica, Taiwan; and the National Taiwan University.

Chi-Huey Wong, Ph.D., who is the Ernest W. Hahn Chair in Chemistry at Scripps Research and a member of The Skaggs Institute of Chemical Biology, said the new finding is an important step in developing a possible drug treatment against SARS. "This new class of inhibitors, called benzotriazole esters, represents the most potent SARS virus protease inhibitors known today," he said.

REFERENCE: *Chemistry and Biology,* 13 (3), 261-268 (March 24, 2006).

Immune Response to HIV in the Brain a "Double-Edged Sword"

A team at Scripps Research has shed new light on the molecular basis of problems with brain function in models chronically infected with an immune deficiency virus similar to human immunodeficiency virus (HIV).

Using multi-disciplinary analysis, the team found both a low-level viral infection in the brain and immune cells that had infiltrated the brain in order to protect against the virus.

"Over the long-term, this immune response may act as a double-edged sword," said Howard Fox, associate professor at Scripps Research and director of Scripps NeuroAIDS Preclinical Studies center, "protecting against rampant viral replication in the brain, but leading to brain dysfunction."

The publication coincides with an $11.2 million award for a five-year renewal of the center called Scripps NeuroAIDS Preclinical Studies (SNAPS), which works with Scripps Research and local, national, and international investigators to understand, treat, and prevent neurological complications of HIV infection.

REFERENCE: *Journal of Neuroscience,* 26 (17), 4577-4585 (April 26, 2006).


CANDY
TTON CANDY

"Sugar tastes good because our brains are tuned to detect sugar; fat tastes good because our brains are tuned to detect fat…Under conditions like those in which humans evolved, when food was scarce, the ability to identify these foods as preferred fuels, seek them out, and eat them promoted survival. Unfortunately, in our current environment of plenty, the excess of such foods is making us sick."

ERIC ZORRILLA, PH.D.

The Power of Sugar and Fat

ERIC ZORRILLA EXPLORES EVOLUTION GONE WRONG

Blame it on taste. If so much food on the market didn't taste so good, America might not be experiencing its current obesity epidemic. Scripps Research Institute scientist Eric Zorrilla, Ph.D., says highly palatable foods, which are often fat and sugar-laden—and are available to a greater degree today than ever before in human history—can be addictive and lead to obesity and sickness.

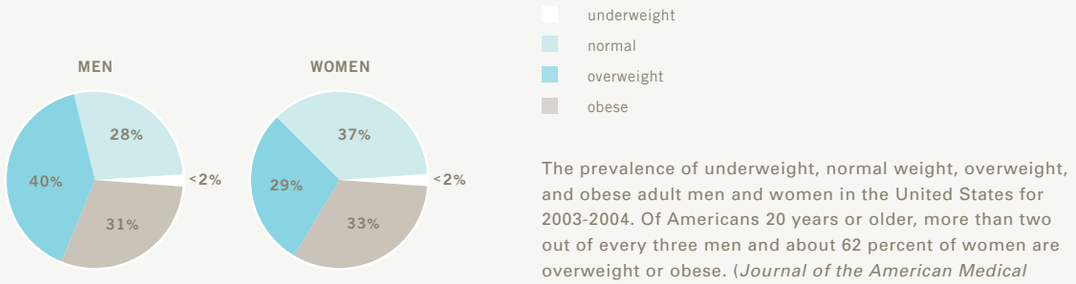
"Evolution favored those genes that allowed individuals to readily detect and be motivated by energy-containing foods," says Zorrilla, an assistant professor in Scripps Research's Molecular and Integrative Neurosciences Department, who has been studying the relationship between palatability and weight gain for several years. "Sugar tastes good because our brains are tuned to detect sugar; fat tastes good because our brains are tuned to detect fat. Things that contain lots of sugar and fat are energy dense. Under conditions like those in which humans evolved, when food was scarce, the ability to identify these foods as preferred fuels, seek them out and eat them promoted survival. Unfortunately, in our current environment of plenty, the excess of such foods is making us sick. It's evolution gone wrong."

Evolution is going wrong for vast numbers of people. U.S. government data from 2003-2004 estimate that two out of every three adults 20 years of age and older are overweight, defined as having a Body Mass Index (BMI—a method used to gauge whether or not a person is overweight) of 25 or greater. About 32 percent of adults—more than 60 million people—are clinically obese with BMIs of 30 or higher. Among children and teens aged six to 19 years old, 17 percent—more than nine million young people—are considered overweight. Being overweight or obese increases the risk of many diseases and health conditions, such as hypertension, dyslipidemia, Type 2 diabetes, coronary heart disease, stroke, and certain cancers.

DRUG-LIKE EFFECTS

Zorrilla, who has previously studied the relationship between drug abuse and stress, says the brain mechanisms that drive a susceptible person to eat ever-greater amounts of palatable food are similar to those that compel certain individuals to abuse drugs.

"Certain highly palatable foods can indeed act like drugs," Zorrilla says. "Changes occur in the brain as a result of drug-taking that may cause an increased vulnerability for subsequent drug abuse. We believe the same thing happens in binge-type eating that is driven by highly desired fatty or sugary foods. The compulsive aspect of binge eating, like drug abuse, is not a weakness of morals or will. It cannot be overcome simply by going on the right diet. To stop binge-eating you have to treat the motivational processes and underlying brain chemicals that override the body's energy homeostasis—the normal bal-



The prevalence of underweight, normal weight, overweight, and obese adult men and women in the United States for 2003-2004. Of Americans 20 years or older, more than two out of every three men and about 62 percent of women are overweight or obese. (*Journal of the American Medical Association*, 2006, 295, 1549-1555)

ance between mechanisms that tell you to eat when you need food and to stop eating once fueled up."

Zorrilla, with Pietro Cottone, a graduate student, and Valentina Sabino, Ph.D., a postdoctoral fellow in his group, developed animal models to test the theory that overeating results from disordered brain chemistry.

In their "binge" model, animals have limited access—10 minutes per day—to chocolaty, sugary foods. The rest of the time they can eat only rat chow, which is healthy but bland. Zorrilla has found that within a week the rats' eating behavior changes dramatically—they begin to consume about half their daily calories during that single 10-minute session. Rats also show more anxious behavior, a hallmark of drug withdrawal, when their sugary food is not available.

"These sweet-deprived rats will eat more in those 10 minutes than rats that haven't had access to any food at all for 24 hours will eat in two hours," Zorrilla says. "Having access to the sugary food after it has been limited makes it extremely attractive to the animals. In this model, the animals aren't eating to survive; they're eating because they crave the hits of sweet food."

This is similar to what happens to people on diets. "When we restrict ourselves from eating highly desired or 'forbidden' foods and then one day open the refrigerator to find cake or ice cream, many of us give in to excess," says Zorrilla. "The restriction creates a cycle, a contrast between the less preferred food and the highly preferred food that leads to binging. It's the reason most diets, which generally restrict not only how much, but also what is eaten, don't work." Interestingly, the scientists have also found that after restriction, binge food is stored by the body as fat more "aggressively" than blander food.

The flip side of binge behavior is "finicky" behavior. Zorrilla has found that if rats in the binge model are not given access to any food for a short period of time, say, two hours, and are then presented with their less preferred food—rat chow—those rats with a history of access to the chocolaty, sugary foods will reject the chow, despite being hungry. In a different model, Zorrilla's team has found that sugar-accustomed rats will continue to reject less-preferred food for five days or longer, despite losing weight.

There are two sides to the disordered eating behavior then—binging and finickiness. The finickiness is important because it shows that as a result of having access to tasty foods, other healthy foods that normally might be eaten suddenly become less appealing. Translated to humans, this might mean that once someone becomes accustomed to the taste of a bacon cheeseburger and a soda for lunch, he or she is less likely to choose a salad with lean chicken.

BRAIN OUT OF BALANCE

Zorrilla and his team have found that in the brain, the opioid receptor system, which is strongly associated with pleasure and mediates rewarding properties of several abused drugs, including heroin, morphine, and alcohol, is involved in both binging and finickiness.

"Certain highly palatable foods can indeed act like drugs."

ERIC ZORRILLA, PH.D.

"If comparisons between pleasurable aspects of foods are what drives both binging and finickiness, then both behaviors should be reduced with an opioid receptor antagonist," Zorrilla says. In fact, this is what happened when they administered the drugs nalmefene or naltrexone, opioid receptor antagonists that slightly dull the pleasurable smell and taste of food in people. Both nalmefene and naltrexone have been tested against alcohol addiction by another Scripps Research scientist, Barbara Mason, Ph.D., and found to lessen relapse in particular episodes of binge drinking.

"These and related drugs could potentially be used to treat people with binge eating disorder, clinical obesity, or bulimia by allowing the body's natural energy homeostasis mechanisms to exert themselves," Zorrilla says. "Food still tastes pleasurable, a person still wants to eat if hungry, but the desire for food becomes less compulsive and overriding. The brain is better able to say 'enough is enough.'"

An individual's proclivity toward binge/finicky eating also may turn out to be genetically determined, Zorrilla says.

"We've found that some rats are more sensitive to relative palatability than others. They'll binge consistently and become finicky consistently. Scientists always talk about the genetic aspect to obesity and we agree completely that in some people, for reasons we don't yet completely understand, palatability is a bigger determinant of how they eat than in others."

To better understand what drives food intake, Zorrilla is also studying how palatability controls eating behavior from meal to meal.

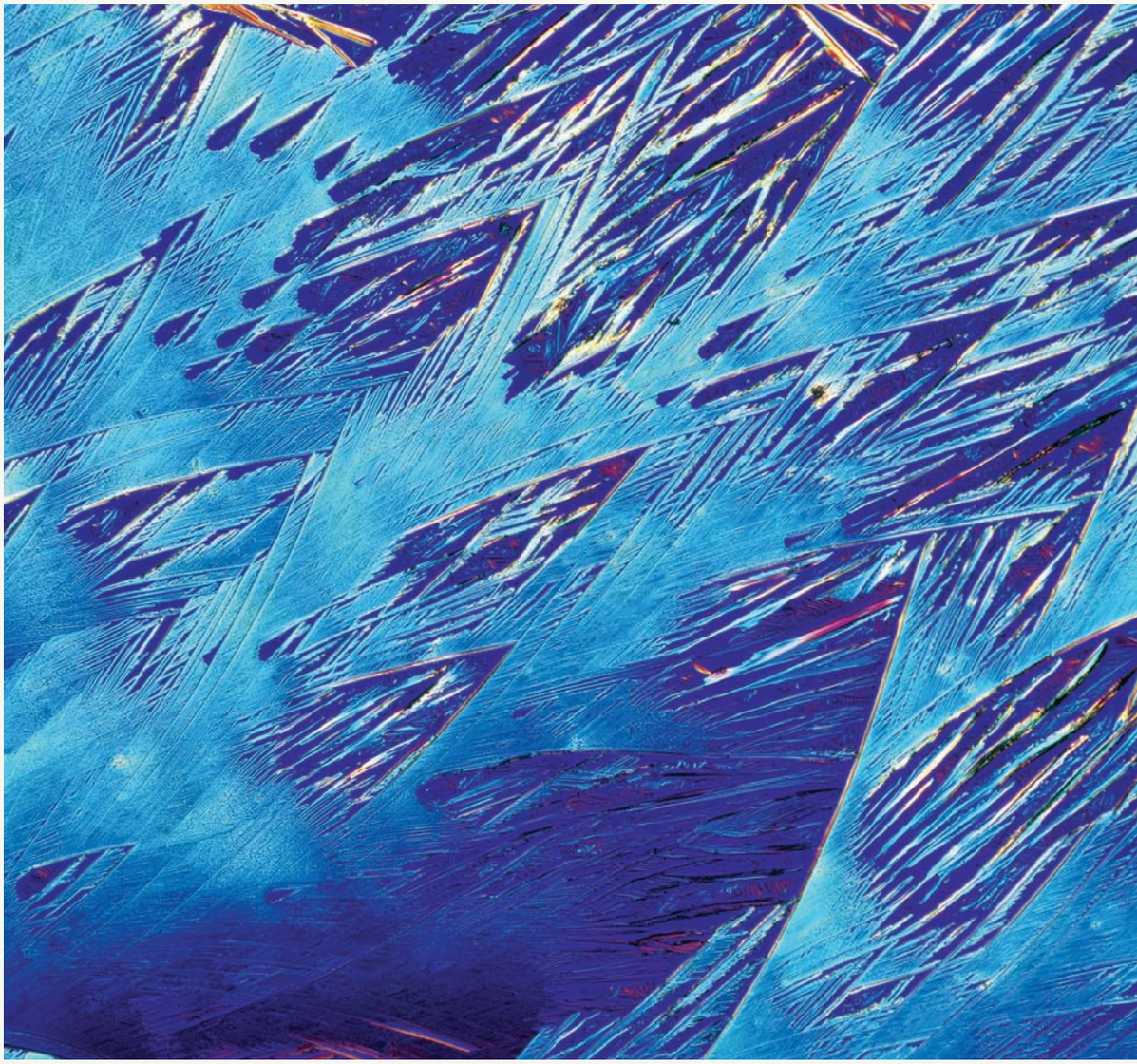
Zorrilla has found that unlike ghrelin, a stomach hormone that initiates meals but does not dictate how much or how fast someone will eat within the meal, palatable food expands meal size, causing faster eating, especially at the start of the meal. Being deprived of food has identical effects.

"When we're hungry, our brains adapt so that food tastes better," Zorrilla says. "However, palatable food seems to activate some of the same brain reward circuits primed by food deprivation so we eat *as if* we were very hungry, even though we may have just eaten. To counter this behavior, it makes sense to look for molecules that have anti-palatability effects, such as nalmefene and naltrexone, which reduce the amount eaten in a meal and also slow down how fast we eat at the start of the meal."

AN OBESITY VACCINE

In addition to his work on the relationship between palatability and obesity, Dr. Zorrilla and a scientist visiting his lab, Shinichi Iwasaki, M.D., Ph.D., in collaboration with investigators Kim Janda, Ph.D., and Michael Meijler, Ph.D., faculty in the Department of Chemistry at Scripps Research, are seeking to develop an obesity vaccine. The scientists have targeted ghrelin, which stimulates appetite and alters metabolism to promote fat storage. Ghrelin is secreted when a person hasn't eaten for several hours, signaling that it's time to eat and to conserve the resulting fuel. After eating sufficiently, ghrelin levels drop off and the urge to eat, as well as metabolism, normalize. →

A polarized light micrograph of crystals of beta-endorphin, a naturally occurring peptide named for its morphine-like actions on pleasure and pain perception that has been found to play a role in food intake. Magnification: x80 at 6x7cm size.



"Our research suggests that once people grow accustomed to highly sweetened food—such as high fructose corn syrup, which is present in so many foods now—their reference point about what food should taste like changes."

ERIC ZORRILLA, PH.D.

Mice designed to lack ghrelin or its receptor are less likely to become obese when high-fat food is available. Ghrelin receptor antagonists decrease appetite and increase energy expenditure. In people, ghrelin levels increase when we diet, stimulating appetite and slowing down metabolism, thereby making it difficult to maintain weight loss. For these reasons, an anti-ghrelin treatment potentially could help people lose weight and keep it off and also might help prevent weight gain.

The vaccine, which only would be administered to obese people with a BMI of 30 or above, would stimulate the production of antibodies against ghrelin. So far, the team has overcome biochemical obstacles and identified "proof of principle" modified ghrelin haptens—substances that led rats to produce antibodies against ghrelin. Rats with the greatest specific antibody response against the active form of ghrelin, which exists in both active and inactive forms, gained the least weight and body fat.

Research on the vaccine is in the early stages and several safety issues need to be studied before human testing. But Zorrilla says such active immunization holds promise because it circumvents the problem of compliance that often arises with prescribed medications.

A QUESTION OF PUBLIC HEALTH

Individuals make personal choices about what to eat, but they make those choices in the context of the societies in which they live. That's why the easy availability of fatty and sugary foods cannot be separated from the rise of obesity.

"Our research suggests that once people grow accustomed to highly sweetened food—such as high fructose corn syrup, which is present in so many foods now—their reference point about what food should taste like changes," Zorrilla says.

Fueling the desire for highly palatable food today is an industry with legions of people working to make food taste better—a situation that didn't exist just a couple of decades ago.

Zorrilla cites diet drinks as an example of how the ante on sweetness has been upped. It used to be that diet sodas had an unpleasant taste, but now that many are sweetened with tasty artificial sweeteners, they are arguably as good as regular soda. So even though the soda itself may not promote weight gain, drinking it raises the expectation of what other foods should taste like. This leads a heavy diet soda drinker to demand the same sweetness from other foods and avoid less pleasing, albeit healthier, alternatives.

Even though it's clear that obesity is related to what people are eating, it's difficult to trace the problem directly back to palatability and to the food industry. "It's analogous to what happened with smoking," Zorrilla says. "It was only when lung cancer rates began to rise dramatically that things started to change. As a society we now have to ask ourselves—have we reached the point where there should be more regulation of the food industry? Should there be warning labels on certain foods? More public education programs? There's going to have to be a cultural sea change to have an effect on the obesity problem. But if something doesn't change, the number of people struggling with obesity will keep rising."

ANNA SOBKOWSKI

"New therapies that target apelin … might enhance the body's checks and balances and bring something that is dysfunctional back into line with the rest of the body."

LAYTON SMITH, PH.D.

A Matter of Balance

LAYTON SMITH PROBES FAT AT THE MOLECULAR LEVEL

Layton Harris Smith sees science as something that must be relevant to society. And with nearly one-third of the U.S. population defined as obese, according to government figures, there's perhaps nothing more relevant than understanding how obesity works.

Smith, associate director of pharmacology at Scripps Florida's Department of Drug Discovery, is leading an effort to figure out how obesity throws the body's normal regulatory system out of balance. He's also probing the series of events triggered by fat cells that lead to cardiovascular disease and diabetes in obese people.

"Everybody knows that being fat and having diabetes are bad for you, but nobody understands the exact reasons why," says Smith. "When someone is obese, it's not that they are just a bigger person. They are a normal sized person wearing a 150-pound coat of fat."

Smith's research probes fat at the molecular level. Using tools at Scripps Florida's Advanced Technologies group, he's searching for drug targets that may prevent or control obesity, keenly focusing on the real-world benefits of the sometimes abstract world of basic biomedical research.

"When it comes to pharmacology, we have an eye toward the human condition," he says. "We ask if what we are doing in the lab is moving us closer to making a better therapy or identifying a way to prevent disease."

A FLORIDA BOY COMES HOME

So how does a Florida boy—born and raised in Tampa—return to study the biology of obesity in the Sunshine State? Credit his mother.

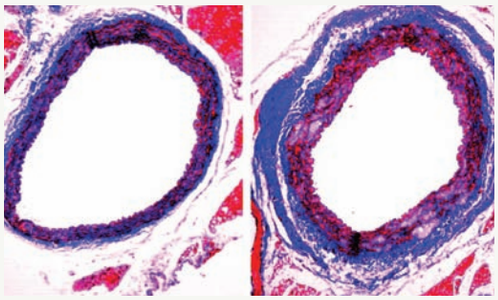
"When I finished my postdoc at Vanderbilt, I was looking at positions and I had a conversation with my mom," he recalls. "I said there's no science in Florida. Within six months they announced the Scripps deal. She called me up and said, 'well there is now.'"

That tip from mom led to a recruiting trip, and a return to a state he calls home. Smith said he's excited about the pioneer spirit at Scripps Research's new biomedical campus.

"It's very much a start-up mentality here," he notes. "We have a good group of young scientists and everyone seems to understand we are doing something new."

Smith has just to look at former generations of his own family for examples of entrepreneurship. His mother's family owned one of Florida's largest cigar companies—Corral, Wodiska Y Ca.—from its founding in 1905 until it was sold in the late 1980s. The family also ran a successful agricultural business, raising oranges, grapefruit, and blooming flowers in the same area.

When it got time to pick a career, however, Smith's father, an attorney, wasn't keen on Layton following in his footsteps. So as a pre-med undergraduate at Tulane University, Smith instead found



Most obese patients are also hypertensive. It's not just that the heart has to work harder because the body is carrying more weight, but rather that there are a series of molecules known as angiotensins produced by fat that contribute to hypertension. Here, aortae infused with angiotensin II (right panel) show signs of vascular fibrosis as indicated by increased staining for collagen around the vessel.

the joy of discovery while studying frog embryos in a genetics lab.

"My father put on a suit and went to work every day," Smith says. "My grandfather did the same thing. This was something completely different. What better way to work than going to a lab and discovering something new?"

REMEMBERING PEOPLE

After graduating from Tulane with a bachelor of science in cell and molecular biology in 1996, Smith decided against medical school. Instead, he opted for the pharmacology program at Vanderbilt. What interested him was the mechanisms of how disease affects the body, and consequently how drugs affect disease. This led him to the laboratory of Douglas Vaughan in Vanderbilt's Division of Cardiovascular Medicine. The team was looking at the effects of statins, the highly popular and powerful drugs that remove cholesterol from arterial walls.

Smith found that, in addition to reducing cholesterol, statins could promote production of prostacyclin, a naturally occurring chemical in the body that helps relax arterial walls and prevent platelets from building up.

"For the first time, we identified a biological dividend of statins that improves vascular health beyond decreasing cholesterol," Smith says. "It was more than a double whammy."

This work on statins became the basis of Smith's doctoral thesis, which he completed in 2002, and led to a productive postdoctoral fellowship during which he received the postdoctoral research award from the International Society for the Study of Xenobiotics in 2003 and the Pfizer Young Investigator Award in 2004.

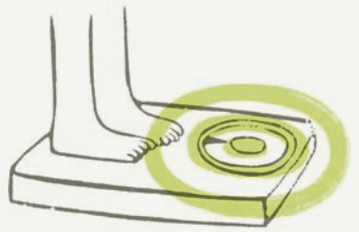
According to Vaughan, Smith has a good understanding of how to use modern research tools such as gene arrays to tackle basic research problems, but is not so dazzled by high-tech wizardry that he forgets about the people who are suffering from these same diseases. "He is motivated to address problems that cause disability and death in people," Vaughan says. "Having a foot in the clinical world… gives him an advantage."

While pursuing a master's in clinical investigation, Smith got face-to-face contact with patients suffering from hypertension and diabetes at the Vanderbilt University Medical Center. They were nearly all obese.

THE YIN AND YANG OF HORMONES

Smith began to think about obesity in a different way as new research was being published showing that fat isn't just a storage depot for extra energy. In fact, scientists now believe that fat behaves more like an organ producing its own hormones and chemical messengers to the brain and the stomach. Smith began a project looking at the proteins associated with obesity and how obesity contributes to development of cardiovascular disease.

Smith has continued working on obesity since arriving at Scripps Florida in April 2005. His current projects are identifying drug targets for hypertension caused by an imbalance in a hormone produced by fat cells.



"If we know how a disease works, we know where to interrupt pathology of that disease to mitigate symptoms or cure the disease. It becomes important to understand what is being produced by the fat that has deleterious effects on cardiovascular disease, particularly hypertension."

LAYTON SMITH, PH.D.

"If we know how a disease works, we know where to interrupt pathology of that disease to mitigate symptoms or cure the disease," he says. "It becomes important to understand what is being produced by the fat that has deleterious effects on cardiovascular disease, particularly hypertension."

It turns out that most obese patients are also hypertensive. It's not just that the heart has to work harder because the body is carrying more weight, but rather that there are a series of molecules known as angiotensins produced by fat that contribute to hypertension.

Angiotensin is part of the larger renin-angiotensin-aldosterone system (RAAS) that is responsible for the long-term regulation of blood pressure. In normal patients, angiotensin is believed to be balanced by another signaling molecule called apelin. We believe that in obese patients, angiotensin takes over and apelin can't keep the system in check, Smith explains. This yin and yang of the two hormones is the central focus of Smith's work at Scripps Florida.

"Clearly, the RAAS system is out of balance in obese people," he says. "New therapies that target apelin might be better than current drugs that simply knock down the aberrant RAAS system. It might enhance the body's checks and balances and bring something that is dysfunctional back into line with the rest of the body."

CREATIVE COLLABORATIONS

Smith has been working with Teresa Reyes, formerly assistant professor at Scripps Florida, Department of Neurobiology, on finding out more about how apelin works. Apelin also plays a role in regulating food intake, but early research in animal models shows contradictory findings: some animals eat more when exposed to apelin in the cortex, others eat less.

"We've been interested in apelin from the standpoint of the brain," Reyes says. "Layton has been interested in its role in cardiovascular disease and obesity."

Smith is taking advantage of the cell-based screening technologies available at Scripps Florida to do analyses on a genome-wide scale. It's one of only a handful of places in the country where that kind of technology is available. In collaboration with the Advanced Technologies group, he's using robots to screen 15,000 mammalian genes—about half the expected genome of humans—to identify regulators of apelin signaling. Until recently, this would have been impossible because it would take years just to test the effects of a few genes.

"We're looking to identify genes that affect the apelin system," Smith said, "and then to find chemicals to exploit the aplin pathway. That way we can see if this system is meaningful and can eventually be targeted therapeutically."

While Smith is looking for new approaches to obesity on a molecular level, he would still like to see stronger prevention efforts—especially when it comes to young people.

"Here in Florida, I see most adults are fairly fit and thin, but their children are overweight or even obese," Smith says. "I'm already looking at the next generation of patients."

ERIC NIILER

"We have all been taught metabolism in college, but once you get deeper into the subject you find out that there's a lot we still do not understand, particularly on how metabolism is regulated."

NATASHA KRALLI, PH.D.

What Lies Beneath

NATASHA KRALLI EXAMINES THE INTRICACIES OF METABOLISM

There are those who believe in the magic bullet theory of science, the single discovery or treatment that suddenly and forever solves a particularly knotty problem.

Natasha Kralli, Ph.D., an associate professor in The Scripps Research Institute Department of Cell Biology, isn't one of them. She believes in finding what lies beneath the surface of things—in this case, of metabolic activity, how it's regulated, and how to keep it from going haywire, twisting itself into disorders like obesity, diabetes, or Parkinson's disease.

GLOBAL SCIENTIFIC TRAINING

Born and raised in Greece, Kralli has spent the last 20 years moving around the globe, turning up in unexpected places and doing unexpected things in her scientific life.

Her parents, who traveled a lot because of their business, encouraged their children to go abroad for their education. Kralli chose England, namely Sussex University. She started out with an interest in marine biology but soon found that she liked molecular biology and biochemistry better.

At the end of her undergraduate work, she moved to the United States for a doctoral program, which offered the opportunity to try different labs, as well as experience a new country where "science was happening." Following a phone interview, she arrived at the University of Pennsylvania in 1986. After completing her Ph.D. work, she went on to postdoctoral training in the laboratory of Keith Yamamoto at the University of California, San Francisco (UCSF), where she worked on genetic screens for steroid hormone receptor activity.

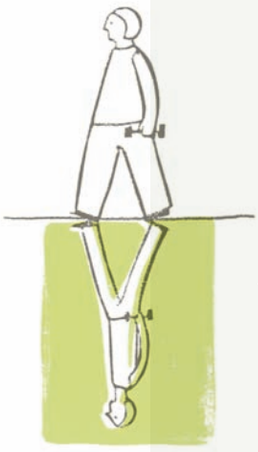
When she left UCSF in 1997, she took her knowledge of yeast genetics and different modulators of steroid hormone receptors to start her own research group—this time in Switzerland, a neutral choice for Kralli and her husband, Ulrich Mueller, Ph.D., who is from Germany (and is now a Scripps Research faculty member).

In her lab in Switzerland, Kralli pursued a growing interest in the intricacies of steroid hormone receptors, also known as nuclear receptors, using yeast as a model system.

Nuclear receptors are a large family of transcription factors that control cellular metabolism including things like growth, inflammation, and glucose, and lipid homeostasis. They are loved by pharmaceutical companies because they are bound and regulated by small molecules, such as natural steroids, retinoids, or synthetic compounds—making them prime drug candidates.

A BIG QUESTION

The big question Kralli had (and still has) was this: How can one nuclear receptor do different things in different cells at different times? This entails a more



"Exercise is one of the best ways to improve muscle mitochondrial function, and there is no question that exercise helps weight loss and general health. However, not all individuals respond to exercise the same way."

NATASHA KRALLI, PH.D.

general question, of how one protein can perform more than one function—in other words, how it can multitask.

Kralli identified a transcriptional coactivator that acts as a partner to nuclear receptors, directing them to specific jobs. The coactivator is present in only some cells, thereby enabling the receptors to have new functions in these cells.

While she was studying how a change in partners could create new molecular pathways—telling the dancer what the dance should be—she became fascinated by a small family of orphan nuclear receptors, receptors that resemble steroid hormone receptors but with as-yet-unknown regulator molecules. These were named estrogen-related receptors (a misnomer according to Kralli because even though they look similar to estrogen receptors, they have very different roles).

Kralli found that these particular orphan receptors are key factors that enable the transcriptional co-activator to regulate mitochondrial function.

"At that moment, a lot of our interest shifted," she says.

So did her work. When Kralli left Switzerland and joined Scripps Research in La Jolla, California, in 2003, she decided to use mice as a model system. It was quite a switch to leave simple, unicellular yeast for the complexity of a mammal. Kralli, however, believes the change was necessary to explore the broader effects of these receptors on mitochondrial function.

Entering the field with fresh eyes, Kralli soon found that while physiology and metabolism have been studied for a long time, many mysteries remain.

"We have all been taught metabolism in college," she says, "but once you get deeper into the subject you find out that there's a lot we still do not understand, particularly on how metabolism is regulated."

MODERN-DAY PATHOLOGIES

The work of her laboratory now—she has five researchers working with her—is on the roles played by these orphan estrogen-related receptors and their partners in the regulation of mitochondrial function.

Mitochondria are, as has been so often noted, cellular power stations, organelles within the cells that convert organic material into usable energy. They take up nearly a quarter of the cell cytoplasm (in some specialized cells they fill the entire cytoplasm), have their own DNA, and, according to the endosymbiotic theory, started out as *external* organisms. These organisms, the theory goes, were a kind of specialized bacteria that were incorporated into the cell because they provided certain evolutionary advantages.

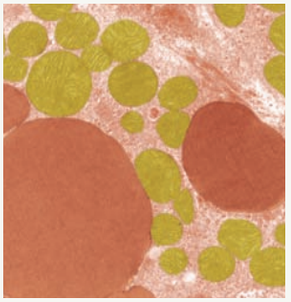
Mitochondrial dysfunction underlies many of our modern-day pathologies, such as diabetes, myopathies, or neurodegenerative diseases. For example, studies have shown that people who are predisposed to diabetes have reduced mitochondrial density and function in muscle cells.

Is this a corollary function or is it a cause? Some evidence suggests that decreased mitochondrial function can be a causative factor, but such a link is far from established. That is part of what Kralli is trying to address right now—with the hope that her findings can one day lead to practical therapeutic applications.

"With mitochondrial activity you don't look for big improvements," she says. "If you can increase it by just a few percent, that's very good. So, we're excited to work with molecules that can boost mitochondrial function."

THE USUAL SUSPECT

For Kralli, the innate complexity of obesity, diabetes, and all the ill-fated stars in this metabolism-driven galaxy makes it virtually impossible to come up with



High magnification electron microscopy images of sections of adipose (fat) cells, showing lipid droplets (in red) next to mitochondria (in green). Mitochondria burn the lipids stored in the droplets to generate usable energy. Cells with more mitochondria have a higher capacity for burning fat and generating energy.

a single cure, a magic bullet. It's multifactorial, she says, which makes it difficult to put everyone in the same basket or to point to a simple cause. In terms of obesity, which has been very much in the news lately, Kralli, like nearly everyone else, puts part of the onus on the usual suspect—a general lack of exercise in the modern American lifestyle.

"I don't think Europeans are necessarily better at sports *per se* but certain aspects of their lifestyle encourage daily physical activity," she notes. "In Switzerland, we would often go to work biking or using public transportation, which meant walking twice a day two to three blocks to catch the bus. Here in San Diego, people get in their cars and drive door-to-door."

One can counteract decreased physical activity by eating less, but of course that is not always easy.

But that's not all. Because, as Kralli points out, there are genetic components that render people susceptible to obesity or diabetes.

"Exercise is one of the best ways to improve muscle mitochondrial function," she says, "and there is no question that exercise helps weight loss and general health. However, not all individuals respond to exercise the same way. There are studies showing that the benefits of exercise, in particularly the increase in oxidative capacity induced by endurance training, depend on genetic factors."

In other words, a person who is diabetic and obese might do the same exercise regimen as a healthy, lean person, and the healthy person might benefit more.

"We do not understand exactly what kinds of switches have been turned around inside the cells and account for these differences," she says. "Because our orphan receptors respond to exercise—their levels go up—and have an impact on mitochondrial function, we believe they are part of the 'control board.' Finding ways to modify these regulator networks could provide an enormous benefit—say, a booster pill that may help those who, for a variety of reasons, do not benefit as they should from exercise."

There might be other benefits as well. For example, it's known that mitochondrial function decreases with age, the reason diabetes is so often associated with aging. Neurodegenerative diseases, such as Parkinson's and Alzheimer's disease, are also associated with aging and with impaired mitochondrial function.

A DELICATE BALANCE

But it isn't an easy or risk-free equation: "In the process of converting what we eat to ATP—the usable energy—mitochondria produce free radicals that damage cells. The big question is how to boost mitochondrial activity without increasing the associated damage. Ideally, you want to boost your defense mechanisms that deal with this damage, right along with increasing mitochondrial function. Science tells us that will be feasible."

So this is where it takes you, back towards an understanding of so many things that lie below the surface of what at first seems so simple, deceptively so.

"I like working in a field where new knowledge can translate to the treatment of human disease," she says. "A good drug not only has to target the right pathway to fix what's broken, but also to spare other pathways so as not to cause side effects. This is not trivial. Understanding the underlying intricacies of the system, all the little details that make it work, provides an essential basis for others, biotech or 'big pharma,' to search for better drugs."

Is she ever just purely amazed by all those underlying intricacies?

"Oh," she says, her voice rising like effervescence, "constantly."

ERIC SAUTER

1. Donors Kim and Barbara Doren, and Dan and LaJuan Fenn at the Frontiers inaugural lecture at the Estancia La Jolla Hotel and Spa, California. 2. Donors Gwen Marinos and Van Blackie Cooke at the second California event in the series.

3. Nicky Lerner, M.D., Ph.D., wife of Scripps Research President Richard A. Lerner, M.D.; Richard M. Krasno, Ph.D., of The William R. Kenan, Jr. Charitable Trust; and his wife, Carin Krasno, at the first Frontiers lecture in Florida, held at the Kravis Center for Performing Arts in West Palm Beach. 4. Charles Weissmann, M.D., Ph.D. (left), professor and chairman of the Scripps Research Department of Infectology, and Professor A. Donny Strosberg, Ph.D. (right), who spoke on "Frontiers in Infectology" at an event held at The Lifelong Learning Society auditorium, Florida Atlantic University, Boca Raton. They are pictured with Paul Mauer, Ph.D., one of the institute's five founding scientists.

Behind the Scenes

Those interested in attending future lectures by Scripps Research scientists should contact Ginny Deary, at (858) 784-9367 or ginnyd@scripps.edu

NEW FRONTIERS FOR SCRIPPS RESEARCH

What is the relationship between ozone and heart disease? How does a pioneering new therapy save infants with a deadly lung disease? What are the hot topics in infectious disease research? These are some of the questions that leading scientists from The Scripps Research Institute are addressing for friends and supporters of the institute in a new bi-coastal lecture series, "Frontiers in Science."

"Our goal is to provide our donors and the public with solid scientific information presented by world-class scientists," says Denise M. Scalzo, vice president of Development, "and to underline the importance and value of biomedical research in a changing world."

The information-packed lectures, which feature scientists from both the California and Florida campuses of Scripps Research, are followed by a reception, where participants can mingle and ask further questions of the researchers.

In the inaugural event in January, Professor Paul Wentworth, Ph.D., and Assistant Professor Jorge Nieva, M.D., shared their perspective on the inflammatory response, the body's first-line defense against microbial pathogens. The inflammatory response may—according to a growing body of evidence—also play a crucial role in some of the most devastating afflictions of modern life, including heart disease, Alzheimer's, and cancer. Studies by the Wentworth lab are suggesting a link between ozone produced by our own bodies during inflammation and toxic compounds in the blood, which Wentworth has dubbed "atheronals."

In another lecture, Charles G. Cochrane, M.D., professor emeritus of immunology and one of the institute's five founding scientists, spoke on his discovery having world-wide implications—the successful synthesis of pulmonary surfactant, a product which will save the lives of severely premature babies and extend the life of adults afflicted with acute respiratory distress syndrome, or lethal, active lung injury.

"The speakers were not only knowledgeable, but engaging and entertaining," said Ruth Graul, who supports Scripps Research with her husband, Bill Graul. "Their presentation was very informative and their research can certainly make a difference in the lives of people."

"What's important is the work these people are doing. They should have the glory."

HELEN DORRIS

Donor Profile: Helen Dorris

Helen Dorris is part of the Scripps Research family. Busy researchers greet her in the hallway and stop to discuss current projects. More than a supporter, she is their friend.

Helen takes a keen interest in the neurosciences and has helped bring several researchers to Scripps Research to explore the mysteries of Alzheimer's, schizophrenia, and other brain disorders.

She is proud of the research she supports but shies away from taking any credit.

"What's important is the work these people are doing," she says. "They should have the glory."

Helen Dorris has made several gifts of real estate to Scripps Research to establish a fellowship to study schizophrenia and to create both the Helen L. Dorris Child and Adolescent Neuro-Psychiatric Disorder Institute and the Harold L. Dorris Neurological Research Institute.

The institutes, now the home of some of the world's top brain researchers, uncover the pathological basis of neurological and psychiatric disorders and expedite the discovery of promising new therapeutic approaches.

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