

The ADDF Drug Discovery for Neurodegeneration Conference was held on February 5-6, 2007, at the Westin Hotel in New York City. It attracted 150 attendees from the pharmaceutical and biotechnology industries and international academic institutions. The focus of the meeting was on increasing scientists' knowledge of the principles and practices of drug discovery for AD and other neurodegenerative diseases, including Parkinson's, Huntington's and Amyotrophic Lateral Sclerosis.

This comprehensive two-day conference gave participants numerous resources and step-by-step instructions on how to develop drug discovery research programs specifically for neurodegenerative diseases. It also addressed barriers and challenges associated with target identification and validation, lead discovery, lead identification and optimization, pre-clinical proof-of-concept and development, drug delivery technologies to the central nervous system, partnering and other models for advancing drug discovery, business development and technology transfer in neurodegeneration.

Conference attendees evaluated the sessions so highly that ADDF will be offering another neurodegenerative disease conference next year. It is tentatively scheduled for February 4-5, 2008 in the Washington, DC area. For more information, please refer to the ADDF website at [www.alzdiscovery.org](http://www.alzdiscovery.org).



**THANK YOU TO OUR MEETING CO-SPONSORS, EXHIBITORS AND ADVERTISING PARTNERS**

**Co-Sponsors:** Athenagen and Ortho-McNeil Neurologics

**Exhibitors:** DOV Pharmaceuticals, Inc., Children's Tumor Foundation, BIOMOL International, LP, Marriott Vacation Club and Parkinson's Disease Foundation

**Advertising Partners:** Alzheimer's Research Forum, rPeptide, American Aging Association and abcam

**ADDF PUBLISHES RECOMMENDATIONS FOR BEST PRACTICES IN THE TREATMENT OF ALZHEIMER'S DISEASE**

The ADDF published recommendations for best practices in the treatment of Alzheimer's disease and related dementias (ADRDs) in managed care in a supplemental issue of the December 2006 *American Journal of Geriatric Pharmacotherapy*. The manuscript was written by Dr. Howard Fillit and a panel of 12 leading experts that held a meeting at the ADDF offices last fall.

Based on available evidence and the informed opinion of the panel experts, the supplement provides practical advice for physicians, medical and pharmacy directors and other healthcare providers regarding early diagnosis, treatment and monitoring of ADRDs. It also addresses societal and managed care implications of the disease.

To obtain a copy of the full publication, contact ADDF Partnership Relations Manager Filomena Machleder at 212-901-8004 or [FMachleder@alzdiscovery.org](mailto:FMachleder@alzdiscovery.org).

A sampling of the recommendations are as follows:

- Screening for cognitive impairment should be conducted, especially for individuals age 75 and over.
- When cognitive impairment is detected, a structured approach to diagnosis should be used. Assessments should include evaluations of cognition, function and behavior.
- Neuroimaging should be conducted as part of a complete diagnostic assessment.
- AD treatment should be determined by the stage of the disease at the time of diagnosis.
- Newly diagnosed patients should be re-evaluated within 2 months and monitored at least every 6 months to ensure appropriate treatment.
- Patients and caregivers should be counseled on realistic expectations of anti-dementia treatment.

**CREDITS:**

Suzanne Grossberg, *Editor-In-Chief* Howard Fillit, MD, *Writer & Editor* Antony Horton, PhD, *Writer* Filomena Machleder, *Writer* Rachel Mante, *Designer*



DISCOVERY RESEARCH NEWS

Vol. 3 Spring/Summer 2007

*Inside This Issue*

**Howard Fillit, MD** explains Dr. Alois Alzheimer's discovery and legacy (Page 2)

**Ely Simon, MD** develops computerized cognitive test for AD comparable to the blood pressure cuff (Page 3)

**Leonard Petrucelli, PhD** finds drug to induce chaperone formation and prevent amyloid aggregation (Page 3)

**Drug Discovery Conference** attracts 150 international scientists (Page 4)

**Best Practices in the Treatment of AD** published in the *Journal of Geriatric Pharmacotherapy* (Page 4)

*In Our Next Issue*

Developing **memory-enhancing** drug targets

Discovering novel therapeutics for **Early Alzheimer's disease**

To subscribe to our **FREE** newsletter contact us at:

**1414 Avenue of the Americas**  
Suite 1502  
New York, NY 10019  
P: 212-935-2402  
F: 212-935-2408  
[www.alzdiscovery.org](http://www.alzdiscovery.org)



**BOARD OF DIRECTOR'S MESSAGE**

*Jon Rotenstreich*

As an investor who has seen the impact of Alzheimer's disease, it is a privilege to be a member of the Alzheimer's Drug Discovery Foundation (ADDF) Board of Directors. The ADDF is like no other charity because it has a highly focused mission and applies venture capital business practices to its grant programs. That is why I joined the Board and wanted to help them capitalize on their exceptional assets.

Toward that end, we developed a separate charitable investment vehicle known as the Fund for Alzheimer's Drug Discovery. The Fund's purpose is to accelerate drug discovery for Alzheimer's disease by making grants to biotechnology companies and academic research centers. ADDF grants enhance a tax deductible contribution with a performance based return of capital to a donor designated 501(c)(3). The grants are the product of the focus and investment choices of Dr. Howard Fillit and the Fund Board of Advisors. The Fund seeks to raise \$10 million, in contribution units of \$50,000 each, over 30 months. A minimum of \$1 million was needed to be raised by April 1, 2007 to commence Fund operations.

I am thrilled to report that as of January 29, we raised \$1.8 million, including a generous \$1 million lead contribution from the Aetna Foundation, Inc. Consequently, we are now preparing to make our initial investments. I encourage anyone interested in finding a cure for Alzheimer's to contact the ADDF and participate in this unique opportunity.

**TARGETING TAU**

There are several neurodegenerative diseases that are collectively referred to as "tauopathies". The tauopathies include fronto-temporal dementia (FTD), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). Alzheimer's disease (AD) is also known to undergo processes that are the characteristic hallmarks of these conditions, although it is still unclear whether this is the chief causative agent in the disease. Over a decade of research has shown that these conditions have a fundamental mechanism underlying the disease process that is centered on the microtubule associated protein "tau".

Tau proteins act together with other proteins called microtubules within nerve cells. The microtubules are structural components that help to internally stabilize nerve cells, forming part of the cellular "skeleton". Together, tau proteins and microtubules form tracks for material transport in nerve cells and are therefore essential for cell specialization, growth and synapse formation.

*It is clear that earlier research on the mechanisms underlying tauopathies has progressed to the point that promising therapeutic strategies targeting tau are now emerging.*

In normally functioning nerve cells, tau proteins undergo a process called phosphorylation that causes them to detach from the microtubules. In FTD and AD, tau proteins form abnormal deposits of aggregated tau protein. The aggregated tau protein is often severely modified through a process called "hyper-phosphorylation". The hyper-phosphorylation of tau leads to massive detachment of tau, which in turn greatly reduces the stability of microtubules



## EXECUTIVE DIRECTOR'S REPORT

Howard Fillit, MD

When Dr. Alois Alzheimer first described AD in 1906 in a 51-year-old woman, he noted her clinical condition as a "presenile dementia." But it was not until she died and he performed an autopsy that the disease was fully described as a "clinical-pathological" syndrome. Professor Alzheimer discovered the unique pathology that the woman suffered from when he saw it under the microscope. What did Alzheimer see?

Using novel dyes, he stained her brain and saw abnormal structures he called senile plaques and neurofibrillary tangles. To this day, his findings remain the sentinel clues to AD. We now know the senile plaques are composed of amyloid. Preventing amyloid deposition in the brain is a focus of current research.

We have also learned that the neurofibrillary tangles are the tombstones of dying and dead neurons (brain cells). The loss of these brain cells leads to cognitive decline and dementia. Furthermore, we understand that the tangles are composed of excess accumulations of an important neuronal protein called "tau." As described in an adjacent article, preventing tau accumulation has become a leading AD drug target.

Thus, Dr. Alzheimer's careful observations of his patient and thorough investigation of her brain have left a great legacy. ADDF/ISOA are funding scientists who are harvesting the fruits of his discovery in order to prevent and treat the loss of mind that continues to afflict the aging brain. In reviewing the numerous research programs being conducted today, we are hopeful that within the next five years there will be effective disease modifying drugs available.

## What's Been Happening?

### CONNOISSEUR'S DINNER: AN EVENING OF WINE AND ART

The ADDF, in partnership with Sotheby's, hosted its first-ever Connoisseur's Dinner on Wednesday, May 2, 2007. The event featured an extraordinary red wine tasting and auction to benefit Alzheimer's research. A special spring menu, focused on healthy dining for improving memory wellness, was created by renowned Chef Daniel Boulud. The event took place at Sotheby's 10th floor galleries, 1334 York Avenue at 72nd Street, in New York City.

ADDF Co-Chairperson Leonard Lauder and President Nancy Corzine chaired the dinner along with Honorary Chairs Cece Cord and Dr. John Baldwin, Francine LeFrak and Rick Friedberg, Anne Hearst and Jay McInerney, James and Lee Niven and Bill and Betsey Ruprecht.

Guests were treated to an exclusive preview of Sotheby's equiste Impressionist and Modern Art exhibit. The auction included rare wines; a lifetime membership to The Napa Valley Reserve and winery visit for eight with accommodations at the Meadowood Napa Valley; an Art Basel Miami Beach VIP package for four with accommodations at the Ritz-Carlton provided by NetJets; and a French winery tour and tasting at Château Mouton Rothschild for four with accommodations at the Plaza Athénée in Paris and flights provided by L'Avion.

The evening was a resounding success, attracting 225 people and raising nearly \$800,000. Additionally, two artists, Chuck Close and Ed Ruscha, donated artwork that was previewed at the event and will be auctioned in Sotheby's fall art auctions. Proceeds from the sales will benefit the ADDF.

Due to such a positive response, ADDF is offering the event again. Mark your calendars for our Second Annual Connoisseur's Dinner on May 1, 2008.

### ADDF/ELAN SCIENTIFIC AWARDS LUNCHEON

The ADDF and Elan Pharmaceuticals, Inc. held it's Second Annual Scientific Awards Luncheon at the St. Regis Hotel in San Francisco, CA. The luncheon recognized the winners of their partnership grant program, *Novel Approaches to Drug Discovery for Alzheimer's Disease*. Six recipients were selected from a highly competitive pool of 32 scientists from 6 countries.

*For upcoming events, visit [www.alzdiscovery.org](http://www.alzdiscovery.org)*



(Left) Leonard Lauder and Nancy Corzine



(Left) Cyrus Vance, Jr. and Jamie Niven



(Left) Mark Germano and John Cooney



(Left) Dr. John Baldwin, Jay McInerney and CeCe Cord



(Left) Gary Cooney, Maria Norem, Carol Norfleet and Philip Norfleet



(Left) Tom Quick, Hilary Geary Ross and Wilbur Ross



(Left) Dr. Dale Schenk  
Dr. Donald Porter  
Dr. Howard Fillit  
Dr. Marty Watterson  
Nancy Corzine  
Dr. Lars Eckman  
Dr. Juan Sanchez-Ramos  
Dr. Yousef Al-Abed  
Dr. Michael Wolfe  
Dr. John Cashman

### TARGETING TAU ... Continued from Page 1

in nerve cells. This abnormal increase in microtubule instability may be one of the main causes of the symptoms of FTD and AD.

If microtubule instability is one of the underlying causes leading to FTD and AD, it follows that stabilizing microtubules would be a good therapeutic strategy to pursue. ADDF and its affiliated private foundation, Institute for the Study of Aging (ISOA), are funding Drs. Eckhardt and Eva-Maria Mandelkow to develop new therapies based on this rationale. Dr. Eckhardt Mandelkow's research is based on reversing the aggregation of tau protein; whereas Dr. Eva-Maria Mandelkow focuses on the enzymes that lead to hyperphosphorylation of tau.

### A BLOOD PRESSURE CUFF FOR ALZHEIMER'S DISEASE?

Most people are familiar with the blood pressure cuff, a device that is used to manage hypertension. Like other chronic diseases, the key to effective care is the ability to detect the disease early with a simple test that a primary care doctor can perform before secondary problems occur like stroke and heart attack. The blood pressure cuff also allows the doctor to monitor therapy and provide immediate patient feedback.

Unfortunately, we do not have the equivalent of the blood pressure cuff for AD. Or do we?

The cardinal clinical symptoms of AD are due to cognitive impairment. Detecting the disease early on and monitoring cognitive function over time is critical to ensuring that AD patients receive quality treatment. The current average delay between onset of first symptoms and diagnosis is two years.

Getting physicians to perform cognitive testing is challenging. Presently, there is no efficient, objective way to measure impairment in primary care practice that is equivalent to the blood pressure cuff. Cognitive testing is time-consuming and not practical for busy physicians who are not trained in this type of testing. Referrals to expert neuropsychologists are expensive and often not feasible.

To fill this need, Ely Simon, MD, a neurologist and entrepreneur, founded NeuroTrax and developed Mindstreams®, a computerized system that enables physicians to conduct cognitive assessments in their offices. Mindstreams®, a scientifically proven program, can evaluate multiple domains of cognitive function, track the rate of disease progression and monitor patients' responses to treatments. AD patients can take the test easily with minimal supervision.

ADDF/ISOA has been funding NeuroTrax since 2003. Today, Mindstreams® is being employed throughout the United States, Canada and other countries. NeuroTrax is also being used by leading clinical researchers in the U.S. and Israel; and featured in over 15 peer-reviewed scientific articles.

So when will there be the equivalent of a blood pressure cuff for AD? That day may be here.

Other strategies for targeting tau focus on genetic changes that alter the accumulation of tau protein. Research by ADDF/ISOA funded investigator Dr. Jianhua Zhou is developing assays based on tau processing with the aim of identifying drugs that can be used for high-throughput screening. Dr. Michael Hutton, another ADDF/ISOA funded investigator, is testing whether several lead compounds previously identified by his laboratory can reduce tau levels in animal models.

It is clear that earlier research on the mechanisms underlying tauopathies has progressed to the point that promising therapeutic strategies targeting tau are now emerging.

### MISFOLDING, CHAPERONES, AGING AND ALZHEIMER'S

Proteins have several different levels of structure. Their primary structure derives from the linear amino acid sequences that compose the protein, based on the DNA that codes the amino acids in the protein. Once a protein is made by a cell, it begins to take a specific shape. It is the 3-dimensional shape that is critical to its function. When proteins fold into the proper shape, they bind relevant molecules that fit their shape like a "lock and key", triggering the biological processes that are important in life.

However, proteins can also "misfold." This happens particularly with aging, as heat, oxidation and other degradative processes change proteins. When proteins misfold they lose function. A practical example of this is the curdling of milk as it grows stale, or the heating of an egg as it changes into a scrambled meal. Evolution has evolved defense mechanisms against misfolding in the face of these environmental injuries. One type of defense is a group of molecules called chaperones, which bind to other proteins and protect them, or induce them to return to their native state and retain function.

*Some scientists think that inducing the production of specific chaperone proteins in the brain could prevent amyloid misfolding.*

In AD, the beta-amyloid protein, which may have a normal function in memory formation, misfolds with aging, forming a "beta helix" that tends to aggregate, becoming toxic to nerve cells, and form the amyloid plaques that are seen in the Alzheimer's brain. Some scientists think that inducing the production of specific chaperone proteins in the brain could prevent amyloid misfolding.

One ADDF/ISOA funded investigator, Dr. Leonard Petrucelli of the Mayo Clinic Jacksonville, has found a potential drug that can induce chaperone formation and prevent amyloid aggregation in animal models of AD. He is currently conducting studies to provide further evidence that this drug target could lead to significant alternative therapeutic strategies for AD and other forms of dementia.