



# DISCOVERY RESEARCH NEWS

*Vol. 1 Spring 2006*

## *Inside This Issue*

Founding Executive Director **Dr. Howard Fillit** explains ADDF's biomedical venture philanthropy model (*Page 2*)

**Dr. Frank Longo** develops small protein mimetics that could **protect brain cells** (*Page 3*)

**Dr. Abraham Fisher** tests a promising **new drug for AD** (*Page 3*)

Learn about **Clinical Trials** for **Alzheimer's** (*Page 4*)

Studies show **Exercise** Improves **Cognitive Function** (*Page 4*)

## *In Our Fall Issue ...*

Is there a drug in **red wine** that is good for the **mind**?

Ways to achieve and maintain **Cognitive Vitality**

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## MESSAGE FROM THE PRESIDENT

*Nancy Corzine*

As the President of the Alzheimer's Drug Discovery Foundation Board of Directors, I am thrilled to introduce our first issue of Discovery Research News. We have been quietly building our charity over the past year and are now ready to open our doors to the community-at-large.

Hearing about the promising results of our grant-funded scientists has made me optimistic about the future. I have the greatest confidence in the decision-making process of our expert Scientific Review Board, Executive Director and Board of Directors. We are taking the risk of investing in novel drug discovery research that will ultimately generate new drugs for AD.

As a businesswoman, I know what it takes to build a smart, innovative and effective company. With Leonard and Ronald Lauder's guidance as Co-Chairpersons, the ADDF is doing just that.

When others partner with us, they know that 90 cents of each dollar contributed goes directly to drug discovery research because the Institute for the Study of Aging (ISOA), an affiliated Lauder family foundation, supports ADDF's administrative overhead.

As the caregiver for my beloved mother who suffered from this devastating illness for over eight years, I know how Alzheimer's disease affects not only patients, but families, our healthcare system and economy. It is imperative that we find a cure. The only way to do this is by working together to accelerate the discovery of new drugs for Alzheimer's disease.

## CREATING A NEW BIOTECH TO ACCELERATE DRUG DISCOVERY: A "DAVID AND GOLIATH" STORY

One hundred years ago, Dr. Alois Alzheimer performed an autopsy on a 51-year-old woman who was senile, losing her mind prematurely. Under the microscope, he saw amyloid plaques and tangled neuronal fibers in the woman's brain. Alzheimer's disease was discovered.

We now know that the plaques contain a small protein called beta-amyloid, derived from a larger molecule known as amyloid-beta precursor protein (APP). Beta-amyloid kills neurons, impairs memory, and may cause Alzheimer's disease. Reducing the formation of beta-amyloid is a major goal in drug discovery for Alzheimer's disease, and should slow the progression of the disease and even prevent it.

Beta-amyloid is formed from APP by two enzymes: beta-secretase and gamma-secretase. Inhibiting these enzymes prevents beta-amyloid formation. Inhibiting gamma-secretase appears to be more difficult, and may have more toxic side effects. Inhibitors of beta-secretase have more exciting potential as new Alzheimer's drugs.

In 2000, Jordan Tang, PhD, and his team at the Oklahoma Medical Research Foundation were the first to crystallize beta-secretase. Understanding the crystal structure of a target molecule is a key first-step in developing new drugs. Dr. Tang succeeded because he is a leading international expert in the medicinal chemistry of aspartyl proteases, the class of enzymes that include beta-secretase.

*Continued on Page 3*



## EXECUTIVE DIRECTOR'S REPORT

*Howard Fillit, MD*

The Alzheimer's Drug Discovery Foundation (ADDF) funds novel research in the discovery and development of new drugs for Alzheimer's disease and related dementias throughout the world. In doing so, ADDF fills the financing gap for high risk, early-stage drug discovery in both academia and in biotechnology companies. To advance our mission, we adapted the principles of venture capital investing to our philanthropic model. Our biomedical venture philanthropy uses a proactive approach to funding, providing strategic assistance to scientists to help them successfully achieve their goals.

Our results demonstrate considerable progress. To date, we have awarded \$25 million for 155 research programs and conferences in 12 countries. ADDF scientists have screened millions of chemicals, developed new classes of drugs, executed numerous licenses and patents, created new biotechnology companies, and brought new drugs into clinical trials for Alzheimer's Disease. As a measure of success, we have received returns on our investments.

ADDF drug discovery programs clearly provide hope that an effective drug to treat or prevent Alzheimer's disease is achievable in the coming decade. Yet, many good ideas for new drugs for Alzheimer's disease remain unfunded.

This newsletter provides exciting and promising news on drug discovery research for Alzheimer's disease. Contact me at [hfillit@alzdiscovery.org](mailto:hfillit@alzdiscovery.org) to find out more about the work we support, or to discuss ways we can work together to accelerate drug discovery for Alzheimer's through venture philanthropy.

## Facts About Alzheimer's Disease (AD)

AD is a neurodegenerative disease that causes progressive, irreversible loss of cognitive function. The following facts illustrate the compelling and timely need to develop new drugs for this fatal condition:

- Presently, there are 18 million cases of AD worldwide and this number is expected to increase to 34 million by 2025.
- AD affects 1 in 10 people over age 65, 1 in 4 over age 75, and 1 in 3 over age 80.
- AD costs U.S. society over \$100 billion annually, making it the third most costly disease after heart disease and cancer.
- A person with AD will live an average of 9 years with progressive loss of mind.
- There are only 4 moderately effective AD symptom-treating drugs on the market and no drugs that treat the underlying neurodegenerative process.

## What's Happening?

**RECENTLY...** *ADDF/Élan Awards Luncheon: January 26, 2006*

The Alzheimer's Drug Discovery Foundation and Élan Pharmaceuticals, Inc. held a luncheon in New York City to announce the winners of their new collaborative research program, *Novel Approaches to Drug Discovery for Alzheimer's Disease*. Four recipients were selected from a competitive pool of 45 scientists from 12 countries. More than 40 guests attended this first annual event at the Lotos Club.



*Kelly Martin, President & Chief Executive Officer, Élan Corporation, Inc. and Leonard Lauder, Chairman, Estée Lauder Companies Inc. and Co-Chairperson, ADDF*



*Award Recipients: (Left) Steven S. Schreiber, MD; Berislav Zlokovic, MD, PhD; Greg R. J. Thatcher, PhD; Nicholas Webster, PhD*

**COMING UP...**

August 7, 2006, Aspen, Colorado

*New Discoveries in Alzheimer's Disease:*

*Conversations with Doctors Howard Fillit and Jordan Tang*

October 11, 2006, New York City

*Dine & Learn: The latest Alzheimer's Research*

October 12-13, 2006, New York City

*7th International Conference on Alzheimer's Disease Drug Discovery*

For event information contact:  
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In 2002, ISOA helped Dr. Tang to co-found a biotechnology company named Zapaq. This initial seed-funding enabled Zapaq to develop its research to the point where a major venture capital company stepped in with millions of dollars in follow-on funding and critical management assistance.

Today, Zapaq has successfully developed candidate drugs that can be taken orally and get into the brain to inhibit beta-

secretase and prevent amyloid formation in animal models of Alzheimer's disease. The company hopes to begin human Phase I clinical trials in early 2007.

Though still a small biotechnology company created just a few years ago by ISOA's venture philanthropy funds, Zapaq may be the "David" biotech that beats the "Goliath" large pharmaceutical companies to create the first disease modifying drug for Alzheimer's disease.

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## NICOTINE FOR ALZHEIMER'S DISEASE?: A NEW DRUG SHOWS PROMISE

There are several neurochemical systems in the brain. The cholinergic system mediates memory and learning, and is impaired in Alzheimer's disease. There are 2 cholinergic subsystems, the nicotinic and muscarinic systems. Both are activated by the neurotransmitter acetylcholine. Neurotransmitters are chemicals that carry signals from one neuron to another.

Today, there are 3 cholinesterase inhibitor drugs approved by the FDA. They prevent the breakdown of acetylcholine and improve cognition, function and behavior in patients with Alzheimer's disease.

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**AF267B reduced amyloid production, prevented brain cell injury, and improved cognition in a mouse model of Alzheimer's disease.**

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One type of cholinergic drug being developed for Alzheimer's disease directly activates the nicotinic subsystem. These drugs also improve cognitive function, may have an effect on amyloid formation, but may not have the side effects generally associated with nicotine itself (such as increased heart rate and gastrointestinal problems).

Another type of cholinergic drug activates the muscarinic subsystem. In fact, muscarinic drugs have already been tested in patients with Alzheimer's disease by pharmaceutical companies. The problem with muscarinic drugs to date has been primarily side effects such as dry eyes and dry mouth.

Abraham Fisher, PhD, of the Israel Institute for Biological Research, is a leading expert on drugs that activate the muscarinic system. Fisher synthesized a new muscarinic drug called AF267B that is more specific for the brain and should not have the side effects of previous compounds. It reduced amyloid production, prevented brain cell injury, and improved cognition in a mouse model of Alzheimer's disease. Some of the initial studies on AF267B were funded by ISOA. AF267B is now being developed by Torrey Pines Therapeutics, and is in early stages of human clinical trials for Alzheimer's disease.

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## MIMICS TO PROTECT THE BRAIN

Our brain's 100 billion neurons receive, process and transmit information to form thoughts and memories. Neurons are dependant on molecules called neurotrophins for their survival and the formation of the critical communication connections between neurons.

Scientists have long sought to harness the powers of neurotrophins into a drug to treat neurodegeneration and improve brain function. A neurotrophin-based drug could be used to treat Alzheimer's disease.

There are barriers to developing a neurotrophin drug. Most drugs are small molecules, but neurotrophins are large. If given orally, they would be degraded in the stomach and lose activity. Even if they passed into the blood, they could not enter the brain's protective barrier, the blood-brain barrier. Small molecule drugs that "mimic" the neurotrophins need to be developed.

Frank Longo, MD, PhD, Chairman of Neurology at Stanford University, is developing neurotrophin mimetics with funding from ISOA, ADDF's affiliated private foundation. These mimetics imitate the function of neurotrophins, are small enough to be taken orally, and get into the brain. Dr. Longo's neurotrophin mimetics are an entirely new class of potential Alzheimer's disease drugs.

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**A neurotrophin-based drug could be used to treat illnesses in which there is significant neuron injury, such as Alzheimer's disease.**

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Recently, Dr. Longo showed that neurotrophin mimetics can be administered orally and reach the brain in high doses without toxicity in an Alzheimer's mouse model. One compound prevented neuronal damage produced by beta-amyloid, the protein believed to cause Alzheimer's disease.

Dr. Longo hopes to begin human clinical trials soon. To accelerate his drug discovery and development work, ADDF is assisting Dr. Longo in founding a biotechnology company dedicated to the development of neurotrophin mimetics.

## GLOBAL CLINICAL TRIALS

Clinical trials determine if a promising Alzheimer's disease (AD) treatment is safe and effective for patients, and can be approved by the FDA. These trials may evaluate drugs already approved for other diseases to assess if the drug may be useful for Alzheimer's disease. They may also evaluate new experimental drugs derived from drug discovery to determine if they improve cognitive function, lessen symptoms, slow disease progression of AD or even prevent it.

Experimental drug trials are conducted in three phases. Phase I trials are conducted with a small number of volunteers over a short period of time to determine safety. Phase II and III trials involve larger numbers of people over longer periods of time to study safety and effectiveness.

It is important for patients and family members to understand as much about a trial as possible before volunteering. The following is a brief sampling of exciting clinical trials for Alzheimer's disease taking place in the U.S., Canada and Europe. To learn more about these clinical trials, visit the **NIH/FDA database at <http://clinicaltrials.gov>**

Scientists at the University of California, Los Angeles are recruiting patients for a Phase II study to examine the safety and tolerability of two different doses of curcumin in patients with mild-to-moderate Alzheimer's disease. Curcumin, found in the spice turmeric (or "curry"), has antioxidant, anti-inflammatory and cholesterol-lowering properties, making it a good candidate for preventing and treating AD. The study is being supported by the John Douglas French Foundation and the Institute for the Study of Aging.

Élan Pharmaceuticals is recruiting patients for a Phase IIA study to assess the safety and tolerability of multiple doses of AAB-001, a vaccine that targets beta-amyloid in patients with mild-to-moderate AD. It is thought the injections of antibody in the vaccine can remove amyloid from the brain of patients with the disease. The study is being conducted in 21 cities throughout the US.

Myriad Genetics is recruiting patients for its Phase III trial to evaluate the experimental drug MPC-7869. One possible mechanism of the drug may be to reduce amyloid formation by inhibiting gamma-secretase. Patients will be given 800mg of MPC-7869 or a placebo twice daily for 18-months. The study will take place in cities throughout the U.S., Canada and Europe.

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### CAN EXERCISE LEAD TO NEW DRUGS FOR ALZHEIMER'S DISEASE?

We know exercise is critical to maintaining a healthy body. Now we know that it also improves brain health.

At the Karolinska Institute in Sweden, Dr. Miia Kivipelto studied approximately 1,500 people ages 65 to 79 whose physical activities were monitored every five years from 1972 through 1987. Dr. Kivipelto discovered that people who did aerobic exercise, such as brisk walking, at least two days a week had 60 percent lower risk of developing Alzheimer's disease than people who did not exercise.

Recent results confirm these findings. Dr. Eric Larson and colleagues at the University of Washington followed 1,740 individuals age 65 and older for an average of six years, collecting information on cognitive function, health, exercise and lifestyle. Participants reported the number of days per week they engaged in at least 15 minutes of physical activity such as walking, bicycling, aerobics and stretching. People who exercised at least three times a week had a 40 percent lower risk of developing dementia.

Art Kramer, PhD, at the University of Illinois, wanted to understand how exercise prevents Alzheimer's disease. He tried to determine if exercise causes a change in the brain of older people who exercise by using scans such as MRI. In a study funded by the Institute for the Study of Aging,

ADDF's affiliated private foundation, Dr. Kramer studied two groups of older adults, aged 60-80. The aerobic exercise group walked briskly three times a week for an average of 30 minutes for six months. The control group did only stretching exercises. The results showed that the group of older people who walked experienced a substantial improvement in their cognitive function as measured by psychological tests, and significant improvements in brain volumes measured by MRI. The group that did not walk showed declines in cognitive function and brain volumes.

What are the implications for drug discovery? Understanding how aerobic exercise improves memory and cognition will give us clues to new drugs. We already know from studies in animals that aerobic exercise causes the release of important neuroprotective molecules in the brain. Drugs that mimic the effects of exercise on the brain can be developed to prevent and treat Alzheimer's disease.

### WHAT IS DRUG DISCOVERY RESEARCH?

Unlike basic research that tries to understand the causes of a disease, drug discovery research is the process by which new drugs are actually created.

This involves screening large numbers of chemicals; identifying active compounds; optimizing their activity through chemistry; testing them in the laboratory and in animal models; and proceeding to human clinical trials.