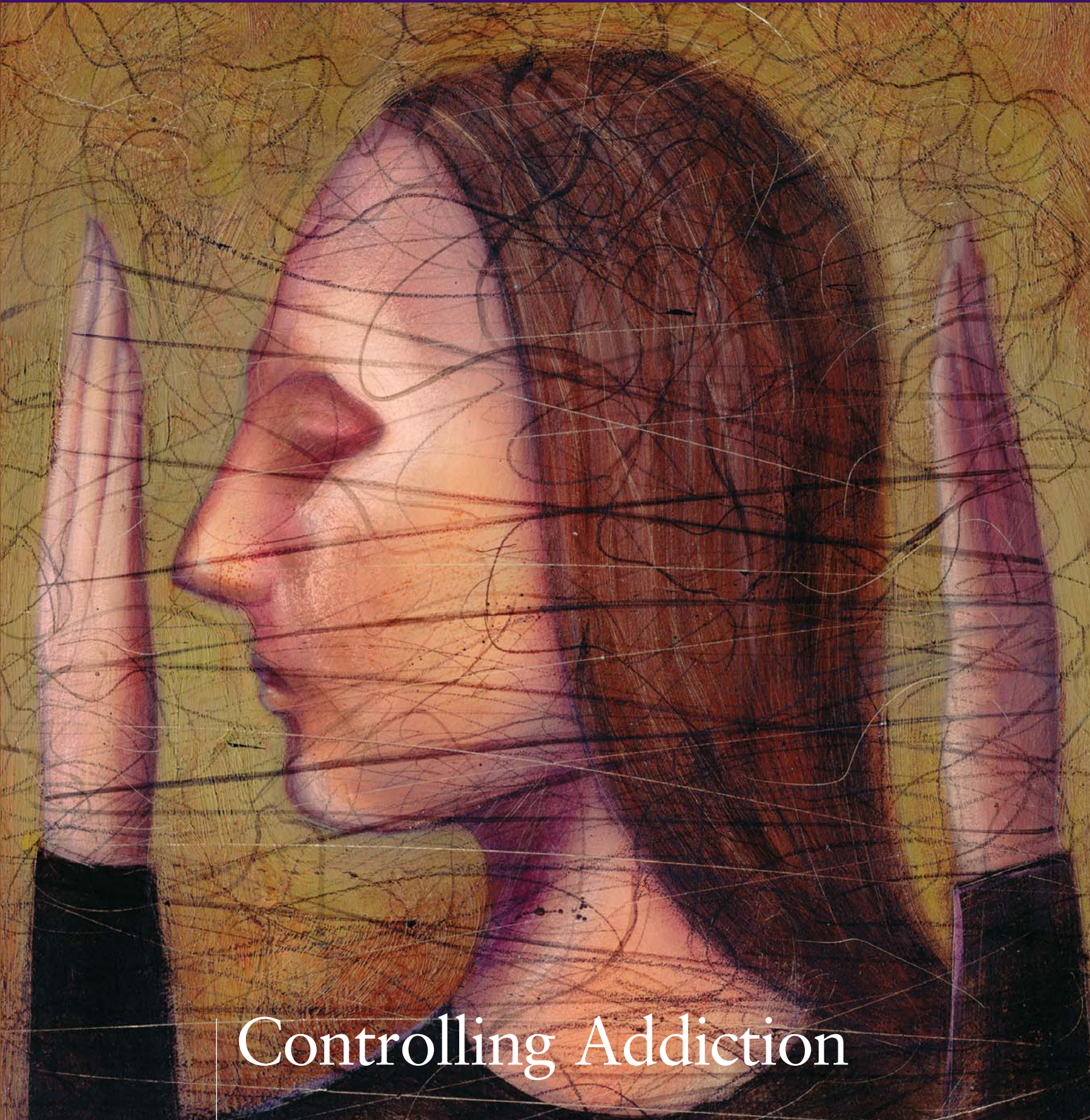


VOLUME EIGHT | NUMBER ONE



# Endeavor

*Spring 2005*



Controlling Addiction

# Endeavor

VOLUME EIGHT | NUMBER ONE

Spring 2005

Addiction takes an enormous toll on individuals, families, and society as a whole. The direct and indirect public health costs of addiction are estimated to be in the hundreds of billions of dollars yearly. What are the biological bases of addiction? How can we more effectively treat and prevent this terrible disease? This issue of *Endeavor* features some investigators at The Scripps Research Institute who are helping to answer these questions.

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## Sandbagging Cancer in the Bloodstream

A team of scientists led by Scripps Research Institute Professor David A. Cheresh and Research Associate Sara Weis has identified a potential treatment strategy against metastatic cancer cells that has never been tried before.

Metastasis is a major problem with cancer because it allows tumor cells to spread to other parts of the body. While solid tumors can be removed surgically or treated with chemotherapy or radiation, metastatic cells that have already entered the circulation are capable of opening a passageway through blood vessels in order to spread to various organs throughout the body.

The treatment strategy, which showed promise in the lab, targets a final step of the metastatic cascade—the exit of the metastatic cells from the bloodstream—increasing the protective barrier strength of the host blood vessels and preventing tumor cells from exiting the bloodstream to establish a new cancer site.

Reference: *J. Cell Bio.*, **167**, 223-229 (2004).

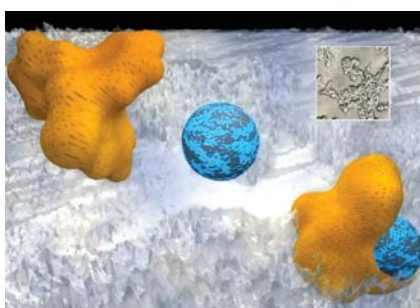
## Scientists Develop New Technology For a “Kit” to Screen for Mercury Contamination

Scientists at Scripps Research and Xenobe Research Institute have developed an improved screening method that can detect mercury contamination in biological samples including fish. At the heart of the new method is a chemical “ligand” synthesized by the scientists that binds to mercury and other toxic heavy metals.

The ligand is inexpensive, easy to synthesize, and causes mercury and other toxic heavy metals to precipitate instantaneously into an easily detectable solid. The method could be developed into a kit that could be used both by consumers and environmental professionals to detect metal contamination.

“The detection is very simple, but very powerful,” says investigator Kim D. Janda, Ph.D., who is the Ely R. Callaway, Jr. Chair in Chemistry and a professor in Scripps Research’s Skaggs Institute for Chemical Biology.

Reference: *J. Am. Chem. Soc.*, **126**(50), 16582-16586 (2004).



The innovative mercury detection method relies on a new ligand molecule (yellow) that combines with a mercuric ion (silver/blue ball) to generate an easily detectable solid. (Artwork by J. La Clair.)

## A Simple Strategy for Blocking HIV Transmission Proves Effective in Pre-Clinical Trials

An international research team recently announced the promising results of a pre-clinical study on a chemical called PSC-RANTES to block male-to-female sexual transmission of human immunodeficiency virus (HIV). The team described how a topical microbicide with a high enough concentration of PSC-RANTES prevented HIV transmission to female rhesus macaques that were challenged with high doses of a modified form of HIV.

PSC-RANTES works by targeting a protein in the body called C-C chemokine receptor 5 (CCR5), the receptor on human cells to which HIV binds. In order for the virus to be transmitted during heterosexual intercourse—the number one way the virus is spread in many parts of the world—the virus must attach to CCR5 in cells within the vaginal mucosa. When these cells are protected with PSC-RANTES, however, the virus cannot attach to them.

“Virtually all HIV [strains] use the CCR5 receptor,” says Scripps Research Professor Donald Mosier, M.D., Ph.D., an author on the paper who did much of the basic science work that led to the selection of PSC-RANTES for pre-clinical trials. “[So, completely] blocking CCR5 would block 99 percent of HIV transmission worldwide.”

Reference: *Science*, **306**, 485-487 (2004).

## “Fossil Record” of the Human Immune System Reveals Antibodies that Block Cancer Metastasis

Scripps Research investigators have reconstructed the “fossil record” of the immune systems of a group of human cancer patients to investigate if they had ever produced antibodies against their disease. The fossil record—constructed out of a “combinatorial” library of all the antibodies in the blood of 20 cancer patients, five of whom had breast cancer—showed that the human body is capable of making numerous antibodies with the ability to recognize metastatic breast cancer tumors.

This finding is highly significant because of the potential for using such antibodies as a new way to treat cancer. Despite recent progress in cancer therapy, no treatment is currently approved for preventing the spread of cancer. Antibodies have been used to treat a number of human diseases ranging from rheumatoid arthritis to leukemia. The work of the team—which includes Scripps Research Associate Professor Brunhilde Felding-Habermann, Ph.D., President Richard A. Lerner, M.D., and Professor Kim D. Janda, Ph.D.—gives hope that antibodies originally produced by cancer patients may help block cancer’s spread and interfere with already existing metastatic disease.

Moreover, the disease-fighting ability of antibodies taken from patients with cancer suggests that the immune system has a natural defense mechanism against cancer cells and perhaps can even maintain an active “immune surveillance” against cancer cells.

Reference: *PNAS*, **101**, 17210-17215 (2004).



A “fossil record” of the immune system suggests that we might fight cancer every day. (Artwork by Art Olson.)



# An Antidote for Addiction

KIM JANDA USES THE IMMUNE SYSTEM TO FIGHT DRUG ABUSE

One Thursday morning in La Jolla late last year, Professor Kim D. Janda, who is the Ely R. Callaway, Jr. Chair in Chemistry and an investigator in The Skaggs Institute for Chemical Biology at The Scripps Research Institute, gave this writer a tour of his office and laboratory.

In his office, Janda discussed his collection of antique scales and balances that occupies most free shelf space there, and chatted about a recent golf outing he went on in Florida with his mother, Dee Janda. They played golf with rock musician Eddie Money, with whom they were randomly paired because a tournament that day meant the course was full.

Then, walking out of his office and into his laboratory in the Beckman Center for Chemical Sciences, Janda moved on to a more pressing subject—his research on ways of using the immune system to fight drug abuse.

He navigated a maze of benches and hoods and scientists working at all levels of research, pointing out a piece of equipment here and there. This is the new fermenter, he said, and here are our old shaker flasks, still used. The chromatography and mass spectrometry room, the synthetic benches, the massive tanks of frozen reagents, the chemical storeroom...

Pausing by the entrance of the chemical storeroom, Janda threw open the heavy metal door and a nose-stinging odor of sulfur-containing chemicals hits us in the face. “You smell that?” he said, echoing an old war movie line. “It smells like victory.”

## **COCAINE AND ITS COSTS TO SOCIETY AND THE BRAIN**

The conversation quickly turned serious, to the work Janda is doing to address addiction to cocaine and other drugs of abuse.

A study published by the White House’s Office of National Drug Control Policy (ONDCP) in the mid-1990s found that Americans spend more on cocaine than on all other illegal drugs combined—\$38 billion on cocaine in the years 1988 to 1995 alone. According to the National Institute on Drug Abuse, about 1.7 million people regularly use

cocaine in the United States, which is a population larger than that of the city of Philadelphia.

Cocaine’s burden extends beyond these direct costs to the high secondary costs of treatment and prevention programs, emergency room visits, lost job productivity, lost earnings, cocaine-related crime, and other drug-related health and social burdens, which are estimated to be in the billions of dollars annually.

The drug is a chemical extracted from the leaf of the *Erythroxylaceae coca* plant, which, once ingested, enters the bloodstream, crosses the blood-brain barrier, and accumulates rapidly in the ventral tegmental area of the brain. This area is connected by nerve cells to the nucleus accumbens, the so-called pleasure center of the brain. There, the cocaine molecules interfere with the normal regulation of dopamine by binding to dopamine transporters and blocking them from recycling the neurotransmitter.

*“People have always looked at ways of going after the pleasure or addictive centers of the brain. We were saying, ‘Let’s go after the drug itself.’”*

—Kim Janda, Ph.D.

This leads to the build-up of dopamine in the brain’s pleasure center, which produces a euphoric feeling in the user, a quick rush that hits seconds after the user takes the drug and lasts several minutes.

For the last two decades, Janda says, he and his colleagues have taken an “immunopharmacotherapy” approach. That is, they have sought to design antibodies that would act as a silver bullet, specifically targeting an abused drug in the bloodstream or stimulating a person’s immune system to clear a drug from his or her system.

This work started in the 1980s, when Janda wanted to come up with a compound that cocaine addicts could take as a substitute for the drug in the context of a treatment program, just as some heroin addicts take methadone.

Janda and his colleagues wondered if they could make cocaine analogues—chemicals with structures →

similar to cocaine. They made these compounds and established a collaboration with George Koob, professor in Scripps Research's Department of Neuropharmacology and co-director of the Pearson Center for Alcoholism and Addiction Research (see story, page 7) to test the compounds in laboratory models.

"We failed miserably," Janda says reflecting on that early work.

#### A COCAINE VACCINE

About the same time the researchers failed in their attempt to design a methadone-type cocaine analogue, Janda and his laboratory began receiving funding to design antibodies as a way of detecting drugs of abuse.

Antibodies are proteins produced by the immune system to recognize protein and lipid components of foreign pathogens and other molecular entities. Janda began by doing what any scientist would: he looked at what had already been done.

"We found that other research groups had constructed detection [methods], but they were detecting metabolites or degradation products of cocaine," says Janda. "Nobody was making antibodies against the drug itself."

The reason, he soon discovered, was that drugs like cocaine are very unstable and break up quickly. The degradation made it difficult to raise the antibodies to these highly strained molecules.

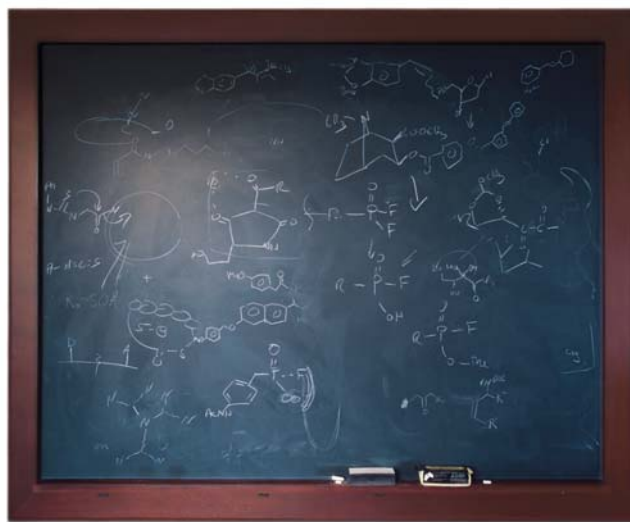
"People have always looked at ways of going after the pleasure or addictive centers of the brain," says Janda. "We were saying, 'let's go after the drug itself.'"

*"People who abuse methamphetamine may be vaccinating themselves against the drug." —Kim Janda, Ph.D.*

The scientists had to use several tricks to get the immune systems of mice to recognize the drug, but the researchers eventually designed some chemical structures that resulted in specific antibodies against cocaine. This was a success, he reckoned, for such applications as detecting cocaine in the bloodstream, but what if he could use such antibodies to block addiction—what if he could develop his compounds into cocaine vaccines?

Cocaine vaccines would not interfere with the neurological targets of cocaine, but instead would

keep cocaine from ever reaching the brain in the first place by inducing an addict's immune system to create antibodies against the drug. If the addict later takes a hit, the antibodies would clear the cocaine from the bloodstream, preventing the addict from experiencing a high.



Sketches like these show how drugs like cocaine react chemically with other molecules.

"These vaccines would suppress the reinforcing aspects of the drug," says Janda. "Blocking it before it gets to the brain—that's the key."

Such vaccines would not address the problem of craving or the discomfort of acute withdrawal, but might help with relapse, which is an unfortunate reality for many addicts. Such an approach might be used in conjunction with other types of treatment, such as group therapy, as part of a rehabilitation process.

Again teaming with Koob, Janda and his laboratory tested their approach in rodent models. The studies show that the vaccine and antibody treatments separately suppress the psychomotor effects of cocaine for up to 12 days following vaccine inoculation—somewhat of a success.

#### VIRUSES AND NICOTINE

In the early 1990s, Janda and his colleagues published these results, and while their strategy received a lot of attention, it did not go far enough. The ability of the antibody to curtail cocaine's effect proved to be somewhat limited in the animal studies.

The problem was that the antibody could not cross the blood-brain barrier and enter the brain as cocaine does. A large dose of cocaine could overwhelm the antibodies in the blood and leak into the brain.

In a recent study, Janda and his colleagues addressed this problem by attaching the antibody to a filamentous virus called phage, which, like many types of viruses, has the ability to enter the central nervous system (brain) through the intranasal passageway. In experiments with rodents, the antibody/phage soaked up the drug inside the brain, reducing the noticeable effects of the drug.

With his ongoing success working with cocaine, Janda has expanded his research over the years to fighting addiction against a wide range of substances, including methamphetamine, MDMA (a.k.a. ecstasy), nicotine, and THC, the active ingredient in marijuana.

These chemicals all act similarly to cocaine in that they readily cross from the bloodstream into the brain and activate pleasure pathways there.

Two years ago, Janda and his colleagues designed a vaccine that stimulates the immune system to neutralize nicotine in the bloodstream and clear it from the body. The idea is that if a smoker later smokes a cigarette, the antibodies clear the nicotine from the system before it reaches the brain.

Developing a nicotine vaccine proved difficult, and, at first, Janda and his colleagues were unable to induce an effective immune response. Then they realized that, in contrast to cocaine, nicotine has a flexible axis that allows it to adopt multiple shapes. The researchers' original attempts had produced a vaccine that was equally flexible. Since this approach was not working, they decided to make one that was rigid and resembled only one form of nicotine. This inflexible vaccine created a more robust immune response, producing higher affinity antibodies in greater numbers.

Having shown the vaccine's effectiveness in laboratory models, Janda and his colleagues have now reformulated the vaccine for investigation in human trials. Eventually, this sort of vaccine could be given to people undergoing smoking cessation to aid in the process. At the moment, however, this approach has not been tested clinically and such a therapy, even if proven safe and effective, is years away from being available to patients.

#### **EVERY GOOD TURN DESERVES ANOTHER**

These efforts have also spurred other avenues of research. For instance, Janda's research on antibodies and vaccines against the drug methamphetamine has led to a new hypothesis that, if true, could have

implications for understanding why methamphetamine users sometimes go on long binges with the drug.

Methamphetamine is a potent psychostimulant that has been referred to for years by its common name, speed, and more recently by a spate of street-wise terms such as ice, crank, crystal, meth, and glass.

Janda and his colleagues are proposing that the immune system recognizes methamphetamine. Last year, Janda and his colleagues demonstrated how, in the test tube, methamphetamine is able to spontaneously react with glucose, the body's main source of energy and an abundant molecule in the bloodstream.

When they react, the glucose and the methamphetamine molecules become permanently attached to one another, forming a "glycated" product. These glycated products then attach to proteins, making glycated proteins. And the presence of glycated proteins in the bloodstream can lead to a response from the immune system, stimulating the production of antibodies that recognize the glycated form of methamphetamine.

"Glycation acts like a linker that allows [the methamphetamine] to be displayed to the immune system," says Janda. "People who abuse methamphetamine may be vaccinating themselves against the drug."

*"These vaccines would suppress the reinforcing aspects of the drug. Blocking it before it gets to the brain—that's the key." —Kim Janda, Ph.D.*

This might be one way that the body acquires resistance, Janda says, and may have implications for why methamphetamine addicts binge. If the antibodies prevent some of the drug from reaching its place of action in the brain, addicts might require increasing amounts of the drug to achieve the same high.

As we finished the tour of Janda's laboratory, he paused to reflect on his immunopharmacotherapeutic research. Developing vaccines against different drugs of abuse has been exciting work, he said, but it has also been an emotionally exhausting experience. Over the years, he has received countless letters and emails from addicts and the families of addicts who are desperately looking for a cure for themselves or their loved ones.

These individuals are all looking for help. "That's what keeps me seeking to perfect our vaccines," Janda says.

•Jason Socrates Bardi





# Working to Understand the Brain's Role in Alcohol Dependence

GEORGE KOOB AND BARBARA MASON SEARCH FOR TREATMENTS THAT WORK OVER THE LONG-TERM



Investigators Barbara Mason and George Koob co-direct the Pearson Center for Alcoholism and Addiction Research at Scripps Research.

“Walk into any emergency room in San Diego County on a Friday night,” suggests George Koob, Ph.D., of The Scripps Research Institute’s Pearson Center for Alcoholism and Addiction Research, “and the destruction alcohol causes will be apparent. Patients with broken limbs and bloodied faces from car wrecks; college kids who have gone on binges and been poisoned by alcohol; people shot or beaten by someone in an alcohol-induced rage; the middle-aged professional in life-threatening alcohol withdrawal. The damage scenarios from the overuse of alcohol are many and often devastating.”

Koob and Barbara Mason, who are co-directors of the two-year-old Pearson Center, are taking a unique approach to battling what they consider the devastating disease—not moral failing—of alcohol addiction.

The goal of the Pearson Center is to get people who are alcohol-dependent to stop drinking and remain abstinent. But here, Mason and Koob complement the standard treatment approach of behavior counseling with their focus on gaining a better understanding of the physiological changes in the brain that drive excessive drinking.

“It’s true that alcoholism is a disease of behavior, but it is also a disease of the brain, which is something traditional treatment often overlooks,” Mason says.

Koob and Mason call alcohol dependence—a condition in which a person’s entire life centers around getting and using alcohol—a brain disease, because in this state the brain’s chemistry has gone haywire after years, or often decades, of alcohol abuse.

“We’re interested in identifying drugs that normalize brain systems, but they must be drugs that alcoholics

will agree to take,” Mason says. “We’re not looking at substituting one addictive drug for another or giving alcoholics the so-called ‘punishment’ drugs that make them sick if they take a drink, because most people simply won’t stick with these types of drugs for very long.”

At the Pearson Center, Koob and the neuropharmacologists and biochemists on his team do the pre-clinical work in animal models that mimic the transition from social drinking to alcoholism in an attempt to identify the brain chemicals and the brain circuits that become dysregulated in alcoholism. Once those chemicals and circuits are identified, Mason, in her “human laboratory,” works with alcohol-dependent volunteers to test the efficacy of specific drugs in bringing the affected brain chemicals back into balance and preventing drinking relapse.

## THE ADDICTION CYCLE

In 2003, an anonymous donor who had lost both his parents to alcoholism brought the Pearson Center to life with a multimillion-dollar gift.

The devastating effects of alcoholism are demonstrated by statistics from The National Institute on Alcohol Abuse and Alcoholism: →

- About 14 million U.S. adults currently meet medical criteria for the diagnosis of alcohol abuse or alcoholism.
- Fetal alcohol syndrome, a serious disorder affecting brain function, is the leading preventable cause of mental retardation in the United States.
- More than 100,000 Americans die of alcohol-related causes each year, making alcohol the third-leading contributor to mortality related to lifestyle in this country.

Alcohol, one of the most powerful toxins known to humankind, is an insidious drug that still holds many secrets about the way it functions in the human body.

“Alcohol is a very small molecule that travels everywhere in the water of the body,” Koob says. “Unlike heroin or cocaine, alcohol doesn’t bind to a single receptor on membranes but attaches instead to pockets inside receptors. This nonspecificity is what makes alcohol so powerful; we simply don’t know how to block its action.”

While alcohol’s biochemical mechanism of action is still not completely understood, the stages of the addiction cycle are known. First, there is a “binge drinking” phase—where someone might drink just to get high. This is followed by the “negative affect” stage—where someone drinks because he or she is dysphoric and wants to relieve this mood. Finally, there is the “preoccupation/anticipation” stage, the hallmark of alcohol dependence—which involves bingeing and withdrawal, with an ensuing craving for more alcohol.

*“We believe it is essential to understand how the brain is wired for addiction in order to fix what’s making the person sick.” –George Koob, Ph.D.*

In this stage, an alcohol-dependent person is particularly vulnerable; he or she may remain abstinent until a stressful life event occurs that sparks a return to drinking. It is generally accepted that if a person remains abstinent for at least a year, he or she stands a good chance of remaining abstinent for an even longer period, but an alcohol-dependent person always remains at risk for relapse even after a decade or more.

## ALCOHOL’S ACTION IN THE BRAIN

Most alcoholism research focuses on one of the three stages of the addiction cycle—that is, by trying to block the desire for a “high,” stopping the craving for alcohol, or relieving withdrawal symptoms.

Pearson researchers are taking a much more targeted approach by trying to learn which brain chemicals are compromised by alcohol during each of these stages.

“Because we are interested in drugs for each stage, we know we probably won’t find a single drug—a so-called ‘dirty drug’—that attacks many sites at once,” says Koob. “It may ultimately turn out that the best pharmacotherapy for alcoholism will be multiple drugs that work during the different stages of the addiction cycle.”

Through work with rodents, Koob and his colleagues have learned that different aspects of addiction—the desire to get high, craving, and withdrawal—occur in different parts of the brain. “If we know, for example, that a certain dopamine receptor in a certain brain area is important in alcohol craving, then we can direct drugs to that specific area,” Koob says. “We need to know that, otherwise we’d never dream of attacking that area.”

He compares the importance of understanding the brain chemicals and circuitry involved in alcoholism to the need to understand the wiring in a television set in order to repair it. “If you don’t know which part of the circuitry controls color and which part controls image, then if something goes wrong you can’t fix it. In the same way, we believe it is essential to understand how the brain is wired for addiction in order to fix what’s making the person sick.”

Koob and his team have identified certain chemicals that maintain a delicate balance in the non-alcoholic, but which go out of kilter in the alcoholic brain. For example, in the early stages of the disease, the “feel-good” chemicals released by drinking—dopamine, serotonin, gamma amino butyric acid (GABA), and Neuropeptide Y—induce euphoria.

But as a person continues drinking to excess, the brain goes into a deficit in relation to these brain chemicals when an alcoholic stops drinking, and the “feel-bad” chemicals take over. Then, the unpleasant sensations of withdrawal kick in—anger, anxiety, dysphoria, a rapid heart rate, sweatiness, shakiness—and, in the grip of this biochemical seesaw, the person feels the need to start drinking again simply to feel better.

“When alcohol first hits the system, the feel-good chemicals go up, and the stress chemicals go down,” Koob says. “But eventually, when alcohol leaves the system, those feel-good chemicals go down and the stress chemicals take over. It’s this stress system that we are interested in normalizing in a safe and healthy way.”

Koob and his colleagues have found that the brain neurotransmitter, corticotropin releasing factor (CRF), plays an especially critical role because it is responsible for activating the pituitary adrenal stress response and the sympathetic and behavioral responses to stressors. The CRF system seems to be central to alcoholism because it instigates many of the negative sensations associated with alcohol withdrawal. Preliminary pre-clinical results have shown that compounds known as CRF antagonists can block the excessive drinking that often follows alcohol withdrawal and abstinence. The center is testing new CRF antagonists that might translate into new treatments.

The researchers are also particularly interested in the neurotransmitter GABA, one of the feel-good chemicals. Alcohol induces intoxication by facilitating GABA receptor function. The GABA-glutamate system can remain in a state of dysregulation for as long as a year after an alcoholic has had his or her last drink, leaving the person particularly vulnerable to relapse. The Pearson researchers are also searching for drugs that normalize this system.

#### TESTING FINDINGS IN THE HUMAN LABORATORY

A critical aspect of the work at the Pearson Center is the synergistic interaction between the pre-clinical and clinical aspects of alcoholism research. While Koob and his colleagues seek to identify the brain chemicals involved in relapse, Mason, who has extensive experience conducting clinical trials related to alcohol addiction, works with volunteers with alcohol dependence to identify the behavioral risk factors for relapse and to test drugs that may prevent relapse.

Through local media, Mason recruits non-treatment-seeking volunteers—individuals who are alcohol-dependent but who have not yet reached the point where they want to quit drinking—and are willing to come to the lab once a week, to test a specific drug as potentially effective for preventing relapse. Beginning with the premise that an individual’s mood is a critical component in relapse, Mason’s team studies effects of the drug while exposing the

volunteer to stimuli that induce negative, positive, and neutral moods.

“We know that negative mood states like depression, and even positive experiences like watching a football game on TV, can make someone vulnerable to drinking,” Mason says. “So we want to look at how alcohol-dependent people respond to various emotional triggers in the presence of alcohol and then see whether the drug dampens their response to alcohol.”

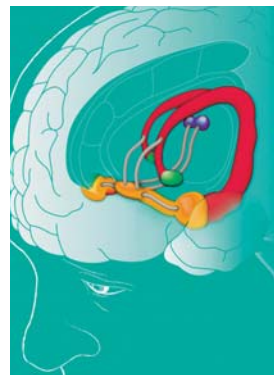
The researchers pour the volunteer’s favorite drink, which he or she may look at and smell but not drink, while physiological responses such as heart rate, sweating, palm moisture, and smiling and frowning are continuously monitored with sensors. The volunteer also uses a computer mouse to provide quick assessments of how strong his or her urge is to drink after exposure to stimuli. In addition, volunteers are asked to subjectively provide information about their sleep quality, moods, and drinking at home during the week they are on the drug. Breath, blood, and urine tests are also administered in the lab.

If the drug in question shows promise after a week of study in the human laboratory, it may become a candidate for a long-term clinical trial conducted by Mason.

In a study funded by the National Institute on Alcohol Abuse and Alcoholism, the Pearson Center has already identified one drug, gabapentin, previously FDA-approved as an anticonvulsant, which appears—in both animal and human testing—to have a normalizing effect on the GABA-glutamate system. The drug has been successful in controlling anxiety and agitation in bipolar disorder and may control the mood and sleep disturbances experienced by alcoholics in early recovery. The drug has the added benefit of not being addicting and having mild side effects, two critical criteria for a drug to be considered by the Pearson researchers for use in humans.

“Alcohol is probably the most destructive of all the addictive drugs because it eventually destroys both the body and the mind,” Koob says. “Certainly, it is incumbent on the alcohol-dependent person to recognize that he or she has a disease and seek treatment, but it’s also necessary to be able to offer the alcoholic treatments that work over the long-term. That’s a daunting goal, but one that is critically important, both for the alcoholic and the rest of society.”

•Anna Sobkowski



The area of the brain known as the extended amygdala may be involved in the reinforcing actions of drugs. (Artwork by Scripps Research BioMedical Graphics.)



# The Seeker

FRIEDBERT WEISS LOOKS FOR ANSWERS IN HOPE OF PREVENTING AND TREATING ADDICTION

He was born in Ulm, Germany, a mid-sized city on the Danube known among other things as the birthplace of Albert Einstein, but found his home in the United States. Friedbert Weiss, Ph.D., an associate professor in The Scripps Research Institute's Department of Neuropharmacology and a pioneer in the study of drug addiction, spent most of his childhood playing along the banks of Germany's legendary river before heading off to a boarding school near Frankfurt to finish his gymnasium—our equivalent of junior college.

Even then, he was pushing boundaries: “Contrary to what you see in the movies, boarding school was actually enjoyable. It really was a character builder—the challenge was to find intelligent ways to do what you wanted to do despite all the restrictions and rules. During that time, I developed bonds with classmates who became lifelong friends. Many now are well-known physicians, artists, and journalists in Germany today.”

Weiss first came to the States in 1978 on a summer visit, invited by a former professor of his who was teaching in California. America was at the bottom of his list for a vacation; he wanted to go to the Far East. He was 25 years old and, after taking a couple years off to try his hand at business, wanted to see the warmer parts of the globe. His old professor—who was living in Marin County at the time—however, offered him an opportunity to see the United States.

Why not? Weiss thought. Shortly after he arrived, his life began to change.

“I saw this country as a breath of fresh air,” he says now. “It was something I had not experienced before, a place where anything seemed possible. Later, my professor told me that's exactly what he thought I would experience. He believed that with my particular talents and ambitions the academic environment in the U.S. would be more conducive to my future scientific career.”

That future work turned out to be the study of the mechanisms and various neuro-circuitries of drug addiction. By examining substance addiction at

the biological level, Weiss has made a number of groundbreaking discoveries about the mechanisms underlying drug addiction. As a result, his research provides a more complete picture of what happens to people in the grip of drug abuse and what keeps them there.

## WHAT'S IN A SMILE?

That very first summer, Weiss decided to stay and eventually went looking for a place to complete his education. With his European background, he found that American universities welcomed him with open arms. He ended up attending the University of San Francisco, graduating *summa cum laude* with a degree in psychology, his mind set on becoming a clinical psychologist or perhaps a psychiatrist. He was at a stage in his life where he felt a strong inclination to go into the clinical area—patient treatment.

*“I am very interested in understanding and defining processes at a reductionistic level, but always with an eye on the eventual practical therapeutic use of my discoveries—to generate some benefit for society in general.”* –Friedbert Weiss, Ph.D.

“I was a bit older than most other students and usually interacted with the professors quite closely,” he remembers. “As a result of my interest in their research, and my academic achievement, I was offered a position as research associate even while I was an undergrad.” It was during this time that Weiss went to work with Paul Ekman, a professor at the University of California, San Francisco. Ekman was the leading figure in the study of emotion and the neural-cultural basis of facial expressions. He theorized that some emotionally charged facial expressions are of biological not cultural origin, a stance similar to what Darwin had suggested decades earlier. Ekman's theories are now widely accepted.

Working with Ekman was Weiss's first exposure to applying the scientific method to the understanding of the mechanisms responsible for even a commonplace phenomenon, a smile for example, →

and linking those phenomena to underlying autonomic and central neural processes.

“I am very interested in understanding and defining processes at a reductionistic level,” he says, “but always with an eye on the eventual practical therapeutic use of my discoveries—to generate some benefit for society in general.”

#### **PAYING ATTENTION**

Finished with his research at UCSF, Weiss moved to the University of California, Santa Barbara for his doctoral work in experimental psychopathology, a clinically oriented program where he was able to combine what was then the emerging field of cognitive neuroscience with the knowledge he’d gained working with Ekman. What eventually pushed him into the harder sciences was his study of attention—a phenomenon that is both the same and something more than the commonly accepted definition of the word.

“Attention is a cognitive process that, simply put, regulates our ability to focus and process important information while excluding irrelevant information,” he says. “It’s also a process that can become automatic. For example, with a certain amount of practice, you learn how to do two things at a time until some outside event forces you to switch attention to the more important aspects of what you’re doing.”

Weiss’s area of research involved measuring how the brain processes information when presented with incongruous stimuli, an especially rich vein of opportunity: “A simple example—the so-called Stroop effect—would be if the word red is printed in the color green, and you are asked to name the color. It will take you much longer if the color is incongruent with the word itself. At that time dysfunctions of these types of processes were thought to be a major factor in some forms of schizophrenia.”

*“Every time I come back to Scripps it feels like coming home.”*

—Friedbert Weiss, Ph.D.

While studying the role of attentional dysfunction in schizophrenia, Weiss made his final decision to switch to the study of biology and neuroscience. However, he still had in mind a future clinical career with the idea that he would go to medical school after he’d received his Ph.D., the perfect way to combine his clinical experience with his growing skills in basic research. That didn’t happen.

By the time he graduated, he had become a hardcore biomedical researcher. A faculty member at Santa Barbara who’d been trained at Scripps Research suggested that he apply for a position at what was then the Research Institute of Scripps Clinic. Weiss was quickly accepted and his medical school plans were put on hold.

That was 1986. Except for some additional post-doctoral experience in Stockholm, where he learned methods to study the neuro-chemical control of behavior, Weiss has been at Scripps Research ever since. With only a minor twinge of regret, he notes his medical degree has remained on hold for nearly 20 years. Scripps has been his home and the place where his research into drug addiction has blossomed: “I travel a lot, nearly 100,000 miles a year for conferences, lectures, and collaborations. Every time I come back to Scripps it feels like coming home.”

#### **TWO ROADS DIVIDING**

To a certain metaphorical degree—and you would be hard-pressed to find another human activity more susceptible to metaphor than addiction in all its forms—Weiss’s research on addiction conjures up the Frost poem about two roads diverging in a yellow wood. Despite all the rational reasons arrayed before them, people prone to addiction almost always choose the wrong road. It has been Weiss’s quest to try to figure out how and why.

In one of his most recently published works, Weiss and his colleagues demonstrated in animals that the stimulus conditioning of a single drug experience—in this case, cocaine—can resonate for up to half of the test animal’s lifetime.

The implications of this serendipitous find—Weiss was working on a larger study pinpointing brain regions that mediate the relationship between cocaine euphoria and specific environmental stimuli—dramatically illustrate the powerful effects of drug abuse. The totality of this conditioning can induce a deep desire for the drug when the subject is again exposed to such cues months or even years later.

As Weiss points out, these particular findings are not about relapse *per se* because addiction hasn’t yet developed. What they do mean, however, is that even a single instance of cocaine conditioning with specific environmental stimuli is a potentially critical risk factor that may contribute to the progression from initial sporadic drug use to addiction. Interestingly, stimuli associated with

availability of a highly palatable natural food substance produced only modest seeking behavior that extinguished rapidly.

Not only has it been shown that this drug-related Pavlovian conditioning persists over months of abstinence, but that extended drug use produces relapse in a way that is impervious to punishment, and that a subject's appetite for the drug can even increase in strength over a period of prolonged abstinence.



Friedbert Weiss grew up in Germany, near the Danube River.

As Weiss's research suggests, it is likely that this drug-related conditioning is regulated by brain circuitries that process other natural pleasurable experiences as well. There is also evidence from some brain imaging studies that the regions of the brain activated by drug cues may not be specific to addiction-related events, but are, in fact, normal circuits that have been activated to an abnormal degree. This creates drug-directed motivational states, tilting normal processes that govern our response to natural rewards essential for well-being towards the search for drugs.

But why, despite all this, do only some people become addicted while others do not?

"If I had unambiguous evidence to answer that question," Weiss says, "I would probably be going to Stockholm for the Nobel. There are many hypotheses, and some progress is being made in finding a solution. Some people may be genetically vulnerable due to some molecular or neuro-chemical dysfunction. The literature suggests that high expression of a dopamine receptor subtype—the D2 receptor—may exert protective effects against developing drug addiction, while the opposite is the case in individuals with deficient D2 function."

In addition, Weiss explains, chronic drug use produces neuro-adaptive changes in the brain that lead to disruption of psychological homeostasis and a rise in problems like anxiety and depression. Drugs briefly restore that sense of equilibrium, motivating continued drug use or relapse. As a variant of the neuro-adaptation theory, other research suggests that chronic drug use sensitizes the neural systems that regulate the desire for drugs at the expense of other essential activities or rewarding experiences.

"Individuals may be more or less susceptible to these types of neuro-adaptive changes," Weiss says. "And not all subjects become sensitized with chronic drug use. Once we understand what causes neural and behavioral sensitization and how it can be reversed, we may have a viable treatment option at least for this aspect of addiction."

#### A DOUBLE-EDGED SWORD

So where exactly does all this rather disheartening information leave us?

"As drug abuse researchers, we have traditionally been preoccupied with what causes drug addiction instead of trying to uncover what is protective of drug addiction," Weiss says. "But this research strategy is rapidly changing and there have already been some encouraging results."

Of course, in the end, it may simply be that human nature is naturally a double-edged sword. Restless, adventurous, even reckless at times, human beings have always searched for what's beyond the accepted horizon, whether it's artistic, geographical, or psychological. The very existence of what many have come to think of as a hardwired desire to push the limits of our own experience may at the same time be part of a mechanism that leads susceptible individuals into the trap of addiction.

"Remember, great minds, thinkers, and artists often have had strange habits that they engaged in while they were creating their most famous works," he says. "They have all undertaken what we might call journeys of expansion. This is not meant to condone drug or substance abuse, but simply to draw attention to the fact that many of us feel compelled to push the limits of our capabilities—whether mental or physical."

Weiss has envisioned his own particular journey. "My own ultimate goal is to develop a thorough understanding of what causes addiction at multiple levels of analysis and to successfully treat and prevent it."

•Eric Sauter

# Behind the Scenes

Public and Private Support  
Funds Research



## New NIH Grant: Detecting the Genes That Contribute to Transplant Rejection

A group of physicians and scientists led by Scripps Research Institute Associate Professor Daniel Salomon, M.D., has been awarded a federal research grant of more than \$12 million over five years to apply cutting-edge genomic technologies to advance our understanding of kidney transplantation.

The National Institute of Allergy and Infectious Diseases (NIAID) grant will enable Salomon and his colleagues to monitor several hundred patients who have had kidney transplant surgeries with technologies for gene expression profiling and proteomics, and several thousand transplant patients by complex trait genetics. One of the team's overall goals is to answer one of the most pressing problems in kidney transplantation: why do some patients do well after a transplant while others do not?

"Fifty percent of transplant patients lose their kidneys within eight to ten years," says Salomon. "[This project] will study some 2,400 patients with kidney transplants, and we will be looking at the genetic basis and control of why some patients do well and others have problems. In practical terms, this will involve advancing our understanding of what causes acute and chronic kidney injury."

Along with Salomon, also a transplant physician and co-director of the Scripps Health Center for Organ and Cell Transplantation at Scripps Green Hospital in La Jolla, the Transplant Genomics Collaborative Group includes Scripps Research Cell Biology Professor John Yates, Steve Head, who is the director of the Scripps Research DNA Array Core Facility, and other investigators around the country.

### KIDNEY FUNCTION AND FAILURE

Kidneys are the organs within the human body that

filter waste from the blood and produce urine. They also secrete certain hormones into the blood that the body needs to maintain a normal blood count, chemical balance, and blood pressure. A person's kidneys are workhorses, filtering all the body's blood every 22 minutes and maintaining the blood's pH, salt concentration, and pressure. Severe damage to these organs can lead to kidney failure, a potentially fatal condition.

One medical strategy in the face of kidney failure is to replace a person's failed kidneys with donated kidneys. Since the first whole organ transplants were successfully performed in the 1950s, kidneys have become one of the most commonly transplanted organs in the United States—some 15,000 are performed each year, though demand for the operation far outstrips the availability of donated kidneys.

Unfortunately, in any "allograft" or transplanted tissue taken from another person, there is the danger of transplant rejection, which arises from the fact that a donated kidney is foreign to the transplant patient's body. Left alone, the person's immune system will detect the foreign tissue, mount an immune response, and attack it. To avoid transplant rejection, doctors use a powerful class of drugs known as immunosuppressants, which weaken the immune response. With immunosuppressants, a transplanted kidney can survive and function well for years.

However, immunosuppressants also have a dark side. Immunosuppressive drugs make transplant patients more likely to suffer heart disease, diabetes, infections, and cancer. These drugs are also toxic and can slowly poison the very kidney they are protecting. In addition, they can cause hypertension and hyperlipidemia, eventually leading to the failure of the new kidney transplant—a condition known as chronic allograft nephropathy. Unlike acute rejection, which is entirely the result of the immune system attacking the transplanted organ, chronic allograft nephropathy may be a result of the immune system,



the immunosuppressive drugs, or both. It is a major problem in kidney transplantation.

A major challenge following transplant surgery is to determine the proper regimen of drugs needed for a patient to avoid on the one hand tissue rejection and on the other chronic allograft neuropathy. Balancing the need for more with the need for less is made more difficult by the fact that every patient responds differently to the immunosuppressant drugs.

#### **IT TAKES TWO TO TRANSPLANT**

In general, says Salomon, if you look at kidney transplant patients a few years after their surgery, they will fall into one of three distinct clinical categories. Some patients will have good kidney function and show no signs of complications or rejection; some will have suffered from acute rejection of their new kidneys; and some patients will have chronic allograft nephropathy, but perhaps without any symptoms.

“The reality,” says Salomon, “is that there is no metric for adequate or safe immunosuppression.”

He and his colleagues would like to change that. They would like to use the discoveries of genomic science to build a new set of tools so doctors can measure and predict how a patient will respond to immunosuppressive drugs. With such tools, transplant doctors could monitor patients regularly to make sure their treatment is optimal. In fact, these same tools could also guide therapy of patients with diabetes, systemic lupus, rheumatoid arthritis, and other immune-related diseases.

The theory is that there may be some genetic “signature” within donors and recipients that predict the best course of treatment following transplant surgery. This signature could be within the tissues of the transplanted organ or in the blood cells. Salomon and his colleagues want to understand this signature and develop ways to detect it within the laboratory.

They have made progress. In a recent article in the *American Journal of Transplantation*, Salomon and his colleagues showed for the first time that one could diagnose acute rejection by profiling gene expression in the peripheral blood using high density

DNA microarrays. Another paper that Salomon published recently showed that they could similarly profile chronic allograft nephropathy in the biopsies of transplanted kidneys.

Now, the NIAID grant promises to further the goal by funding a large genomic study of transplant patients. “It is the beginning of applying new technologies to understanding how to diagnose, manage patients, and improve the safety of therapies for organ and cell transplantation,” says Salomon.

A unique feature of this research effort is that all the genetics will be done on both the patients and their kidney donors.

“The grant contains three major projects, all involving the analysis of kidney donors and of patients who have recently undergone kidney transplants. The grant supports a network of 11 major clinical transplant centers in the United States. They are doing about 1,400 adult kidney transplants per year and following about 15,000 total patients,” says Salomon. “In the next five years, blood and kidney biopsy samples from some 2,400 patients at these centers will be flown to La Jolla to be profiled.”

*“[Our research] is the beginning of applying new technologies to understanding how to diagnose, manage patients, and improve the safety of therapies for organ and cell transplantation.” –Daniel Salomon, M.D.*

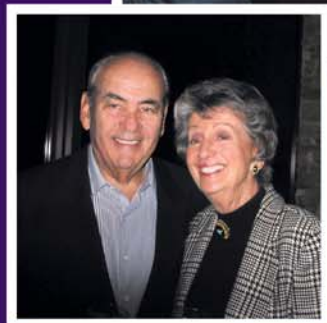
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“The genetics of the patient [receiving the kidney] determines the character of the immune response, but it’s the genetics of the donor that determines the impact of the transplantation,” says Salomon. “What we’re hoping to come out with is an understanding of what makes a good donor, and what it is about the donor organ that determines the long-term outcome of the transplant.”

Such a tool may also be useful for the development of a new generation of post-transplant drugs to treat patients or to protect the kidneys of patients with early kidney disease that still have good function. The ultimate medical strategy would be to prevent kidney failure and eliminate the need for kidney transplantation. In the meantime, improving the safety of transplantation is an important goal.

•Jason Socrates Bardi

## Photo Essay: Events Build Momentum for Scripps Research



- 1 In celebration of Scripps Research's first Board of Trustees meeting in Florida, 80 guests enjoyed cocktails on November 6 at the Palm Beach home of Nancy Brinker, founder of the Susan G. Komen Breast Cancer Foundation and former ambassador to Hungary. Here, Brinker chats with Scripps Research Trustee Ralph Shapiro, chair of the Development Committee.
- 2 The next evening, Alexander Dreyfoos, a Scripps Research Board member from Florida, and his wife Renate hosted a cocktail hour and dinner for Scripps Research Board members, Florida elected officials, and Florida donors at the Raymond F. Kravis Center for the Performing Arts in West Palm Beach. Here, the couple welcomes Scripps Research friends and supporters. The couple announced a gift of \$1 million to Scripps Research at the event.
- 3 Attending the Dreyfoos event are Board member Phillip Frost, M.D., and his wife Patricia.
- 4 In honor of Scripps Research's Nobel laureates, National Academy of Science members, and Wolf Prize-winning faculty, Los Angeles business leader Ron Burkle hosted an evening of dining and conversation about science at his La Jolla estate October 28. Here, Scripps Research Professor and Nobel laureate Kurt Wüthrich, Ph.D., (left) and Vice President for Academic Affairs and Dean of Graduate Studies Jeffery Kelly, Ph.D., (center) are shown enjoying Burkle's hospitality.
- 5 Burkle's La Jolla event was attended by Scripps Research Nobel laureates Barry Sharpless, Ph.D., Gerald Edelman, M.D., Ph.D., and Kurt Wüthrich, Ph.D. Other guests included actor and Scripps Research Trustee Warren Beatty and his wife, actress Annette Bening; visiting Nobel laureate Manfred Eigen, Ph.D.; Anthony Kiedis, lead singer for the Red Hot Chili Peppers; Claudia Luttrell, president of the Skaggs Research Institute; the Honorable Alice D. Sullivan (retired), chair of the Board of Trustees; and Richard Lerner, president of Scripps Research. Here, Edelman (left) exchanges views with Beatty and Scripps Research Director of Medical Education Katja Van Herle, M.D.
- 6 In November, Associate Professor Stephen P. Mayfield, Ph.D., addressed an intimate dinner gathering of Scripps Research donors and friends at the Indian Wells Country Club. Among the guests were donors Sheldon and Izetta Magazine (pictured here). Mayfield educated the audience on his lab's development of a protein expression technology, using algae, that provides a more effective and efficient way to make human therapeutic proteins on a massive scale.



The Piziali Family: Rob, Tia, and Alison.

## Mother Raises More Than \$300,000 for Lab

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It's amazing where an idea can take you.

Alison Piziali had the idea that she could make a difference for her young daughter, Tia, and other children afflicted with phenylketonuria (PKU) by raising money to support research in a Scripps Research Institute lab.

After her daughter Tia was diagnosed with PKU soon after birth, Alison had quickly become aware of the limitations of the current treatment strategy for the disease. Children with PKU, an inherited metabolic disorder, cannot convert phenylalanine, a part of a protein, to tyrosine in the liver. Phenylalanine thus becomes toxic to the central nervous system, especially the brain.

Since phenylalanine occurs in meat, fish, all dairy, flour, and even fruits and vegetables, children with PKU must go through life on a severely restricted diet and be monitored by frequent blood tests. Limiting phenylalanine in the diet is so difficult that many fail to avoid behavioral and intellectual problems as adolescents and adults. Since drug development takes so long, Alison knew she needed to act immediately if she wanted to see new therapeutics available for Tia when she became an adolescent.

Alison and her husband Rob Piziali wanted a better fate for their daughter. That's when they learned that Scripps Research Professor Raymond Stevens was working with BioMarin Pharmaceuticals on a potential treatment strategy for PKU and similar diseases. This research showed the promise of using natural cofactors to provide some protection against the toxic effects of phenylalanine for patients with mild PKU and an enzyme replacement strategy for patients with severe PKU.

Alison hit on the idea of throwing an event, which she dubbed "Tuxes for Tia and All People with PKU," in San Francisco to raise money for the Stevens lab and to speed investigations toward new treatments. The initial goal was to raise \$75,000. Alison also hoped the event would raise awareness about the disease.

The response to the event was good—very good. In fact, Alison soon realized that the room she had booked wouldn't hold all the people who wanted to attend. She changed the venue to the Ritz-Carlton.

In the meantime, Alison's parents, Richard and Virginia Michaux, stepped up to support the cause, donating \$75,000 for a fellowship in the Stevens lab. Over and above that contribution, they gave \$30,000 to support the lab's PKU research. And Alison's in-laws, Robert and Kathy Piziali, donated another \$25,000.

The date of the event arrived, and 376 guests from 17 states enjoyed an elegant evening of cocktails and dancing. When the proceeds were tallied (without counting the prior Michaux and Piziali gifts), they totaled more than \$300,000.

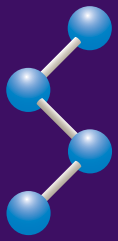
Stevens, for his part, calls the fund-raising event "incredible" and states that it has unequivocally accelerated his work on PKU therapeutic development. "[Tuxes for Tia] was one of those lifetime events that goes beyond words and that I will always remember with absolute amazement," he says. "Now it is up to us to accomplish our task of developing PKU therapeutics on a similar level."

For information on ways to give to Scripps Research, the latest research news, and upcoming programs and events, please visit the "Giving to TSRI" page on the Scripps Research Web site, [www.scripps.edu](http://www.scripps.edu).

## One Person's Legacy Can Make a Difference

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You are cordially invited to join The Scripps Legacy Society. Scripps Legacy Society members are committed to supporting Scripps Research and have included Scripps Research in their estate plans. The Scripps Legacy Society symbolizes one generation sharing their resources and values with future generations. For more information, please contact Planned Giving Counsel Cheryl H. Dean, Esq. at (858) 784-2380 or [cdean@scripps.edu](mailto:cdean@scripps.edu).



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