



# Discovery Research News

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## Our mission

The Alzheimer's Drug Discovery Foundation's (ADDF) sole mission is to rapidly accelerate the discovery and development of drugs to prevent, treat and cure Alzheimer's disease, related dementias and cognitive aging.

## Cancer Drug Surprise GCSF may treat Alzheimer's disease

The human growth factor drug *granulocyte colony-stimulating factor* (GCSF) has an established history of helping cancer patients. Now preliminary studies suggest that it may prove to be a highly effective therapy for Alzheimer's disease as well.

Juan Sanchez-Ramos, MD, PhD, and his colleagues at the University of South Florida's Alzheimer's Institute, came to the

reduced the levels of the brain-clogging protein beta-amyloid in a mouse model of Alzheimer's. It also increased production of new nerve cells in the brain and the connections between the nerve cells.

In laboratory experiments, the memory of Alzheimer's mice treated with GCSF improved within a few weeks to where they performed as well as normal mice

**"GCSF has been used and studied clinically for a long time but we are the first to apply it to Alzheimer's disease."**

— Juan Sanchez-Ramos, MD, PhD, University of South Florida

ADDF seeking funding to expand their mouse study using GCSF, which appears to heal damaged brain tissue. Instead of taking the next step in his animal experiments, the ADDF's Executive Director Howard Fillit, MD encouraged Dr. Sanchez-Ramos to launch a clinical study with humans, and that promising trial is now under way.

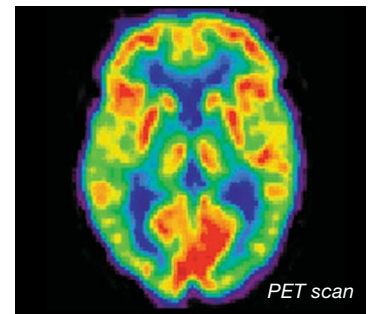
GCSF has for years been routinely administered to cancer patients because it helps boost immune system function after chemotherapy and radiation. The research team found that GCSF, which stimulates bone marrow stem cells, significantly

in tests evaluating their learning behavior.

The evidence that GCSF might help generate healthy brain cells originally came as a surprise. In Dr. Sanchez-Ramos' past research, also funded by the ADDF, he had found that in lab-grown bone marrow tissue, stem cells could be coaxed into developing into brain cells. After his finding, other researchers demonstrated in living mice that bone marrow stem cells can indeed travel into the brain. Subsequently, Dr. Sanchez-Ramos and his research team discovered that these stem cells matured in the brain and were actually able to remove deposits of beta-amyloid, *continued on page 2*

## Picture This A predictive tool for Alzheimer's disease

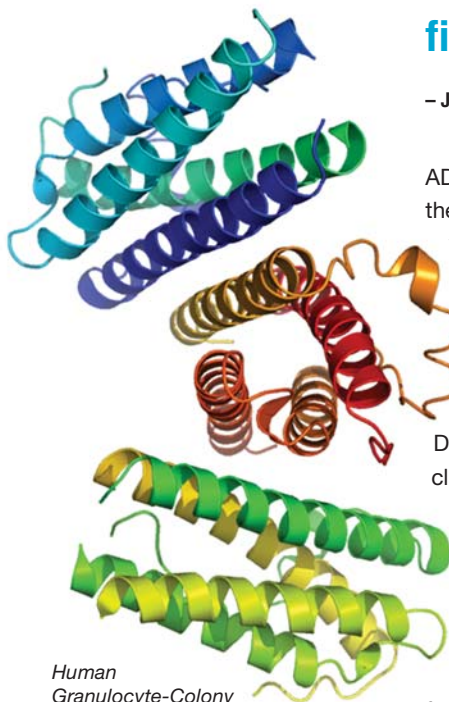
Today, due to the difficulty of diagnosing Alzheimer's disease, treatment often begins only after the disease has progressed, and a confirmed diagnosis of Alzheimer's can be



PET scan

achieved only with a post-mortem examination of the brain. To deal with these urgent problems, the biotechnology company Abiant, in Deerfield, Illinois, is developing a software technology that will be able to differentiate Alzheimer's disease from other dementias and detect disease changes early, before symptoms appear.

If successful, Abiant's work, which was funded by a \$200,000 grant from the ADDF, could also provide an important step in analyzing the effectiveness of drug regimens by using the company's refined positron emission tomography images (PET scan) interpretations to monitor drug effectiveness and adjust clinical trials accordingly. *continued on page 2*



Human Granulocyte-Colony Stimulating Factor (GCSF)

## Anesthesia compromises brain function in some patients

With help from the ADDF, Emmanuel Planel, PhD from the Université Laval in Quebec is searching for the causes of *postoperative cognitive disorder* (POCD), an impairment that can afflict older people after major surgery.

As part of his research, Dr. Planel is investigating the impact of anesthesia on elderly surgery patients, which may shed some light on the mysteries of POCD and, perhaps, the clinical onset of Alzheimer's.

The causes of POCD are unclear but the elderly seem particularly vulnerable. Past studies have shown that up to 50 percent of older patients suffer some degree of POCD — confusion, memory problems, difficulty concentrating — during the first week after major surgery. Up to 30 percent of them continue to show impairment 6 to 18 months later. These percentages are something to think about, given that some 7 million surgeries are performed on the elderly each year in the United States.



Dr. Emmanuel Planel

Dr. Planel conducted experiments which found that anesthesia can lead to changes in tau, a protein thought to kill neurons and that accumulates to form damaging deposits in the brains of Alzheimer's patients.

But there was more to the story. Dr. Planel also discovered that anesthesia can lower body temperature to 95° F or below during surgery, and can contribute to cognitive impairment, at least in mice. When Dr. Planel allowed

mice (genetically-altered to develop neurodegenerative disease) to become hypothermic while anesthetized, their brains accumulated *neurofibrillary tangles* containing tau. Those tangles were similar to ones found in Alzheimer's patients. When Dr. Planel kept the anesthetized mice warm, they did not develop the tau masses.

"In this case, it is the hypothermia that is causing tau to accumulate," he said, "and not the anesthetics per se." Dr. Planel is now exploring an important idea about why this happens, which holds out the hope of a new drug treatment for POCD: at low body temperatures, the function of an enzyme called *protein phosphatase 2* (or PP2A) becomes compromised, and when it does, tau protein is more likely to accumulate. He has been able to confirm this in animal experiments where he found that lab mice that were cold from starvation, insulin overdose, or even exposure to cold water, developed these tau accumulations.

Armed with those results, Dr. Planel began investigating ways to mimic the effects of warming patients during surgery with an Alzheimer's disease drug, and perhaps prevent tau changes. That is easier said than done, but he is focusing in on memantine, an FDA-approved drug for Alzheimer's disease that can activate PP2A.

With a \$100,000 research grant from the ADDF, Dr. Planel plans to administer memantine to brain cells at low temperatures. He will also give the drug to normal mice before anesthetizing them, as well as to mice that have been genetically modified to develop neurodegenerative disease. The goal, he explains, is to better understand what is happening in the brain at low body temperatures, and, perhaps, find a way to prevent the toxic effects on the brain during major surgery.

As with GCSF (see "Cancer Drug Surprise"), the fact that memantine is already an FDA-approved drug means that successful results with a mouse model could soon translate to human trials. ■

## ■ Cancer Drug Surprise *continued from page 1*

an important feature seen in the brain of Alzheimer's patients.

Alzheimer's damages the brain in many ways, Dr. Sanchez-Ramos points out: "You need a treatment that will protect cells from dying, enhance the production of the brain's own new neurons, and enhance synaptic connections," the links between nerve cells that enable them to communicate. Remarkably, in his mouse experiments, GCSF did all these things.

The preliminary human trial that the ADDF is now supporting with a grant of \$180,000 is enrolling 12 participants ages 55 and older, suffering from mild to moderate Alzheimer's. The 14-week, randomized, controlled

study is the first of its kind. As Dr. Sanchez-Ramos administers GCSF, he will use sensitive cognitive tests to look for improvements.

New drug development and FDA approval take years, often decades. The promise of this investigation lies in the fact that GCSF is already an FDA-approved drug. Thus, despite the trial's small size, it could have far-reaching results before long if the desired benefits in humans are achieved.

The best of all possible results of course would be as Dr. Sanchez-Ramos hopes: "GCSF may actually reverse the disease, not just alleviate symptoms like currently available drugs." ■

## ■ Picture This *continued from page 1*

Abiant's approach uses important advances in PET scans of the brain in combination with the company's own pattern-recognition tools for image analysis, which consolidate data from academic centers worldwide.

PET scans are not widely used to diagnose Alzheimer's disease now because results are so variable. Each machine and protocol can produce different images, leaving radiologists to interpret their scans subjectively. The promise of this Abiant work is a precise, automated measurement of metabolism in the hippocampus, a brain structure critical to new memory formation, which is compromised early in Alzheimer's disease.

The need for this program

results from the fact that Alzheimer's has no biomarkers, such as cholesterol for heart disease. In the absence of *biomarkers* for Alzheimer's, it is very difficult to track the effectiveness of treatments, or even confirm that the disease is present.

Preliminary work has already demonstrated that this approach is successful in distinguishing different dementias. In a test of 548 patients, Abiant's software accurately recognized fronto-temporal dementia, Lewy body dementia and healthy aging brains. The next steps for Abiant are to incorporate Alzheimer's disease into its analyses and then fine-tune its program to prepare the software for a commercial launch. ■

# What is drug discovery?

by Howard Fillit, MD

It is harder to develop a disease modifying drug for Alzheimer's disease than to put a man on the moon. How do we know this? Well, in fact, we have already put people on the moon. But we don't yet have disease modifying drugs for Alzheimer's disease. Indeed, creating a "little white pill" that can prevent and treat Alzheimer's disease, a scourge of old age known for millennia, is an incredibly hard thing to do.

Billions of dollars and decades of time have been spent on "basic" research in neurodegeneration, the kind of research conducted by scientists in universities and medical schools to understand the causes of Alzheimer's disease. Basic research results in potential new "targets" for the development of new drugs.

During the past 30 years, basic research scientists have made significant progress in understanding the causes and pathways of how Alzheimer's disease happens. We have learned about the "plaques" and "tangles" that may kill brain cells in Alzheimer's patients. But we have not been able to translate this knowledge into new drugs (yet!).

Having new targets for drugs from basic research is just the very beginning, the very earliest stages of developing a drug. Drug discovery and development costs about \$1.2 billion per drug, and it takes about 12 to 15 years to bring a drug to market. And this is a very risky proposition.

One way that drug discovery often begins is with a process called "screening." "Libraries" of 10,000 to 1 million chemicals are screened for activity against a new target (often cells or enzymes) that comes from basic research. Only one of these may eventually become a drug.

Another way drug discovery gets started is called "rational

chemistry." As opposed to "screening" (looking for a needle in a haystack or the shotgun approach), medicinal chemists get involved. Medicinal chemists are scientists who are specially trained in the synthesis of drugs. They know that while there are many trillions of chemicals in the universe, only a very, very small number of these chemicals have the special characteristics of drugs that can be taken by humans. Medicinal chemists are wizards. They can see molecules and change them to make new drugs. They are the ones who actually make the "little white pills" that can prevent and treat a disease.

But these early stages of drug discovery are still just the beginning of the process! After "leads" (potential drug candidates) are identified, they must be further tested in cells, and then in animal models of the disease to see if they work. Often, they are then altered and chemically "optimized" and



Howard Fillit, MD

improved. Developing an agent that gets into the brain is particularly difficult since the brain is protected by a special barrier. A drug for Alzheimer's disease must be able to cross this "blood-brain barrier" to access the brain and fight the disease.

Then, toxicity and safety testing begins. In the preclinical stages, optimized lead chemicals are tested by pharmaceutical scientists (another member of the drug discovery and development team)

## Big protein to little pill

### Delivering peptidomimetics across the blood brain barrier

The ADDF funds innovative research in Alzheimer's, related dementias and aging in the United States and around the world. In Austria, the ADDF has supported research at JSW Life Sciences, a company that specializes in animal models of brain disorders.

The ADDF's \$120,000 grant to JSW is focused on *beta-synuclein*. This peptide occurs naturally in the brain and may be able to counter the build-up of protein masses known as *Lewy bodies*, which are found in 60 percent of Alzheimer's patients and are also markers of Parkinson's and Lewy body dementia. In Alzheimer's patients, beta-synuclein may also be able to fight the accumulation of *amyloid plaques*.

The challenge in developing a drug targeting beta-synuclein is that it is a long chain of amino acids that is too big to pass through the brain's protective barriers when externally administered as a pill or an inoculation. A team lead by Dr. Manfred Windisch, PhD, CEO and President of JSW, is looking for a version of the peptide that will enter into the brain.

In pursuit of their goal, the research team used beta-synuclein's structure as a template to create several smaller compounds, *peptidomimetics*, with the aim of developing a pill that will send effective quantities of a molecule that mimics beta-synuclein into the brain.

With support from the ADDF, the most promising peptidomimetic was tested in a mouse model of Alzheimer's disease and the results were strong: it reduced brain damage from amyloid plaques by 80 to 90 percent, and improved memory in the experimental mice.

In addition to Alzheimer's disease, Dr. Windisch hopes that beta-synuclein-based drugs might eventually be used to treat Parkinson's and Lewy body dementia, which is a less common form of degenerative brain disease.

"All the data so far are certainly extremely promising," says Dr. Windisch. Future experiments will further characterize the peptidomimetic's properties, such as how fast it is metabolized and whether it might pose any safety risks. ■

for a whole variety of characteristics that may predict whether these leads will ultimately be safe in humans and not have dangerous side effects. Many potential drugs fail at this stage.

Finally, once an optimized lead chemical has been shown to be effective in an animal model, and without apparent toxicity to cells and animals, the lead may be chosen to be a "clinical candidate." This means that a decision has been made to bring the chemical into human testing for "drug development," requiring up to an additional seven years and hundreds of millions of dollars until drug approval, if successful. More on this in a later issue.

Funding is hard to come by for drug discovery stage research because it is so risky. Investors consider drug discovery too preliminary to invest in. Pharma-

ceutical companies have traditionally done most of this drug discovery work, but they are often unwilling to take risks on innovative therapies at the early stages of drug discovery.

This funding gap — translating an idea into a potentially new drug through drug discovery — is where philanthropy, like the Alzheimer's Drug Discovery Foundation, can play a meaningful role with relatively modest funds. Drug discovery research programs are high risk, but potentially have high reward. They feed the pipeline for clinical testing in humans. Philanthropy can provide catalyst funding to de-risk these programs so they can get more extensive funding for clinical development in the future.

With your help we can advance exciting ideas of today into the drugs of tomorrow for Alzheimer's disease, related dementias and cognitive aging. ■

## UPCOMING EVENTS

### ▶ **FOURTH ANNUAL CONNOISSEUR'S DINNER**

**April 29, 2010** ■ **New York City**

The Foundation's Fourth Annual Connoisseur's Dinner, "To Live is to Think," will be held at Sotheby's, New York. Event co-chairs are Leonard Lauder, the ADDF's Co-Founder and Co-Chairman, and Nancy Corzine, Board President.

### ▶ **MITOCHONDRIAL FUNCTION AS A THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE**

**May 13, 2010** ■ **New York City**

This symposium will explore the role of mitochondria in Alzheimer's disease pathogenesis and will feature presentations on therapeutic programs targeting mitochondrial pathways for Alzheimer's.

### ▶ **FIRST TASTE OF SUMMER**

**June 23, 2010** ■ **New York City**

The ADDF's Young Professionals Committee will host its *2nd Annual Taste of Summer* cocktail party at Bumble and Bumble.

### ▶ **11<sup>TH</sup> INTERNATIONAL ALZHEIMER'S DISEASE DRUG DISCOVERY CONFERENCE**

**September 27-28, 2010** ■ **Jersey City, NJ**

The ADDF's annual two-day global conference for research scientists from academia, industry and government facilitates collaboration and the sharing of scientific findings on Alzheimer's disease drug discovery research.

## ADDF Events Recap

The ADDF's 4<sup>TH</sup> **DRUG DISCOVERY FOR NEURODEGENERATION** conference was held on February 1-2, 2010 in Houston, TX. Designed as a comprehensive course, this conference provided scientists with fundamental knowledge and resources on creating new drugs to treat and prevent neurodegenerative disease. The meeting attracted 100 academic, industry and government scientists from around the world. ■ In tandem with the conference, the ADDF organized two special events in Houston for friends of the foundation. A cocktail reception was held on February 2, 2010 at the Houston Museum of Natural Sciences to provide information on current drug discovery research for Alzheimer's disease. Dr. Fillit spoke on February 3, 2010 at The Buckingham, Houston's premier five-star, resort-style retirement community. ■ **CHILI CHALLENGE** was held on February 27, 2010 at SideBar in New York City. Over 140 guests joined the ADDF's Young Professionals Committee to judge 17 chili-cooking teams. ■ **A SCIENTIFIC UPDATE** for contributors to the *Fund for Alzheimer's Drug Discovery* was held at Nancy Corzine's New York City home on March 3, 2010. The Fund has invested a total of \$2 million to date in 8 biotechnology companies that have promising, novel drug discovery programs for Alzheimer's disease and related dementias. ■ Dr. Fillit participated in the **ALZHEIMER'S DISEASE: HOW STEM CELL RESEARCH WILL MAKE A DIFFERENCE** panel discussion with leading stem cell scientists, policy makers and patient advocates. The event was hosted on March 25, 2010. During the event, the New York Stem Cell Foundation announced the launch of the *Alzheimer's Disease Stem Cell Research Program*, which they are undertaking with support from the ADDF and the New York Community Trust. ■ The ADDF presented a panel session entitled **ALZHEIMER'S DRUG DISCOVERY IN NEW YORK CITY** for the New York Academy of Biotechnology Association's annual conference on April 20, 2010.



Attendees enjoying a Connoisseur's Dinner.

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