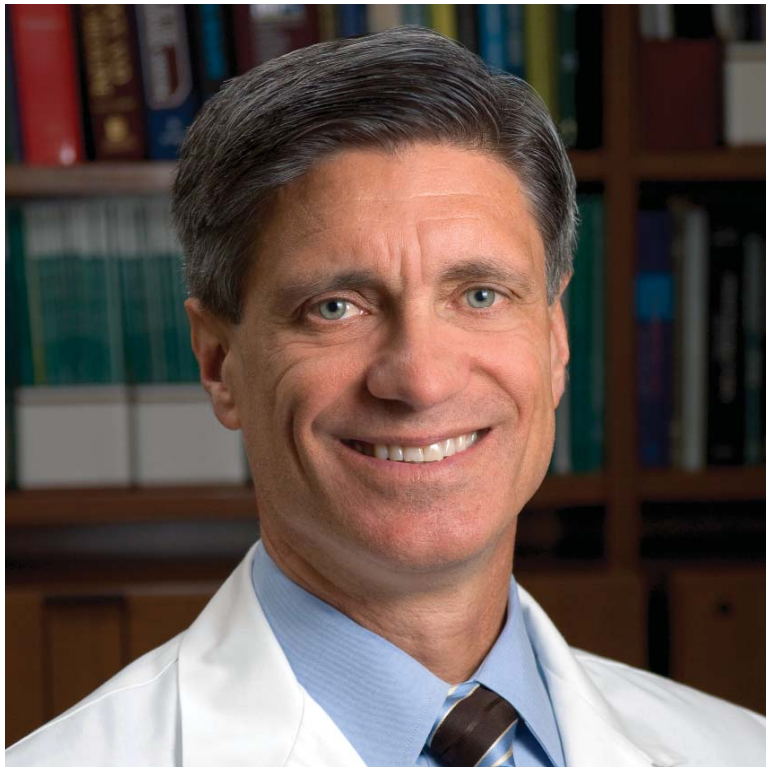
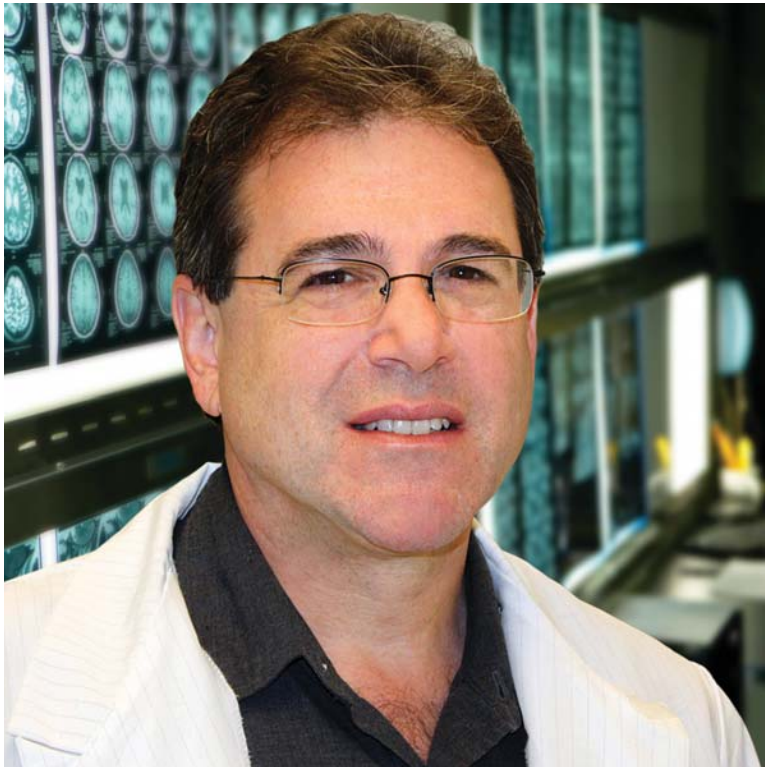
Alzheimer's Drug Discovery Foundation

profiles of PROGRESS





2008 Annual Highlights

reporting on our QUEST

The Alzheimer's Drug Discovery Foundation's (ADDF) 2008 annual highlights emphasize our ongoing commitment to finding a cure for Alzheimer's disease through drug discovery research. This year we received almost 200 requests for funding and awarded 32 programs. While the majority of our funding went to academic drug discovery programs, 33% of research funds went to support early-stage biotechnology companies. The programs listed in these pages represent innovative approaches to developing effective therapies to treat, prevent and cure Alzheimer's disease, cognitive aging and related dementias.

The academic programs funded over this past year encompass 16 unique drug targets. Sidney Strickland, Rockefeller University, is screening for molecules directed to fibrinogen, the main constituent of blood clots in the brain. Reducing or preventing these clots allows vital nutrients to reach the brain, preventing cell death and inflammation. Mark Tuszynski, University of California, San Diego, is working on a new target, a growth factor called brain-derived neurotrophic factor (BDNF). He recently demonstrated that BDNF treatment prevented neuron death and reversed cognitive impairment in animal models of Alzheimer's disease. Both of these approaches could eventually be translated to humans as effective treatments.

About 10% of funding in 2008 went to support pilot clinical trials. Adam Boxer, University of California, San Francisco, was funded to conduct a pilot trial of a new drug called NAP, administered as a nasal spray, in patients with a frontotemporal dementia (FTD) related disease. FTD shares similarities to Alzheimer's disease in that both diseases exhibit a buildup of toxic forms of tau protein in the brain. NAP blocks the accumulation of toxic tau protein, improving disease in animal models and in early-stage Alzheimer's disease patients. Dr. Boxer was able to leverage ADDF funding with additional funds from CurePSP and Allon Therapeutics. ADDF provided funding to establish Allon in 2002 through the ADDF Biotechnology Founders Program.

ADDF's *Fund for Alzheimer's Drug Discovery* ("the Fund") biotechnology portfolio is expanding with three new investments. sGC Pharma, C_2N Diagnostics and P2D Biosciences were selected for investment by the Fund after careful due diligence by our scientific staff and Board of Advisors. The Fund's initial investment, PharmatrophiX, continues to make significant progress and is highlighted in this report.

Given the exciting outcomes in 2008, ADDF is looking forward to an outstanding 2009. With your help, we can increase our outreach and networking efforts, provide follow-on funding to our successful programs and fund new investigators. Together, we can accelerate drug discovery towards a cure for Alzheimer's disease. ▶ **HOWARD FILLIT, MD**, Executive Director

Accelerating Alzheimer's drug discovery through venture philanthropy

OUR MISSION

The Alzheimer's Drug Discovery Foundation (ADDF) is the only public charity whose 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.

We raise and award funds to academic and biotechnology scientists conducting drug discovery research in this field.

ADDF uses a venture philanthropy model to bridge the worldwide funding gap between basic research and later-stage development, using any return on investment to support new research.

WHAT WE DO

FUNDING SCIENCE ▶ ADDF funds drug discovery research in academia and the biotechnology industry worldwide. We fund high risk, early stage drug discovery and development projects and catalyze scientists to enter the drug discovery field.

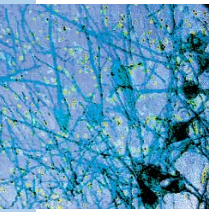
ADDF conducts comprehensive due diligence reviews of each application and works with the scientists to develop the most efficient and cost effective drug discovery research program possible.

Awarded investigators are held to highly accountable milestones, both scientifically and financially. ADDF staff monitors all awarded programs and requires scientists to submit semi-annual reports describing the progress of their research and use of funds. The grant program is assessed annually to determine future directions and adjustments needed to increase its success.

EDUCATION & NETWORKING ▶ ADDF organizes and hosts two respected international scientific conferences annually to increase scientists' knowledge of the field. Our Annual International Conference for Alzheimer's Drug Discovery, held in the fall, focuses on the discovery and development of novel drugs targeting Alzheimer's disease and related dementias. The conference is also an opportunity for ADDF investigators to present their most recent findings, network to exchange ideas and foster alliances to accelerate research and the field.

The Drug Discovery for Neurodegeneration conference, held in February, is designed to educate scientists on the process of translating basic neuroscience research into innovative therapies for all neurodegenerative disease. This conference is developed in collaboration with the National Institutes of Health and with the support of many corporate sponsors.

partnership PROGRAMS



THE FUND FOR ALZHEIMER'S DRUG DISCOVERY

The Fund supports promising biotechnology companies conducting early and novel drug discovery research in Alzheimer's disease.

The Fund is a venture philanthropy vehicle adapted from a venture capital model. Contributors to the Fund designate a 501(c)(3) nonprofit organization to receive a *pro rata* return on investment, if and when biotechnology companies supported through the Fund achieve contractual milestones.

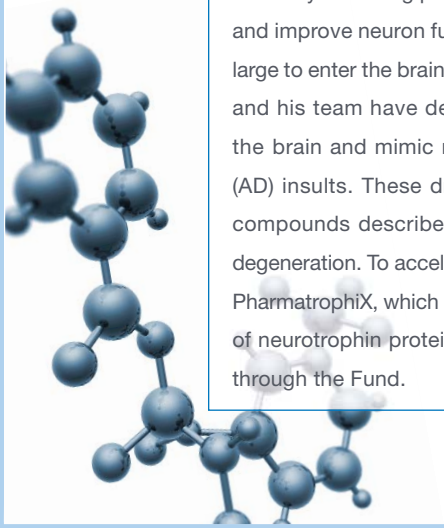
ADDF has awarded a total of $1,195,300 to four biotechnology companies through the Fund and has this far raised $2.15M, including a $1M capital commitment from the Aetna Foundation. PharmatrophiX was the Fund's inaugural investment.

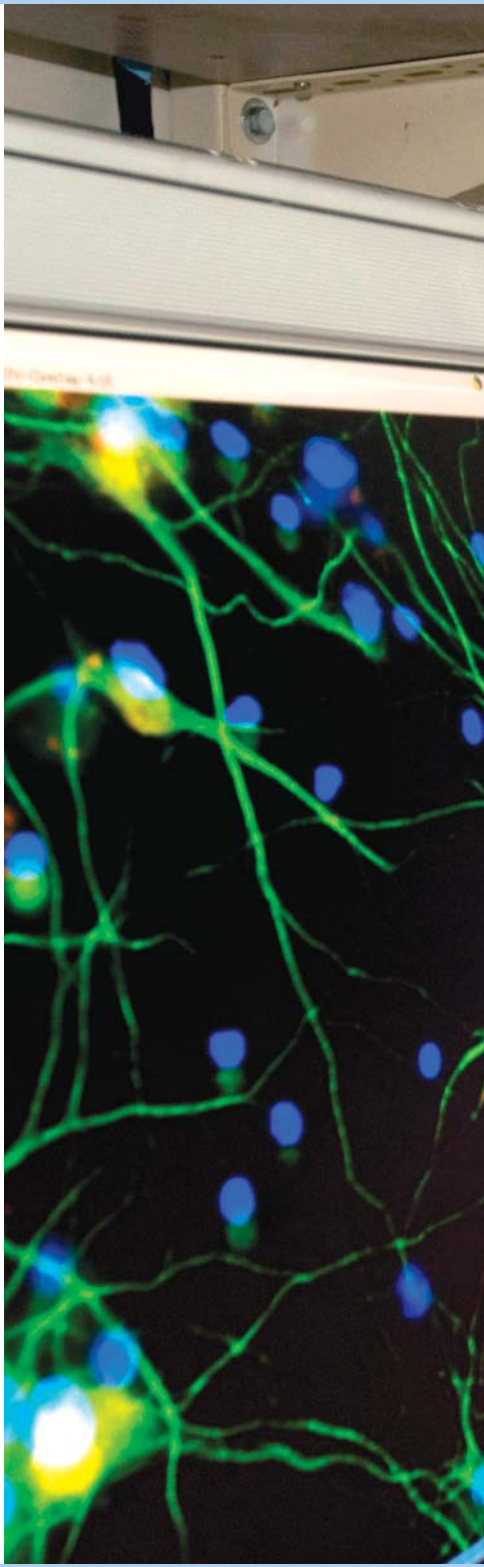
PharmatrophiX

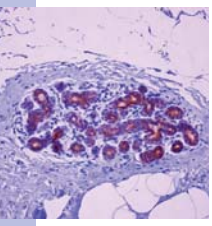
FRANK LONGO, MD, PHD

Founder of PharmatrophiX and Chairman of Neurology and Neurosciences at Stanford University Medical Center

Naturally occurring proteins called "neurotrophins" inhibit neuronal degeneration and improve neuron function. Unfortunately, these neurotrophin proteins are too large to enter the brain and are not stable enough to be useful as drugs. Dr. Longo and his team have designed drug-like small molecules that are able to enter the brain and mimic neurotrophins, protecting cells from Alzheimer's disease (AD) insults. These drug-like small molecules are among the most potent of compounds described to date that are capable of preventing AD associated degeneration. To accelerate this research, ADDF assisted Dr. Longo in establishing PharmatrophiX, which is dedicated to the development of small molecule mimetics of neurotrophin proteins. PharmatrophiX received a $300,000 investment grant through the Fund.







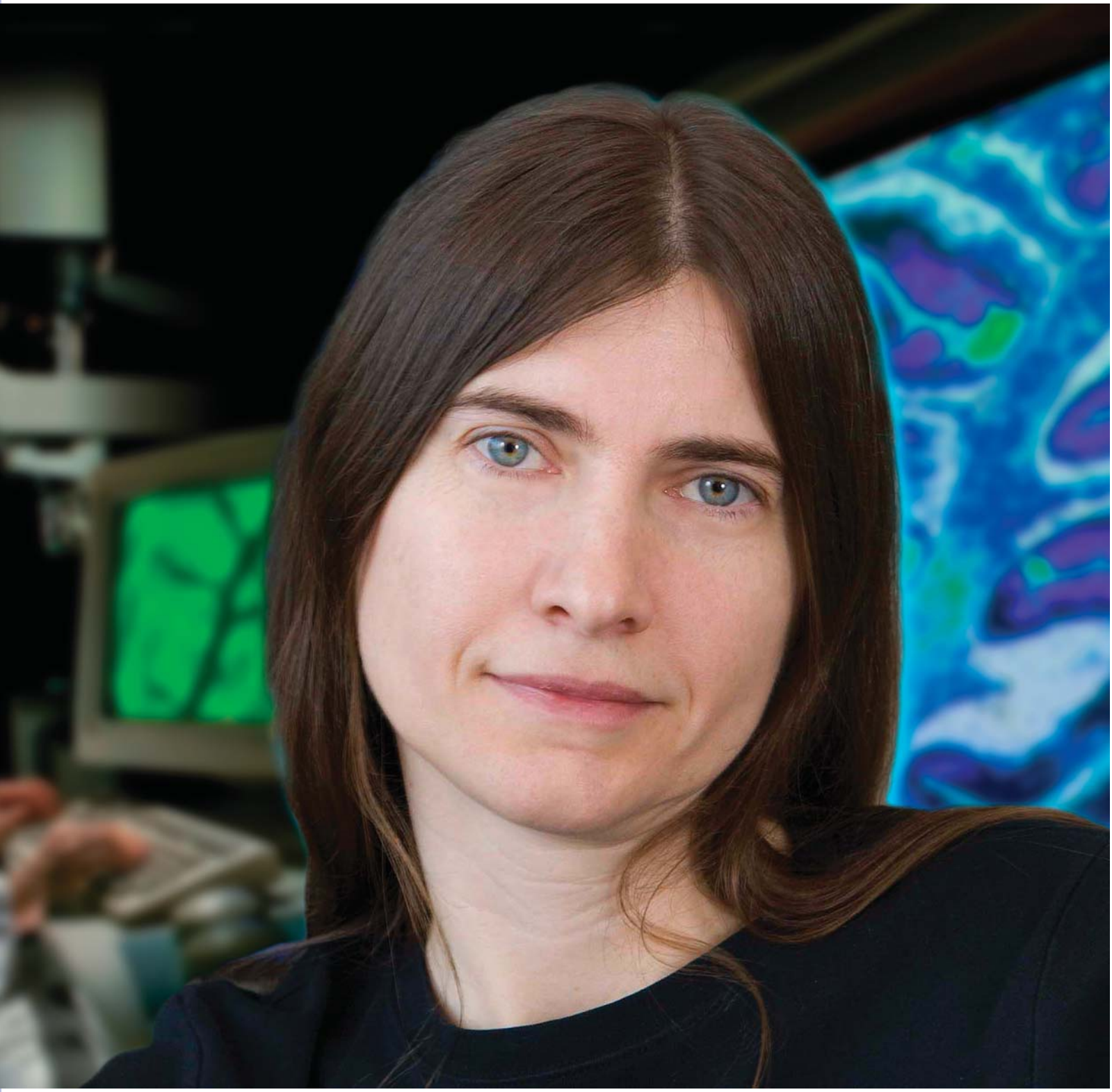
FRONTOTEMPORAL DEMENTIA DRUG DISCOVERY PROGRAM

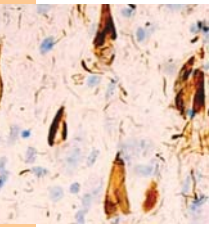
ADDF and The Association for Frontotemporal Dementias (AFTD) established a joint award program to fund scientists developing drugs to combat frontotemporal dementia (FTD). Alzheimer's disease and FTD share common features so that collaboration and cross fertilization of ideas are mutually beneficial. Dr. Gabriela Chiosis was one of three scientists to receive an award through this program in 2008.

GABRIELA CHIOSIS, PHD

Memorial Sloan-Kettering Cancer Center, New York

Frontotemporal dementia (FTD) and Alzheimer's disease (AD) are characterized in part by abnormal accumulation of the protein tau within the cell. As more and more tau clumps together, neurofibrillary tangles are formed, resulting in neuronal dysfunction and death. Through studies in both cell cultures and in mouse models, Dr. Chiosis has shown that a protein called Hsp90 promotes the formation and accumulation of abnormal tau, resulting in cell death. Inhibiting Hsp90 prevents buildup of the tau protein. Therefore, if this Hsp90 inhibitor could be developed into a drug, it could block neurofibrillary tangle formation and protect neurons from death in FTD and AD. Dr. Chiosis was funded previously through ADDF to develop Hsp90 inhibitors that could be used as drugs. These efforts were successful and resulted in the discovery of several exciting compounds with drug potential. Dr. Chiosis now plans to further evaluate these compounds in order to move them forward into clinical testing for FTD and AD. Dr. Chiosis received $100,000 for this project.





NOVEL APPROACHES TO DRUG DISCOVERY FOR ALZHEIMER'S DISEASE PROGRAM

The ADDF/Elan Novel Approaches to Drug Discovery for Alzheimer's Disease Program, now in its fourth year, enables ADDF and Elan Pharmaceuticals, Inc. to pool resources and expertise. The collaboration funds new therapies that may effectively treat Alzheimer's disease. Dr. Jeff Kuret was one of four scientists to receive an award through the program in 2008.

JEFF KURET, PHD

Ohio State University, Columbus, OH

Brains of Alzheimer's patients contain twisted filaments that accumulate within neurons, causing dysfunction and ultimately cell death. These twisted filaments are called neurofibrillary tangles and have been used as the gold standard to diagnose and stage the disease at autopsy. Dr. Kuret is developing small molecule probes that specifically bind to neurofibrillary tangles and could be developed into neuroimaging agents to detect tangles in living patients. Successful development of these imaging agents will allow for early diagnosis and monitoring of disease progression in patients with Alzheimer's disease and other tangle associated diseases. Noninvasive quantitative measures of disease progression are crucial for determining response to novel treatments in clinical trials and diagnosing early stage patients in order to initiate treatment when it will be most beneficial. Dr. Kuret received a $135,000 grant through this partnership program.

support from our CONTRIBUTORS

Thanks to the generosity of the following contributing partners, ADDF raised approximately 2.8 million in 2008 to bring the total funding for our first four years of operation to over 8.8 million. Your support enabled us to advance our mission of accelerating drug discovery research for Alzheimer's disease, related dementias and cognitive aging.

$1,000,000 AND ABOVE

Estée Lauder Trust

$100,000 AND ABOVE

Aetna Foundation
The Association for Frontotemporal Dementias
Ms. Nancy Corzine
Elan Pharmaceuticals, Inc.
Mr. and Mrs. Randal Sandler

$50,000 AND ABOVE

The Chisholm Foundation
The Estée Lauder Companies Inc.
The Lauder Foundation, Leonard and Evelyn Lauder Fund
National Institutes for Health
David Schwartz Foundation

$25,000 AND ABOVE

Mr. and Mrs. Dominic Camera
Dalio Family Foundation
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Ms. Ann Marie Huebner and Mr. Ross P. Waller
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The Andrew M. Paul Family Foundation
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$5,000 AND ABOVE

Baxter Healthcare Corporation, through its BioScience Business Unit
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$1,000 AND ABOVE

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The Saxon Hotel
Shamwari Game Reserve
Sotheby's
Starwood Capital Group
Steenberg Hotel and Winery
Mr. and Mrs. Steven Walske
Wine Spectator Magazine

2008 GRANTS

ACADEMIC PROGRAMS

James Bamburg, PhD
Colorado State University
Peptidomimetics for Elimination of Cofilin Pathology in Alzheimer's Disease
Award: $115,000

Ilya Bezprozvanny, PhD
UT Southwestern Medical Center at Dallas
Ryanodine Receptor as Target for AD
Award: $122,000

Michelle Block, PhD
Virginia Commonwealth University
NADPH Oxidase as a Therapeutic Target in Alzheimer's Disease
Award: $175,228

Adam Boxer, MD, PhD
University of California, San Francisco
A Pilot Clinical Trial of NAP (AL-108) for Corticobasal Degeneration and Frontotemporal Lobar Degeneration with Predicted Corticobasal Degeneration Pathology
Award: $100,000

Gabriela Chiosis, PhD
Memorial Sloan-Kettering Cancer Center
Hsp90 Inhibitors in Tauopathies: In Vivo Pre-Clinical Development
Award: $100,000

Pierre Goloubinoff, PhD
University of Lausanne
Plant-Based Primary Screen and Animal-Based Secondary Screens for Chaperone-Inducing Drugs Against Protein Misfolding and Inflammation in Alzheimer's Disease
Award: $80,000

Varghese John, PhD
Buck Institute for Age Research
Identification of Inhibitors for the C-Terminal D664 Cleavage of APP as Potential Therapeutic Agents for Alzheimer's Disease
Award: $125,000

Graham Jones, PhD
Northeastern University
Expedient and Versatile Methods for the Production of Investigational Drugs for SPECT and PET Imaging of AD
Award: $78,978

Jeff A. Kuret, PhD
Ohio State University
Contrast Agents for Premortem Diagnosis and Staging of Alzheimer's Disease
Award: $135,000

Daniel Laskowitz, PhD
Duke University Medical Center
A Novel apoE-Derived Therapeutic Reduces AD Pathology
Award: $85,000

Kelvin Lee, PhD
University of Delaware
Spinal Fluid Proteomics for IVIg Immunotherapy
Award: $100,000

Virginia M. Y. Lee, PhD
Hospital of the University of Pennsylvania
Frontotemporal Lobar Degeneration (FTLD) Biomarker Assays
Award: $100,000

Emmanuel Planel, PhD
Columbia University Medical Center / Research Foundation for Mental Hygiene
Effect of Memantine on Alzheimer's Disease Pathogenesis Induced by Anesthesia In Vivo
Award: $100,000

Juan Sanchez-Ramos, MD, PhD
University of South Florida
Efficacy and Safety of Filgastrim (Neupogen®) as a Pro-cognitive Agent for Alzheimer's Disease
Award: $180,000

Michael Sierks, PhD
Arizona State University
Targeted Hydrolysis of Beta-Amyloid with Engineered Antibody Fragments
Award: $100,000

Sidney Strickland, PhD
Rockefeller University
Interaction Between A-Beta and Fibrinogen: A New Therapeutic Target for Alzheimer's Disease
Award: $150,000

Mark H. Tuszynski, MD, PhD
University of California, San Diego
Preventing Neuronal Loss in the Non-Human Primate Cortex
Award: $50,000

Ray Watts, MD
University of Alabama, Birmingham
Oral Amyloid AAV Vaccine for Alzheimer's Disease
Award: $130,794

Nicholas Webster, PhD
Veterans Medical Research Foundation
Development of Cell-Permeable NGF Mimetics
Award: $130,000

Philip Williams, PhD
University of Hawaii, Manoa
New Methods to Explore Marine Resources for Alzheimer's Disease Drug Leads
Award: $100,000

Ken Witt, PhD
Southern Illinois University, Edwardsville
Somatostatin Agonist Treatment for Cognitive Aging and Dementia
Award: $125,000

Michael S. Wolfe, PhD
Brigham & Women's Hospital
Selective Amyloid-Lowering Agents: Year 2
Award: $130,000

BIOTECHNOLOGY PROGRAMS

Andrew Blackwell, PhD
Cambridge Cognition
Prototype Development for the Guided Neuropsychological Evaluation (G:NE) System for the Early Detection and Differential Diagnosis of Alzhiemer's Disease
Award: $200,000

Doug Cowart, PhD
sGC Pharma
Development of a Sustained Release Oral Formulation of sGC 1061, A New Therapeutic Agent for the Treatment of Alzheimer's Disease Related Cognitive Deficiency
Award: $295,300

Thomas Darling, PhD
Edunn Biotechnology, Inc.
Early Pre-clinical Development of OL-1
Award: $100,000

Ajay Gupta, PhD
Osta Biotechnologies, Inc.
Suppression of Glial HO-1 Activity as a Potential Neurotherapeutic Intervention in Alzheimer's Disease
Award: $247,106

Tim West, PhD
C2N Diagnostics
Validation and Optimization of an Immunoprecipitation Assay for Amyloid Beta from Human Cerebrospinal Fluid Using Novel Antibodies
Award: $300,000

CONFERENCES

Amos Korczyn, MD
Tel Aviv University
The 2nd World Congress on Controversies in Neurology - CONy
Award: $2,000

Bruce L. Miller, MD
University of California, San Francisco
Bridging Cultures: Improving Evaluation and Treatment of Cognitive Disorders
Award: $2,000

Andrew Robertson, PhD
Keystone Symposia on Molecular and Cellular Biology
Concurrent 2009 Keystone Symposia Meetings Entitled: Neurodegenerative Diseases: New Molecular Mechanisms and Axonal Connections: Molecular Cues for Development and Regeneration
Award: $2,000

Andrew Robertson, PhD
Keystone Symposia on Molecular and Cellular Biology
2008 Conference on Alzheimer's Disease
Award: $2,500

Kenneth Rockwood, MD, FRCPC
Geriatric Medicine Research Unit
10th International Symposium on the Treatment of Alzheimer Disease
Award: $2,000

impact of FUNDING

ADDF is affiliated with the Institute for the Study of Aging (ISOA), a private foundation created by the Estée Lauder family in 1998. ISOA provides substantial financial support so that funds raised by ADDF can be used directly for research.

In 2008, ADDF and ISOA approved $3.8 million in grants to 27 research programs and 5 conferences worldwide. The total grant spending for 2008 (including on-going commitments) was $3.5 million.

Since 1998, ADDF and ISOA have awarded $36M for more than 260 research programs and conferences in 14 countries. The impact of our funding is demonstrated through our investment in successful research programs. Our scientists have created entirely new classes of drugs in development for Alzheimer's disease, screened millions of compounds, identified hundreds of leads, executed tens of patents and licenses and have advanced compounds into clinical trials.

HELP US FUND SCIENCE

Presently 16 million Americans suffer with Alzheimer's disease (AD), mild cognitive impairment and age-related cognitive decline. AD costs U.S. society more than $140 billion annually, making it the third most costly disease in the country.

For AD sufferers and their caregivers, there are still no drugs for preventing or effectively slowing the rate of disease progression. In fact, there are only four drugs on the market that are only moderately effective in treating the symptoms of AD.

Currently, ADDF can fund about 15% of the proposals we receive, leaving many opportunities for new drugs unfunded. Your help has never been more urgently needed. The only solution to the growing AD epidemic is the development of disease modifying drugs to treat, prevent and cure the disease.

Alzheimer's Drug Discovery Foundation

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