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ENDEAVOR



Issues in
**MOOD
DISORDERS**

THE SCRIPPS RESEARCH INSTITUTE

ENDEAVOR

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This issue of *Endeavor* magazine features a few of the outstanding neuroscientists at The Scripps Research Institute, highlighting their work to advance the understanding and treatment of mood disorders.

Scientists Find Seizure Drug Reverses Cellular Effects of Alcohol Addiction in Models

New findings from scientists at The Scripps Research Institute provide evidence that the drug gabapentin affects certain components of the alcohol addiction cycle in the brain, supporting the idea that the medication, which is approved by the U.S. Food and Drug Administration for treating seizures and pain, also holds potential for the treatment of alcohol dependence.

In the new research, the team found that gabapentin normalizes the action of certain brain cells altered by chronic alcohol abuse in an area of the brain known as the central amygdala, which plays an important role in fear- and stress-related behaviors, as well as in regulating alcohol drinking. In the study, alcohol-dependent rodents receiving gabapentin drank less alcohol.

“Our research shows that gabapentin not only changes the alcohol-consumption patterns of addicted rats (and not of the control group), but also may reverse some of the effects of addiction on a specific neurotransmitter in the brain,” says Scripps Research Assistant Professor Marisa Roberto, Ph.D.

REFERENCE: *Journal of Neuroscience*, 28(22) (May 28, 2008).

T Cell Multiplication Unexpectedly Delayed After Infection

In a surprising outcome that overturns the conventional wisdom on the body’s immune response to infection, scientists at Scripps Research have shown that T cells do not begin proliferation until up to three days after infection.

Until now, it was generally believed that memory T cells, lymphocytes that recognize pathogens from previous infections, begin cell division at a far earlier point than naïve T cells, fresh cells that respond to new infections. The findings suggest that the delay may be an evolutionary safeguard against the risk of an autoimmune response from an explosive proliferation of T cells.

“It was thought that memory T cells responded more effectively to infection by starting cell division earlier than naïve cells and by multiplying more rapidly after that,” says Professor Lindsay Whitton, M.D., Ph.D. “Our study shows that neither assumption is true. Even though memory cells detected and responded to virus infection within a few hours, they did not begin to divide until after a lengthy delay. After that, cell division was rapid for both naïve and memory cells.”

REFERENCE: *PLoS Pathogens*, 4(4) (April 10, 2008).

Crystal Structure Reveals Mystery Behind Three Rare Childhood Disorders

A team of researchers from Scripps Research, the Lawrence Berkeley National Laboratory, and the San Diego Supercomputer Center has figured out how it is that tiny mutations in a single gene can produce three strikingly different childhood diseases—disorders that increase cancer risk thousands of times in some young patients and premature aging or a complete failure to develop in others. Investigators say that knowing more about the mechanisms of these diseases may provide insights into how therapeutic drugs can be designed.

All of the disorders occur due to inherited defects in a crucial DNA repair enzyme, the XPD helicase, which unwinds DNA to fix damage that regularly occurs. In the new study, the researchers describe how they “built” the first crystal structure of the enzyme, and how that led them to see defects in the function of the protein that help explain these diseases.

“The results from the combined biochemical and structural experiments were like turning on a light in a dark room and suddenly seeing for the first time how XPD—a key piece of machinery needed to open DNA to make proteins or to repair the DNA—was really working,” says Professor John Tainer, Ph.D.

REFERENCE: *Cell*, 133 (May 30, 2008).

“Darwinian Evolution on a Chip”

Under the control of a computer, a population of billions of genes morphed through 500 cycles of forced adaptation to emerge as molecules that could grow faster and faster on a continually dwindling source of chemical fuel—a feat that researchers describe as an example of “Darwinian evolution on a chip.”

The super molecules that resulted, a species of RNA enzyme, were produced in about 70 hours using an automated tool that is about the size of a compact disc, according to Gerald Joyce, M.D., Ph.D., professor, dean of the faculty, and member of the Skaggs Institute for Chemical Biology at Scripps Research. The scientists note that the findings provide an example of the Darwinian principle of selective pressure at work, seen in real time. The evolved enzymes that resulted exhibited a new set of 11 mutations that improved their ability to survive under substrate-starvation conditions by 90-fold, compared to the starting molecules.

REFERENCE: *PLoS Biology*, 6(4) (April 8, 2008).



“In the last ten years, we have come to regard the treatment of major depression as a must.”

TAMAS BARTFAI, Ph.D.



Searching for a Faster Antidepressant

03

TAMAS BARTFAI MAKES HIS MARK ON THE NEXT BIG CHALLENGE

TAMAS BARTFAI, Ph.D.

Google the word *depression* and you will find hundreds of different pages that all seem to say the same thing. Depression is widespread, it is debilitating, and words used to describe people who suffer from it include sad, empty, hopeless, listless, indecisive, unfocused, annoyed, drowsy, and sleepless.

Many of these words have their exact opposite on the same list, which suggests how personal depression is when it strikes. Some people lose sleep and gain weight. Others lose weight and are unable to rise from the bed.

In fact, the only word on any list of depressive symptoms that stands alone is the one that is often listed last: suicide—one of the core risks of serious depression and the eleventh leading cause of death in the United States in 2004, accounting for 32,439 deaths that year. Almost every credible list describing major depression ends in suicide. Sadly, the lives of far too many people who are depressed also end in suicide.

“Fighting depression is very important,” says Professor Tamas Bartfai, Ph.D., chair of the Molecular and Integrative Neurosciences Department, director of the Harold L. Dorris Neurological Research Center, and member of the Skaggs Institute of Chemical Biology at The Scripps Research Institute. In Bartfai’s own lifetime, more young people have died from suicide than from the fighting in World War II. Even if you or your loved ones do not lose their lives to depression, he adds, it can steal years from your life.

Depression is so common that the National Institute of Mental Health estimates that in a given year it affects approximately 14.8 million American adults, or about 6.7 percent of the U.S. population age 18 and older. It is the leading cause of disability in the United States for people ages 15 to 44.

One of Bartfai’s main scientific objectives is to find new treatments for depression—particularly an effective fast-acting antidepressant drug.

SECOND GENERATION, A GENERATION AGO

Treating depression has changed a lot over the last half century. Since World War II, many powerful drugs to treat depression have been developed.

The first two classes of modern antidepressants, discovered in the 1950s, are the tricyclics and the monoamine oxidase inhibitors. Until recent decades, the two ruled. These drugs are good, says Bartfai, except for notable side effects, such as dry mouth and fatigue.

Though the tricyclics were discovered without knowledge of their mechanisms of action, we now know they affect serotonin and norepinephrine levels in the brain by inhibiting reuptake (reabsorption) into cells. The problem is that tricyclics also target other mechanisms as well, such as signaling by acetylcholine and histamine. These other actions account for the drug’s side effects.

Tricyclics and monoamine oxidase inhibitors are still widely prescribed, although their use has →

“We need drugs that produce an antidepressant effect with an increased will to live and increased belief in one’s future and worth, before they also increase the activity and energy of the depressed person.”

TAMAS BARTFAI, Ph.D.

been eclipsed by newer drugs with fewer side effects (today, the major use of tricyclics is for treatment of pain). The so-called “second-generation” antidepressants include drugs with familiar names like Wellbutrin,[™] Paxil,[™] Zoloft,[™] Effexor,[™] and Prozac.[™]

“They basically have the same mechanism as the tricyclics of the 1950s,” says Bartfai. The major difference is these drugs are more selective in which brain mechanisms they target. The drugs are referred to as selective serotonin reuptake inhibitors (SSRIs) because they block the reuptake of serotonin without affecting the levels of norepinephrine and histamine; they do not block cholinergic receptors.

Also, these drugs are much safer than the monoamine oxidase inhibitors, thus general practitioners, not only psychiatrists, can and do prescribe them. One result is that more patients in rural areas are treated with antidepressants.

Second-generation antidepressants have undergone another change in the last few years as many have come off patent, becoming cheaper. According to a study published by *Consumer Reports*, the cost of a month’s supply of several of the most common antidepressants in 2005 was less than \$100—even without insurance. Larger social changes have occurred as well.

“Depression has become [socially] accepted and many more people are diagnosed than three decades ago,” says Bartfai. “In the last ten years, we have come to regard the treatment of major depression as a must.”

Still, even with the advent of SSRIs, therapy for depression remains problematic for many. These second generation drugs still have some side effects, and for a certain percentage of the population, the drugs do not work. Moreover, they have not improved the speed of therapy. There is no way to immediately treat somebody’s depression—except with the much demonized electroconvulsive shock therapy in a hos-

pital setting. Antidepressant drugs—even the most powerful ones—take two to three weeks to work.

A PRESCRIPTION FOR A FAST-ACTING ANTIDEPRESSANT

When you take Prozac, the chemical passes down the esophagus into the digestive tract, where it is absorbed into the bloodstream. From there, it travels into the brain, where its chemical effect is felt almost immediately. Serotonin levels respond right away.

For reasons that are not entirely understood, however, the antidepressant effects take longer to kick in. In other words, you may have increased serotonin, but you won’t stop feeling blue for a few weeks.

There can be some sinister twists to this delay. Giving some kinds of SSRIs to a severely depressed teen can be dangerous, increasing his or her energy level enough so the teen finally commits suicide. That’s the reason that since 2004 many fewer SSRIs have been prescribed for adolescents.

“We need drugs that produce an antidepressant effect with an increased will to live and increased belief in one’s future and worth,” says Bartfai, “before they also increase the activity and energy of the depressed person.”

Certain therapies, like electroconvulsive therapy and clinically monitored sleep deprivation, are known to bring on a rapid antidepressive response, and they are often used in emergency situations. While effective in the short term, neither method produces long-lasting effects, however. The antidepressant effect of sleep deprivation, for example, only lasts about 48 hours.

One of Bartfai’s long-standing goals is to develop a fast-acting compound for the treatment of depression. “We just don’t know how to make a tablet that replaces electroconvulsive shock or sleep deprivation yet,” he says. In the last few years, he and his colleagues have taken steps toward this goal.



ADVANCING RESEARCH

Bartfai has a lot of experience with drug development. He describes himself as a molecular neurobiologist—someone who attempts to associate cellular and molecular mechanisms to phenomena like cognition, memory, and emotional states.

As a pharmaceutical executive and as a consultant, he has worked on treatments for depression and a number of other neurological diseases for decades. Bartfai is former chair of the Department of Neurochemistry and Neurotoxicity at Stockholm University. As a consultant for ASTRA (now ASTRA-Zeneca), he was involved in the development of Zimelidine, the first selective serotonin reuptake inhibitor (SSRI), which preceded Prozac by years, and two anti-psychotic agents used in the treatment of schizophrenia.

Before joining Scripps Research in 2000, Bartfai was head of central nervous system research at the Swiss drug maker Hoffman-LaRoche, a department most famous for the drug Valium and for its Parkinson's disease drugs. He joined Hoffman-LaRoche to develop a major human genetics effort to aid discovery of new treatments for schizophrenia and Alzheimer's disease.

Bartfai came to Scripps Research as a professor of neuropharmacology in 2000, and was appointed director of the Harold L. Dorris Neurological Research Center a few months later. The center was founded with a remarkable \$10 million endowment from Helen L. Dorris of San Diego—the largest gift Scripps Research had ever received for research in the neurosciences. In 2005, he became head of the Department of Neuropharmacology, which was reorganized and renamed the Molecular and Integrative Neuroscience Department (MIND).

Under his direction, the Harold L. Dorris Center aims to advance research on a number of fronts, developing new models for schizophrenia, addressing basic questions involving fever and sleep as they

tie into depression, and examining the role of cytokines in inflammation and pain.

The center's effort to find faster-acting antidepressants centers around a system of short proteins in the brain—"neuropeptides"—and in particular one called galanin.

GALANIN IN THE GAPS

Discovered in the early 1980s, galanin is a peptide, which is basically just a string of different amino acids.

First isolated in pig intestines, galanin's function was initially not completely understood. Over the past 25 years, Bartfai and his colleagues have developed genetic and pharmacological tools for the study of the effects of galanin on the brain.

In the brain, galanin is involved in a number of neurological processes, from feeding and control of seizures to pain sensing and stress. Whenever you experience stress and start to release stress hormones, you will release galanin as well.

Galanin also seems to play an important role in psychiatric disorders. It is a key neuropeptide in the part of the brain known as the hippocampus—a ridge of tissue where scientists think many of the chemical processes important for forming and retaining memories take place. As a neuropeptide, galanin is released into the gaps, or synapses, between two neurons during the signaling from one neuron to another during cognitive processes.

Bartfai and his colleagues have evidence that galanin's action plays an important role in mood disorders. The hippocampus has a number of progenitor cells that connect up as new neurons throughout life. One current theory of depression is that it is linked to this formation of new neurons—neurogenesis.

Many scientists embrace the idea that antidepressants work by promoting this growth of new neurons, and this connection is well-established in



“Seeing first-hand the suffering that these disorders can inflict leaves a lasting impression.”

PAUL KENNY, Ph.D.

Star-Crossed Pair

PAUL KENNY UNTANGLES THE TIES BETWEEN DEPRESSION AND ADDICTION

At first blush, the idea that depression and addiction go together makes sense, but in fact it has only been in recent years that a scientific link has been established.

Paul Kenny, a 35-year-old associate professor of molecular therapeutics at the Florida campus of The Scripps Research Institute, is one of a handful of scientists who has helped illuminate the connections between them and who continues to work to uncover the underlying pathways common to both disorders.

“The death of the reward response in the brain provides the link between the two conditions,” Kenny says. “In addiction, the brain’s reward system collapses in response to over-stimulation by an addictive drug, leading to damped down reward pathways. Then, to feel normal, the brain needs more drugs. In depression, a deficit of brain reward pathways results in an inability to experience pleasure or reward.”

Kenny, who was born in Dublin, Ireland, saw the ravages of addiction first hand at St. Patrick’s Hospital, that city’s main psychiatric hospital, where he spent a year after his graduation from Trinity College Dublin. The impression he got was a lasting one.

“It was shocking then, and it’s still shocking now how terrible these addictions really are,” he says. “I had no idea of the suffering, but when you

see it first hand, you can’t distance yourself from it. I also worked with people suffering from depression, especially those unfortunate enough to be resistant to conventional antidepressant drugs and requiring the more drastic approach of electroconvulsive therapy. Seeing first-hand the suffering that these disorders can inflict leaves a lasting impression.”

NICOTINE GIVETH AND NICOTINE TAKETH AWAY

Kenny’s research at Scripps Florida has, to a great degree, focused on one particular kind of addiction—to nicotine.

In a 2006 study published in the journal *Neuropsychopharmacology*, Kenny and his colleagues make the point that nicotine is in a category by itself when it comes to addictive properties. The study shows that nicotine acutely increases the sensitivity of the brain’s reward systems, and these stimulatory actions are extraordinarily long lasting compared with other drugs like cocaine, and may have a distinctive mechanism of action.

Nicotine is a highly complex, two-faced drug that is to a great degree still a mystery, doing a great many things that appear to be in contradiction. Nicotine is known to have mood-enhancing effects that make you feel good, perhaps in part by raising levels of serotonin, a neurotransmitter that can modulate mood, emotion, sleep, and even appetite. →





“[There is] an internal conflict between what you really need to survive and what you only think you need to survive but which may actually be damaging your health.”

PAUL KENNY, Ph.D.

“A lot of depressed people smoke,” Kenny says. “However, an important question is whether they smoke because they’re depressed, or they become depressed because they smoke.”

The answer is, Kenny believes, a mixture of both. “While people may say they feel better if they smoke, it’s becoming clear that, in addition to the mood-enhancing effects of nicotine, the drug itself is also a major risk factor for the development of depression and a number of other psychological disorders,” he says. “There is a high correlation between smoking and schizophrenia, for example. It’s a drug that gives with one hand, and takes away with the other.”

Nicotine enhances mood, but also has damaging effects on the brain. Indeed, nicotine kills new cells that are born in the brains of adult animals—and scientists increasingly believe that antidepressant drugs may work at least partly by promoting the growth of these cells. This new cell growth is known as “hippocampus neurogenesis”—new neuron growth in the hippocampus, a structure involved in memory and emotion so named because it’s shaped like a seahorse (from the Greek *hippos* or horse; *kampos* or sea monster). This action of nicotine is particularly important in the context of depression, as proper levels of hippocampal neurogenesis may be necessary to achieve the therapeutic responses to antidepressant drugs, and deficits in neurogenesis may also contribute to vulnerability to depression.

“Data over recent years have shown that nicotine and other addictive drugs actually kill these new brain cells outright or by inhibiting trophic factors like brain-derived neurotrophic factor (BDNF) that are necessary for their survival,” Kenny says. “So, it may be that nicotine initially gives you that acute upward spike in mood, but underlying this effect are toxic actions that may increase your vulnerability to depression.”

THE DOORS OF PERCEPTION

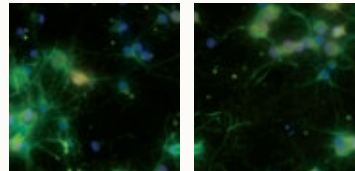
If nicotine has such contradictory actions, why do smokers only seem to focus on the positive aspects of tobacco smoking?

Smokers’ distorted perception seems to play a major role in this dichotomy, Kenny notes. The mood-enhancing effects of smoking are understood subjectively; that is, if you smoke you focus on the fact that cigarettes make you feel good immediately. But when evaluated objectively, by neutral observers, it becomes clear that over time your mood actually deteriorates with smoking.

“There was a study published by the *American Journal of Psychiatry* in the late 1990s,” Kenny says. “It was always assumed, and rightly so, that smoking is stress-related, and that if a smoker quit, his or her anxiety and stress levels would increase and this would also increase the likelihood of relapse. However, the situation appears a little more complex. This study showed that when a smoker quit, the smoker’s own perception of their stress and anxiety levels increased, whereas their baseline anxiety levels measured objectively by an independent observer actually went *down* over time. But if you asked smokers, they would say that they felt better—less anxious—when smoking. That strongly supports the idea that subjective and objective experience is disconnected.”

What it may come down to, Kenny notes, is basic Pavlovian theory. Your brain learns that smoking makes you feel good from that initial burst of chemicals that occurs almost immediately after you smoke. But it may not make the association between smoking and the negative effects that emerge more slowly over the long run.

That skewed perception, a witch’s brew of physical or genetic traits with a complex host of psychosocial additives, contributes to the addicted person’s inability to change behavioral patterns.



Cultured brain cells provide clues for the Kenny laboratory's investigations of the molecular mechanisms by which nicotine produces its addictive effects and mood states.

PROCESSING DEFICITS

For those suffering from depression, skewed perception means focusing on a few events that seem to spark a prolonged negative affect. Kenny notes that depressed people may have developed a hyper-response to negative stimuli or stress.

“The brains of depressed people are attuned to certain types of negative issues or events, and this combines with a genetic predisposition to depression,” Kenny said. “When confronted with stressful events—divorce or the death of a parent, let’s say—the depression-prone brain can’t seem to overcome those circumstances as robustly as the less vulnerable brain. There’s a lack of an ability to process the information in what might be called, for lack of a better term, a normal fashion.”

But it is in these processing deficits, Kenny notes, where addiction and depression also significantly overlap, as shown clearly in animal models. Both depression and addiction are characterized by enhanced ‘salience’ or importance of certain cues to the individual. In the case of depression, enhanced focus is on negative stimuli. In the case of addiction, heightened responsiveness occurs to drug-associated environmental stimuli—the smell of a cigarette, the time of day when smoking usually occurs, etc.

Physiologically, the conditions appear to intersect at the level of the nicotinic receptors in the brain, the sites at which nicotine acts to induce its behavioral effects, but which may also play an important role in antidepressants’ therapeutic actions. According to Kenny, almost all clinically effective antidepressant drugs are known to block nicotinic receptors in the brain, the very same receptors that respond so enormously well to the nicotine contained in cigarettes. Many ongoing drug discovery efforts have been initiated based on this knowledge, and are directed toward the development of antidepressant compounds that act in the brain at the same site as nicotine.

One example of such a compound is the widely available hypertension treatment mecamylamine. This drug happens to be a small molecule nicotinic receptor antagonist that has the desirable ability to cross the blood-brain barrier. It has also been used to treat nicotine addiction and has been shown to be somewhat effective in the treatment of depression.

For Kenny, all this shows clearly that nicotinic receptors, integral components of the cholinergic system, play an important role in regulating mood processes. The information also goes a long way to explain why nicotine is such a potent chemical and why it is so addictive.

BIOLOGY RUN AMOK

So, like star-crossed lovers, addiction and depression march arm in arm together into the darkness.

“In the case of tobacco addiction, you have to weigh immediate reward against long-term negative health and psychological consequences of smoking,” says Kenny. “Interestingly, the brain’s ability to make that decision may be seriously impaired by the drug—a pernicious aspect of drug addiction. It makes your choice to stop using the drug very difficult because the drug itself may damage the parts of your brain involved in such choices.”

Kenny notes that the forces of biology run amok can be powerful, which is why he is working so hard to try to figure out how to set them right.

“People try to fulfill needs,” he says. “They consciously and subconsciously do what their bodies tell them to do. Their behavior may sometimes appear to be irrational but they’re simply responding to these great internal signals. It really is an internal conflict between what you *really* need to survive and what you only *think* you need to survive but which may actually be damaging your health.”

ERIC SAUTER



“Many people with schizophrenia live on a rollercoaster, going on and off different drugs as they and their doctors search for the one that might relieve symptoms.”

BETH THOMAS, Ph.D.



Genes of the Mind

BETH THOMAS LOOKS FOR WAYS TO GET AHEAD OF NEUROPSYCHIATRIC DISEASES

Throughout Elizabeth Thomas’s career as a neuroscientist, she has been driven by one overriding goal—to alleviate the suffering caused by psychiatric disorders. As an undergraduate biochemistry student at the University of California, Berkeley, in the 1980s, the mentally ill homeless people that Thomas saw on the street every day heightened her interest in studying pharmacology and anti-psychotic drugs.

As a postdoctoral fellow at The Scripps Research Institute in the 1990s, the desire to help a colleague in her lab who was at risk for Huntington’s disease led her to expand her research focus to encompass that condition as well.

Today, as an assistant professor at Scripps Research on the California campus, Thomas continues to work tirelessly to investigate the role of genes in brain-destroying diseases.

A DIFFERENT APPROACH TO SCHIZOPHRENIA RESEARCH

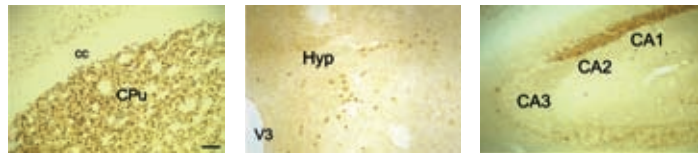
About a century ago, German psychiatrists identified a distinct mental illness characterized by rapid cognitive disintegration, usually beginning in the late teens or early adulthood, and called it “dementia praecox” (premature dementia). A few years later, the term schizophrenia, which means “fragmented mind,” came into popular use. Its cause was, and still is, unknown.

Today, much more is understood about the physical aspects of the disease, whose symptoms are characterized as either “positive” or “negative.” Positive symptoms, which are more dominant in the early stages, include delusions, hallucinations, and bizarre behavior. Negative symptoms, such as depression, social withdrawal, apathy, and poor communication skills, are more prevalent and severe in the later stages. But even within these relatively well-defined phases, people exhibit widely diverse symptoms. One person in the positive phase may suffer from delusions and hallucinations, while another may have the unreal conviction that he or she is an alien from another planet. Thus, one of the most frustrating aspects of schizophrenia is the lack of treatments that are effective for everyone.

Most schizophrenia drugs work by blocking receptors for dopamine, a neurotransmitter that regulates behavior, cognition, motor function, and addiction in the brain region known as the striatum. The drugs are most effective during the positive phase of the illness when dopamine levels are highest; they are largely ineffective against negative symptoms. Thus, it is estimated that as many as 25 percent of patients are not helped by currently available drugs.

“Many people with schizophrenia live on a rollercoaster, going on and off different drugs as they and their doctors search for the one that might →

Different regions of the brain express the striatal transcription factor Bcl11b, which is important for the control of gene expression in Huntington's disease.



relieve symptoms,” Thomas says. “With a disease estimated to affect about one percent of the population worldwide, that is a lot of people for whom little can be done.”

Thomas and her team are investigating what goes awry in schizophrenia at the level of the gene. Using microarray technology, a method that enables analysis of thousands of genes at once, Thomas searches for gene expression patterns in post-mortem tissues from the brains of schizophrenia patients who died after having the disease for differing periods of time—two years from initial diagnosis to as long as 53 years of illness. The tissue is provided by the brain bank at the Mental Health Research Institute of Victoria, Australia.

Thomas has already found a striking number of dysfunctional genes—as many as 3,000—in the tissue samples of those individuals who died within five years of disease onset, as opposed to perhaps 300 abnormal genes in those who had lived longer with the disease. This discovery supports the idea that gene expression is vastly different over the course of the disease and thus should be treated differently at different stages.

“Our studies underscore the idea that early intervention is critical,” Thomas says. “It seems that the longer genes are allowed to express themselves fully, the higher the probability that they will trigger a downward spiral of physical and mental symptoms.”

A MOVING TARGET

In additional studies, Thomas is studying the genetic causes for the wide behavioral variations, or the heterogeneity, seen in schizophrenia.

“If we could link the many behavioral subtypes to specific gene profiles, then it might be possible one day to sit down with a newly diagnosed person, match the gene profile to his or her specific subtype, and prescribe an individual treatment plan,” she says. “This

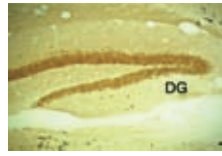
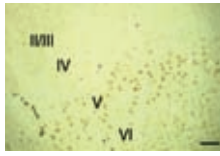
is the personalized medicine we hear so much about these days, and in a disease like schizophrenia it may very likely turn out to be the most effective route.”

Thomas is also investigating one of the most troublesome aspects of anti-psychotic treatment—weight gain. “Excess weight puts a person at risk for diabetes and heart disease, and even if someone is mentally ill, he or she doesn’t want to put on weight,” Thomas says. “This accounts for a lot of the non-compliance seen among schizophrenia patients. We are studying whether a simple step, like taking agents that alter cholesterol levels along with the anti-psychotic drugs, will neutralize this negative aspect of treatment.”

Thomas makes a point of reading accounts by those with mental illness, and cites the recently published memoir, *The Center Cannot Hold: My Journey Through Madness* by Elyn Saks, as a moving example of what it is like to live with schizophrenia.

In one passage, Saks writes about how hard it is for someone with schizophrenia to filter out external stimuli: “...every sight, every sound, every smell coming at you carries equal weight; every thought, feeling, memory, and idea presents itself to you with an equally strong and demanding intensity....you’re receiving a dozen different messages in a dozen different media ... it’s the crowd at the Super Bowl and they’re all yelling directly at you.”

Says Thomas: “Saks’ story illustrates the ongoing battle people with schizophrenia face in getting proper care and treatment over the course of their lives. In general, schizophrenia remains a poorly diagnosed, poorly understood, and inadequately treated illness, one that is especially heartbreaking because it strikes people in their teens and early 20s. Our gene expression studies are providing evidence that schizophrenia is not a static disease, but one that changes over time. These results may lead to a change in how the illness is treated.”



A FASCINATION WITH MOOD DISORDERS

Thomas's interest in the effects of drugs on the brain and central nervous system began while she studied for her doctorate in pharmacology at UC Irvine in the early 1990s. She came to Scripps Research in 1995 to pursue postdoctoral studies in genetic brain research in the lab of Professor Greg Sutcliffe, a pioneer in the study of gene expression in the brain.

"Greg has always been an incredible mentor to me," Thomas says. "He taught me always to ask myself, 'What are we going to learn from doing this particular experiment?'" In my studies of brain disorders, that remains the guiding principle."

Now, Thomas makes the time to bring several high school students and undergraduates into her lab each summer, mentoring them as they pursue interests in science, as she herself was mentored.

Two of Thomas's early projects as a postdoc were related to mood disorders. The first involved characterizing signaling pathways of certain newly discovered serotonin receptors. Fluctuations in serotonin levels in the brain alter mood, thus, many treatments for depression involve drugs that adjust serotonin levels. In another study, Thomas studied the effects of antipsychotic drugs, most of which act as dopamine receptors, on gene expression levels in the brain.

Thomas also began studying bipolar disorder as a postdoc, and it is an active area of investigation for her and her colleagues today. Bipolar disorder is similar to schizophrenia in several epidemiologic respects, including age of onset, lifetime risk, worldwide incidence, risk for suicide, and genetic susceptibility. The two diseases also show certain similarities in neurotransmitter dysfunction. Much debate still exists about the nature of the two illnesses—that is, whether they can be considered essentially the same, completely different, or whether they represent different points along a psychiatric continuum. Thomas has looked at differential gene expression between these two disorders; in particular, she has studied gene expression of apolipoprotein

D (apoD), a protein associated with high-density lipoproteins in human plasma. The gene for apoD is highly expressed in the brain, where, in a 2001 study, Thomas found that apoD expression patterns could differentiate between the neuro-anatomical sites that are important for schizophrenia and bipolar disorder.

PROGRESS AND HOPE IN HUNTINGTON'S DISEASE RESEARCH

Thomas's interest in Huntington's disease—which is characterized by progressively worsening involuntary movements, loss of intellectual faculties, emotional disturbances and premature death—was initially piqued by a Scripps Research friend and colleague who was at risk because her mother had the disease.

Accompanying her friend to support group meetings only intensified Thomas's resolve to study Huntington's disease, the most common inherited neurodegenerative disease. About one in 10,000 Americans has Huntington's disease and 150,000 people are believed to be at risk, meaning that one of their parents inherited the disease, giving them a 50 percent chance of developing it as well.

"It was unbelievably moving to witness how Huntington's disease rips apart those who have the disease, those at risk, and their families," says Thomas. "I felt I had to do whatever I could to help better understand this terrible disease that strikes people when they are relatively young—in their 40s or even younger, and still in the prime of their lives."

Huntington's disease is caused by a genetic mutation on chromosome 4 in which certain nucleotides—the chemical building blocks of DNA—are repeated many more times than normal. The nucleotides—cytosine (C), adenine (A) and guanine (G)—may be repeated anywhere from 40 to 100 times, with the large repeats resulting in a juvenile form of the disease (onset before 20 years of age); normally they would repeat →

less than about 35 times. Even as few as five to 10 extra CAG repeats are enough to cause Huntington's disease. Since nucleotides are the template for producing proteins, more CAG means more defective protein is made. The brain region most severely affected in this disease is the striatum.

"Even though the defective Huntington's gene has already been discovered and we know that the mutation is caused by CAG repeats, we still don't know how this results in the nerve cell death in the brains of people with Huntington's disease," Thomas says. "This disease is turning out to be very complex."

Thomas works with so-called "transgenic" mice—those whose DNA has been altered so that the mouse exhibits the characteristics of a specific disease, in this case, Huntington's—to try to understand the genetic basis for the disease. Using microarray technology, as in her schizophrenia studies, she has identified many genes expressed in the striatum of the transgenic mice that seem to be involved in both early and late stage neurodegeneration. In recent studies, Thomas and her Scripps Research colleagues discovered two important proteins called transcription factors, which act to control gene expression specifically in the striatum. They found that these proteins interact with the defective Huntington's disease protein to cause widespread disturbances in the striatum, thus further implicating this area of the brain in the pathology of Huntington's disease.

Because the brains of these Huntington's disease transgenic mouse models show high levels of abnormal gene expression, Thomas, in collabora-

"[My mentor, Scripps Research Professor Greg Suttcliffe,] taught me always to ask myself, 'What are we going to learn from doing this particular experiment?' In my studies of brain disorders, this remains my guiding principle."

BETH THOMAS, Ph.D.

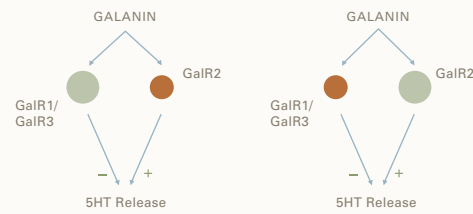
tion with Scripps Research Professor Joel Gottesfeld, Ph.D., has made progress investigating new drug candidates that may regulate gene expression to prevent Huntington's disease symptoms.

FAMILY, SURF, AND SNOW

Thomas and her husband, Steve Granger, an immunologist, live in Encinitas, California, where they are raising their children, Holly, 4, and Tom, 1. Surfing is a family passion—Granger makes the family's surfboards—and even little Tommy is already hitting the waves. Snowboarding is another longtime hobby—Thomas worked at Lake Tahoe before becoming a doctoral student in pharmacology at the University of California, Irvine in 1990. "We're waiting until the kids are a bit older before we begin snowboarding as a family," she says. In the meantime, Thomas practices yoga with her daughter and plays Ultimate Frisbee—a sport she played competitively prior to having kids—on Saturday mornings with a group of women who no longer have the time to train for competitions but still love the exercise and camaraderie.

All this outdoor, physical activity is a counterpoint to the many hours Thomas spends in her lab on the research she hopes one day may result in better lives for people with neurological diseases.

"In the end, nothing would make me happier as a scientist than to have a role in making it possible for people with schizophrenia to be able to function better in society, and to contribute to a possible cure for Huntington's," Thomas says. "These goals motivate me every day."



The Bartfai lab has shown that fluoxetine (Prozac) shifts the action of the peptide galanin in parts of the brain.

Searching for a Faster Antidepressant

(continued from page 05)

some ways. If you give animals Prozac, for instance, they will grow new neurons in their brains. This sort of observation has led many scientists to embrace the theory that antidepressants need to be neurogenic to work.

Galanin is a growth-promoting molecule, and its local expression is required for the growth of certain neurons. Several years ago, Bartfai and others hypothesized that targeting galanin receptors could have an antidepressant effect.

STEPS FORWARD

In 2005, Bartfai and his colleagues did an interesting experiment comparing the effects of Prozac, sleep deprivation, and electroconvulsive therapy on galanin levels in rats. They discovered that galanin was induced in many parts of the brain, along with the molecule that galanin interacts with—a protein called galanin receptor type II (GalR2). This increased expression occurred in many different parts of the brain, including those associated with depression. At the same time, the rats demonstrated fewer behavioral symptoms of depression.

In rats given Prozac for two weeks, the galanin system kicks in, says Scripps Research Assistant Professor Xiaoying Lu, who led the study with Bartfai. “It pointed to the possibility that GalR2 was mediating an antidepressant effect.”

The scientists thought galanin might just be mediating the effect of Prozac, so they did another study in which they gave rats Prozac for two weeks and then on the last day gave them a compound that blocks the GalR2 receptor. The effectiveness of the

Prozac declined.

Since 2005, the scientists have conducted studies to show that GalR2 is key to an antidepressant effect by working with a “knockout” mouse that has no GalR2 receptors. This mouse is persistently depressed, and these results raise hopes that GalR2 could be a target in the development of new antidepressants.

The current problem, though, is that scientists don’t have good compounds to activate this particular receptor selectively. The compound used in studies to date activates GalR2, but also blocks other types of receptors—indicating potential problems with toxicities or side effects.

What is needed, says Bartfai, is a clean selective GalR2 agonist. In recent years, he and his colleagues have been trying to create compounds that would target the galanin receptors more selectively. Bartfai and his team are collaborating with Scripps Research chemists Julius Rebeck, Ph.D., and Ed Roberts, Ph.D., in this endeavor.

Even if the scientists can find such a compound, a long road lies ahead in developing it into a drug. As with any pharmaceutical, it would face lengthy pre-clinical development and a rigorous approval process required by the U.S. Food and Drug Administration. Demonstrating the effectiveness of antidepressants is particularly complicated—as history has shown. “Remember,” says Bartfai, “Prozac had seven clinical trials before three could show conclusively that it worked.”

But lives are at stake and the scientists continue to work toward the next breakthrough antidepressant treatment that they hope will give faster relief.

THE LEGACY OF THE SKAGGS FAMILY

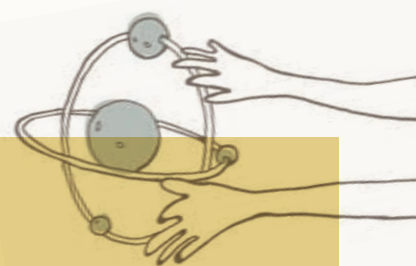
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SPECIAL TRIBUTE TO THE SKAGGS FAMILY

*“I am confident that,
teamed together, we can
and will continue to
achieve biomedical
milestones that further
advance health care and
my father’s vision.”*

CLAUDIA SKAGGS LUTTRELL





Dramatic Discoveries Open New Pathways for the Treatment of Disease

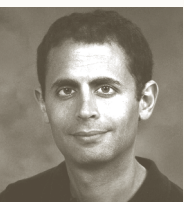
The Skaggs family has a vision—excellence in biomedical science and education that leads to new medicines, diagnostic tests, and methods to combat disease and promote human health. For more than two decades, the Skaggs family has supported efforts at The Scripps Research Institute to turn that vision into an unprecedented reality.

The family's gifts at Scripps Research have ranged from support of new facilities, such as the Aline W. and L.S. Skaggs Nuclear Magnetic Resonance Spectroscopy Center, to forward-thinking educational efforts, including the Skaggs Clinical Scholars Program, which brings together research-oriented clinicians with Scripps Research scientists.

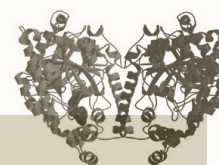
The centerpiece of the family's efforts has been the Skaggs Institute for Chemical Biology, established in 1996 with one of the largest gifts ever received by a biomedical research institute—a \$100 million pledge to Scripps Research by L. S. "Sam" and Aline Skaggs. By integrating the distinct but complementary expertise of chemists and biologists, the Skaggs Institute has had a profound effect on research outcomes.

During the past decade, virtually every major research center has sought to emulate this approach to biomedical research. From the University of California, Berkeley, to Harvard University, and from the University of Oxford to China's Peking University, the concept of chemical biology is now incorporated into leading research centers and universities around the world. Biologists ask key questions about human physiology and disease, and chemists facilitate therapeutic answers. For Scripps Research, the impact of chemical biology has been monumental. Not only has chemical biology laid the groundwork for Scripps Florida and its drug discovery program, the new discipline has led to an impressive list of research innovations and a generation of young scientists trained in the laboratories of the Skaggs Institute.

This is the first in a series of articles highlighting some of the many significant accomplishments made possible by the generosity of the Skaggs family. This installment features a few "bench to bedside" projects that Skaggs Institute investigators have brought to the point of clinical development.



BENJAMIN
CRAVATT, Ph.D.



Structure of FAAH as
determined by x-ray
crystallography

IN SEARCH OF NEW TREATMENTS FOR CHRONIC PAIN, INFLAMMATION, AND NEUROPSYCHIATRIC DISORDERS

Scripps Research Professor Benjamin Cravatt, Ph.D., who serves as chair of the Department of Chemical Physiology, has built a long-standing and successful collaboration with pharmaceutical giant Pfizer, Inc. to develop inhibitors for the fatty acid amide hydrolase (FAAH) enzyme. FAAH plays a key role in regulating a large number of signaling lipids in the nervous system and peripheral tissues. Cravatt's preclinical studies have shown that genetic or pharmacological blockade of FAAH produces a range of beneficial effects, including the reduction of pain, inflammation, depression, and anxiety.

Based on these results, Cravatt and Pfizer began a "Drug Pfunder" program in 2002 to develop potent and selective FAAH inhibitors for the treatment of chronic pain and inflammation, as well as neuropsychiatric disorders. Over the past five years, the team has taken the FAAH project from conception to a fully realized clinical candidate scheduled to enter its first in-human Phase I trials this year.

Along the way, the collaboration has produced an impressive number of key scientific advances, including the creation of a novel class of FAAH inhibitors displaying unprecedented potency and selectivity, and the determination that inhibition of FAAH reduces inflammation and pain responses in preclinical models of osteoarthritis.

"Uniting the basic research expertise of Scripps Research with the drug development process of Pfizer makes for an extremely potent combination that promises to accelerate generation of new therapeutics for the most pressing 21st century diseases," says Cravatt. "Without Skaggs support at the formative stages of our research, the path to FAAH discovery and drug development would not have been possible."

"Without Skaggs support at the formative stages of our research, the path to FAAH discovery and drug development would not have been possible."

BENJAMIN CRAVATT, Ph.D.



“We’re so appreciative of the Skaggs Institute funding that empowers us to do the painstaking, cutting-edge research required for development of first-in-class drugs. We hope to help people with disabling medical conditions that currently have no treatments.”

JEFFERY KELLY, Ph.D.

➤ HOMING IN ON FIRST-IN-CLASS DRUG THERAPIES FOR CARDIOMYOPATHY AND POLYNEUROPATHY

The misfolding and/or misassembly of proteins appears to be the underlying cause of many chronic and late onset neurodegenerative diseases including well-known conditions such as Alzheimer’s and Parkinson’s, as well as rarer diseases such as Huntington’s, familial amyloid polyneuropathy, familial amyloid cardiomyopathy, and inclusion body myositis. Scripps Research’s Jeffery Kelly, Ph.D., who is the Lita Annenberg Hazen Professor of Chemistry, is one of the world’s leading experts in protein misfolding diseases.

In 1997, Kelly and his colleague Evan Powers designed and synthesized several compounds that stabilized transthyretin, a protein found in blood. Transthyretin is the second most prominent blood protein and can be found in all of us. Unfortunately, in some people this protein misfolds and misassembles into a structured aggregate referred to as amyloid fibrils and this process, known as amyloidogenesis, can cause a variety of diseases. The molecules discovered in Kelly’s laboratory prevented this process of amyloidogenesis.

Kelly founded FoldRx Pharmaceuticals and Scripps Research licensed these compounds to the company, which took one of them into clinical trials. Having fared well in a Phase 1 trial, these compounds are currently being evaluated for use in treating familial amyloid polyneuropathy through a fully enrolled 120-person Phase II/

III placebo-controlled trial. Results will be available next summer. A similar underlying etiology appears to cause familial amyloid cardiomyopathy, a disease first characterized by Scripps Research Professor Joel Buxbaum, and senile systemic amyloidosis, which can cause heart disease in African-American and Caucasian men. These more prevalent diseases could be amenable to treatment by the Scripps Research/FoldRx compound.

The compound’s mechanism of action is novel and if the Phase II/III clinical trial is successful, it will be a first-in-class drug. This so-called “kinetic stabilizer” locks transthyretin into an active shape, precluding the process of amyloidogenesis that is thought to cause polyneuropathy and cardiomyopathy.

Through screening, Kelly’s laboratory also discovered that Diflunisal, which is a Merck non-steroidal anti-inflammatory drug, also acts as a “kinetic stabilizer.” Diflunisal is being evaluated for treatment of polyneuropathy by a National Institutes of Health/U.S. Food and Drug Administration-sponsored Phase II/III clinical trial.

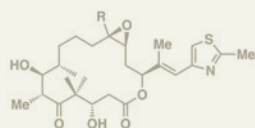
“We’re so appreciative of the Skaggs Institute funding that empowers us to do the painstaking, cutting-edge research required for development of first-in-class drugs,” says Kelly. “We hope to help people with disabling medical conditions that currently have no treatments.”



K.C. NICOLAOU, Ph.D.

“Being part of the Skaggs Institute is a wonderful privilege, one that allows me and my students to move quickly into new areas of research and to make breakthroughs that facilitate the drug discovery and development process.”

K.C. NICOLAOU, Ph.D.



epothilones A and B

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FROM THE BANKS OF THE ZAMBESI RIVER TO THE TREATMENT OF VARIOUS CANCERS

K.C. Nicolaou, Ph.D., who is Darlene Shiley Professor of Chemistry and chair of the Department of Chemistry at Scripps Research, has designed an epothilone—a compound in a newly discovered class of water-soluble molecules—which has been licensed by Abraxis, a California-based biotechnology company, for development as a potential “next-generation” anticancer drug. This synthetic compound is patterned after two naturally occurring epothilones found in certain bacteria collected from the banks of the Zambesi River in Southern Africa.

Currently in preclinical development, this epothilone analog holds promise for the treatment of various cancers, especially those resistant to Taxol®. Taxol®, a widely used anticancer drug, was synthesized in Nicolaou’s laboratory in 1994 in what is considered a classic feat in organic chemistry. Another epothilone from Nicolaou’s laboratory has entered Phase I clinical trials.

“Nature’s medicine cabinet is a wonderful source of cures for disease, especially cancer and infectious disease,” says Nicolaou. “Chemical synthesis is often inspired by the discovery of biologically active molecules from nature whose secrets we are still trying to unravel. These wonder molecules are found in the forest as

constituents of plants and trees, in the soil where bacteria and fungi wage chemical warfare against each other by secreting antibiotics, and in the ocean where marine creatures use cytotoxic agents as defenses against their predators.

“Scarce natural products endowed with important biological activities can be made in the laboratory in large quantities for biological and clinical investigations,” he continues. “Furthermore, synthetic chemists have the ability to fine-tune the molecular structures of these natural products in order to improve their pharmacological properties. It is in this way that chemical synthesis enables and facilitates biology and medicine.

Nicolaou’s new book, *Molecules that Changed the World* (Wiley-VCH, 2008), describes the enormous impact of chemistry on society.

“We are grateful to the Skaggs family for its generous support, without which we would undoubtedly not be where we are today in our research and educational endeavors,” says Nicolaou. “Being part of the Skaggs Institute is a wonderful privilege, one that allows me and my students to move quickly into new areas of research and to make breakthroughs that facilitate the drug discovery and development process.”



“Only through funding from the Skaggs Institute could such high-risk, high-reward studies be pursued in today’s funding environment.”

CARLOS BARBAS III, Ph.D.

❖ A NEW CLASS OF DRUGS FOR A WIDE RANGE OF INDICATIONS

A catalytic antibody discovery made at Scripps Research has formed the basis of the acquisition of biotechnology venture CovX by Pfizer. Empowered by compelling results in his laboratory’s development of a new class of drugs, Scripps Research Professor Carlos Barbas III, Ph.D., set out to found CovX in 2002. He teamed up with his colleague Scripps Research President Richard A. Lerner, M.D., with whom he had developed a unique and powerful class of catalytic antibodies.

This work offers a groundbreaking way to physically combine antibodies, which are large, soluble molecules that remain in the body for long periods of time, with small molecule drugs and peptides, which can kill disease-causing cells, but may be expelled from the body too quickly to be effective as a therapy. These hybrid molecules, called “chemically programmed antibodies,” have the desired properties of each—killing disease-causing cells and staying in circulation long enough to dramatically enhance the drug’s effectiveness.

The approach has led to a number of compounds under development against cancer, HIV-1, and metabolic disease. Barbas and his colleagues found that the hybrid molecules they developed had a profound effect on the size of tumors in mouse models, shrinking tumors of melanoma, breast, and colon cancer. “We were able to show the chemically programmed complex had at least 1,000-fold increase in the therapeutic effect compared with the small molecule alone,” says Barbas. “With that came the idea that this was too powerful an approach not to push into human studies.”

Today, two of the hybrid compounds developed by CovX have completed preclinical work with promising results as anti-tumor agents and have been approved for testing in humans. One compound just finished Phase I trials and a second just entered Phase I trials. A third and fourth compound to treat diabetes should be in human testing by the end of the year. This technology represents the first time catalytic antibodies have been used in human therapy.

“It’s very rare that an entirely new class of drugs is developed that can be applied in so many therapeutic areas,” says Barbas. “Only through funding from the Skaggs Institute could such high-risk, high-reward studies be pursued in today’s funding environment.”



You, too, can help support breakthroughs like these. To learn more about the Skaggs Institute and other initiatives at Scripps Research, or to make a donation, call the Office of Philanthropy at (858) 784-2915 (main office) or (561) 656-6400 (Florida). Also, see www.scripps.edu/philanthropy.

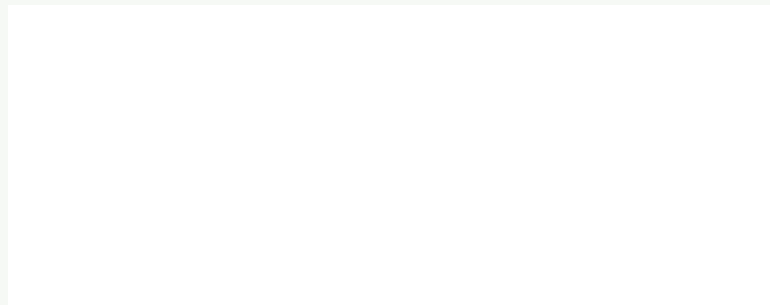


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