

THE PATHS TO A CURE



Alzheimer's
Drug Discovery
Foundation

2014 ANNUAL REPORT

The Alzheimer's Drug Discovery Foundation's mission is to rapidly accelerate the discovery of drugs to prevent, treat and cure Alzheimer's disease.

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TOGETHER WE CAN CONQUER ALZHEIMER'S DISEASE

Dear Friends,

More than 44 million people worldwide suffer from Alzheimer's disease and related dementias—and there remains no way to cure or even slow the progress of this devastating illness. **But there is hope in drug discovery.**

The Alzheimer's Drug Discovery Foundation (ADDF) is supporting scientists around the globe who are investigating novel drugs to prevent, treat and cure Alzheimer's disease. Thanks to your generous contributions, these researchers are making remarkable progress.

With your continued support, they can take the steps necessary to bring forth a cure for this devastating disease. **Together we can and will conquer Alzheimer's disease.**

With our deepest thanks,



A handwritten signature of Leonard A. Lauder in blue ink, written in a cursive style.

LEONARD A. LAUDER

Co-Chairman and Co-Founder



A handwritten signature of Ronald S. Lauder in blue ink, written in a cursive style.

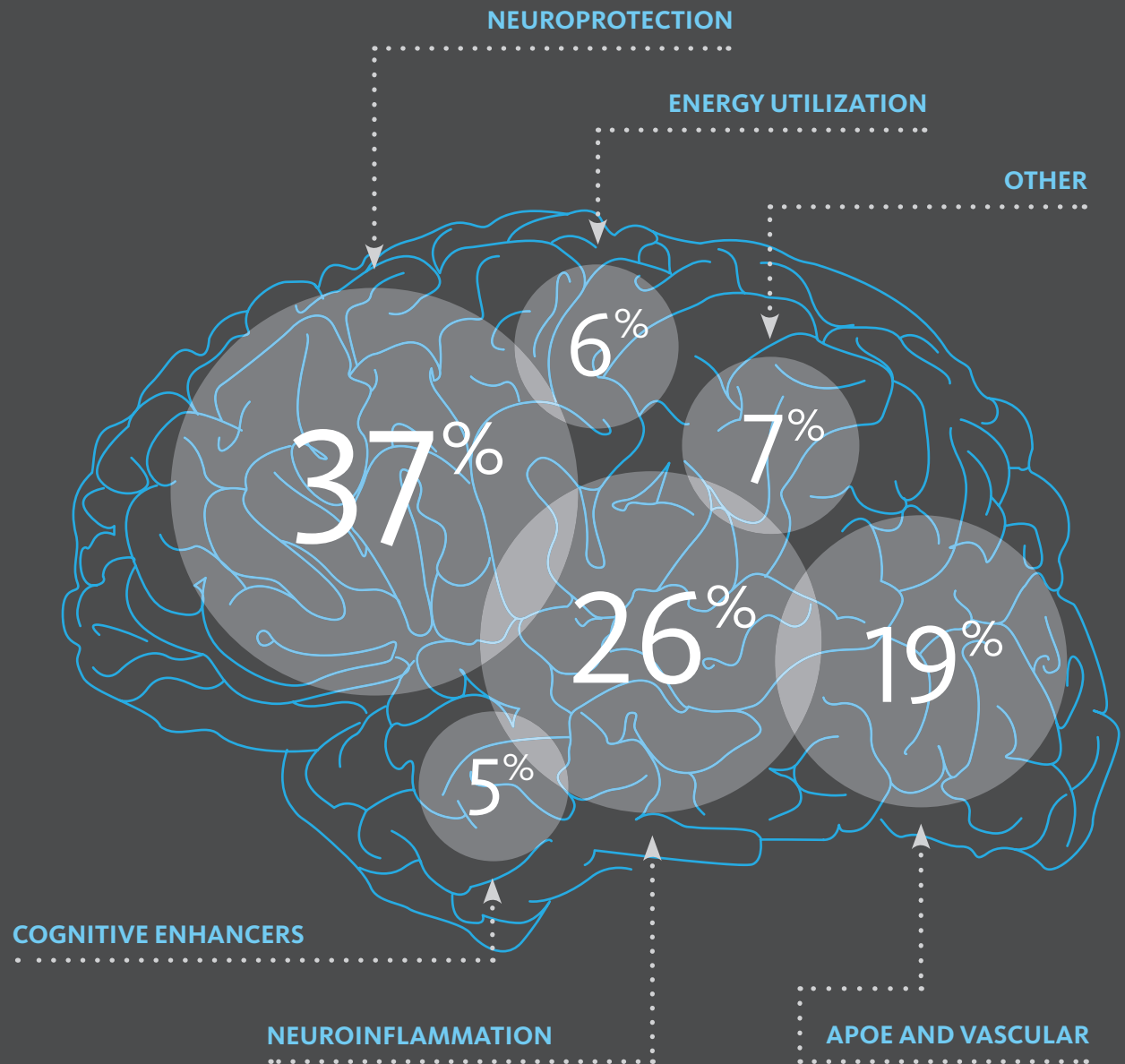
RONALD S. LAUDER

Co-Chairman and Co-Founder

A DIVERSIFIED PORTFOLIO OF ALZHEIMER'S DRUG TARGETS

Will the first disease-modifying drug for Alzheimer's work by minimizing inflammation in the brain? Or will it protect neurons from damage and death? While researchers have a number of promising hypotheses, they do not yet know which Alzheimer's drug target will ultimately offer the greatest benefit to the largest number of patients.

That's why we are investing in a diverse portfolio of therapeutic approaches. We feature projects using several of these approaches in this Annual Report. By spreading our funding across a number of potential drug targets, we increase the likelihood of identifying an effective treatment—and ultimately a cure—for Alzheimer's disease.



**Data represents the Alzheimer's Drug Discovery Foundation's investments in 2014.*

DEAR FRIENDS,

Thanks to your continued generosity, the Alzheimer's Drug Discovery Foundation was able to support a diverse array of Alzheimer's research in 2014. Over the course of the year, we awarded 35 new grants to scientists who have already made tremendous progress in their search for effective drugs to prevent, treat and cure this devastating disease. In total, our team is actively managing 125 scientific programs.

While our funded investigators share a common goal, they are pursuing different therapeutic strategies. There are many hypotheses for drug discovery in Alzheimer's disease, and the scientists we support are exploring a multitude of these. Today, most researchers believe that we'll need more than one drug to tackle Alzheimer's disease. Like with heart disease—which can require a combination of drugs to lower cholesterol, reduce blood pressure and prevent blood clots—overcoming Alzheimer's will likely involve a multi-pronged approach to prevention and treatment.

Our research funding is strategically positioned across a diverse portfolio to increase the odds of developing effective treatments for Alzheimer's. In 2014, our investment choices included:

- More drug discovery and development science than ever before, with \$9.6 million in Alzheimer's drug investments.
- Increased investment in Alzheimer's clinical trials, recognizing that research in the field is rapidly advancing and that the need to test new drugs in humans is urgent.



LETTER FROM HOWARD FILLIT, MD

Founding Executive Director and
Chief Science Officer

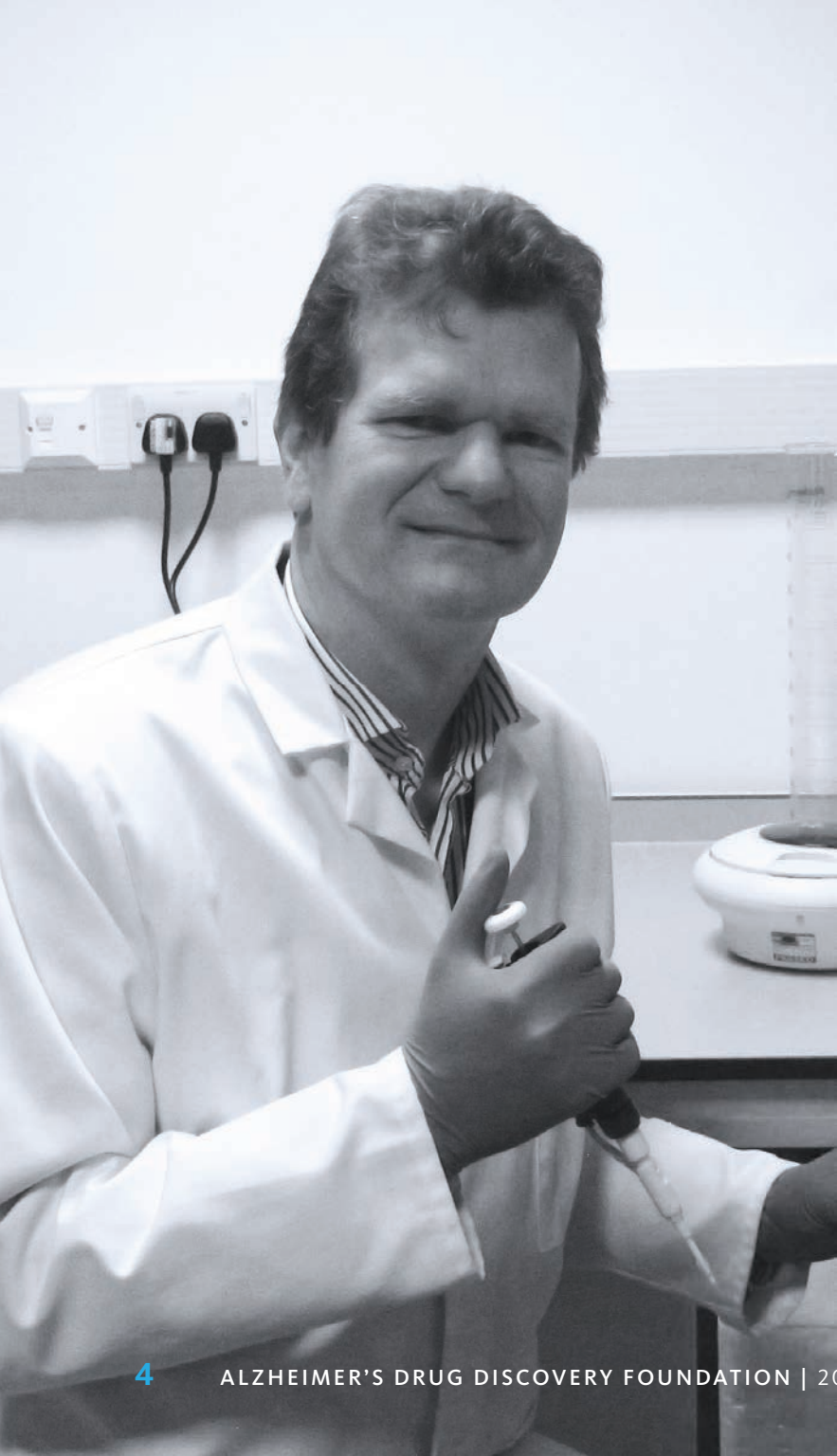
- More funding for clinical trials of existing and approved drugs through repurposing, which can reach patients more quickly and at a lower cost.
- Increased investment in innovative, entrepreneurial biotechnology companies.
- Development of critical educational and networking resources for researchers, ensuring that they have the tools and partners they need to share ideas, contract work and further their expertise.
- Launch of Cognitive Vitality, an online resource that empowers people to protect their aging brain.

In this Annual Report, you will learn even more about the groundbreaking research your generous donations make possible. Your investment in the ADDF and our network of dedicated scientists means that the 44 million people worldwide living with Alzheimer's and the millions more who love them have hope.

As always, thank you for the privilege of working with you to accelerate the development of effective drugs for Alzheimer's disease.

Sincerely,

A handwritten signature in black ink that reads "Howard".



OUR ALZHEIMER'S ARMY

In a lab in northern England, Dr. Christian Holscher unpacks new laboratory equipment and carefully inspects the pieces. Dr. Holscher and his team, who are based at Lancaster University, are preparing to investigate whether two experimental diabetes drugs could help prevent the onset of Alzheimer's disease. If the results of their trial are successful, the most promising of these repurposed drugs could be available to patients with Alzheimer's disease in the next three to five years.

Dr. Holscher is one of 35 grantees working in Europe, the U.S., and Canada, who received funding from the Alzheimer's Drug Discovery Foundation in 2014. These researchers—whose projects were vetted by panels of leading experts in Alzheimer's drug discovery and development—represent some of the best and brightest scientific minds in the world.

In the pages that follow, we'll introduce you to some of our grantees and the research projects they are driving forward. You can rest assured knowing that these leading Alzheimer's scientists are doing everything in their power to end this devastating disease—work that would be impossible without your ongoing support.

“It’s impossible to travel in life and not meet people who have a family story to tell about Alzheimer’s.”



MARTIN JEFSON, MD
RODIN THERAPEUTICS

Martin Jefson, PhD, says of his work in Alzheimer’s research, “I find it fascinating for all the reasons that most people do. It’s a disorder with a high unmet need. It’s a disease with high economic, social and familial costs.”

But he’s also intrigued by Alzheimer’s for purely scientific reasons. “It’s an absorbing and challenging scientific problem,” Dr. Jefson says. “It’s a classical drug discovery and development opportunity. That is my training and my passion.”

Dr. Jefson is using that training to test the safety and usefulness of a new treatment for Alzheimer’s disease in animal models. The drug, designed to improve brain function and cognition, works through epigenetic mechanisms. It’s a pioneering approach to treating Alzheimer’s, affecting changes in brain function by modifying gene expression and protein levels.

“Funding from the Alzheimer’s Drug Discovery Foundation has been critical to our work,” Dr. Jefson says. “It allowed us to transition from in vitro studies to animal experiments.”

There are currently no other drugs under study to treat cognitive impairment that work through epigenetic mechanisms. It’s not entirely uncharted territory, however. There are now drugs for cancer and other diseases that work similarly.

NEUROPROTECTION

As Alzheimer’s disease progresses, neurons (or nerve cells) lose their connections and begin to die, causing the loss of memory and other essential cognitive functions. Scientists are exploring “neuroprotective” treatment strategies to shield nerve cells from damage and death.

APOE

ApoE (apolipoprotein E) is the most significant genetic risk factor for late-onset Alzheimer's disease, with one variant—ApoE4—increasing a person's risk by up to 20 times the normal population. Scientists are investigating several strategies to modify this genetic risk.

RONALD CRYSTAL, MD

GREG PETSKO, DPHIL

WEILL CORNELL MEDICAL COLLEGE

Can we modify our risk of developing Alzheimer's disease? Ronald Crystal, MD, thinks there's a good chance we can. Like Dr. Hyman, Dr. Crystal—along with his colleague Greg Petsko, DPhil—is investigating APOE2 gene therapy.

"The problem is figuring out how to get APOE2 to the brain," explains Dr. Crystal. "Gene therapy is essentially a drug delivery device. Instead of using a protein, we're using the gene as a drug and a virus as a Trojan horse to deliver the gene to cells." Dr. Crystal, Dr. Petsko, and their team are working on a viral vector to deliver APOE2 directly to the brain. With funding from the ADDF, they are beginning preparations to manufacture the viral vector and create the data and documentation necessary to fast-track the project to human clinical trials.

"It is fantastic that the ADDF is supporting research like this."



BRADLEY HYMAN, MD, PHD

HARVARD MEDICAL SCHOOL
AND MASSACHUSETTS
GENERAL HOSPITAL

After more than three decades in Alzheimer's research, it's safe to say that Bradley Hyman, MD, PhD, has a wealth of experience in Alzheimer's drug discovery. He's equally well-versed in patient care, something that deeply informs his work in the lab. "I regularly see patients with this tragic illness," he says. "We need to help now."

Dr. Hyman is investigating APOE2 gene therapy for Alzheimer's disease. People with the APOE4 gene have the highest risk of developing Alzheimer's disease, while those with the APOE2 gene have a decreased risk. Gene therapy would use APOE2 as a treatment for people with the high-risk APOE4 gene. "We have an idea of how to take advantage of information about the genetics of Alzheimer's disease and a protective gene—APOE2—and turn that knowledge into a way to help patients," says Dr. Hyman. Research has already demonstrated that treating mice with APOE2 gene therapy can suppress the development of amyloid plaques characteristic of Alzheimer's disease.

With funding from the Alzheimer's Drug Discovery Foundation, Dr. Hyman and his team are evaluating the safety and therapeutic benefit of two different APOE2 viral vector approaches. "The ADDF has helped enormously," he says. "Our research is a little futuristic, and it is fantastic that the ADDF is supporting research like this."

You might be surprised to hear that Michela Gallagher, PhD, is on sabbatical. So what is she doing with all of her “free” time? She’s buckling down in the lab at AgeneBio in preparation for a Phase 3 trial of AGB101, a new treatment for early-stage Alzheimer’s disease. Its work that she says wouldn’t be possible without the Alzheimer’s Drug Discovery Foundation’s initial support in 2010.

“I don’t know how we would have gotten started at AgeneBio without the ADDF,” Dr. Gallagher says. “It was the bridge to a program that is still doing very well, and we’re tremendously grateful to the Foundation for its continued support.”

The ADDF has been unyielding in its enthusiasm for Dr. Gallagher’s work, most recently investing \$900,000 to enable preparations for AgeneBio’s upcoming Phase 3 trial of AGB101. The study will test the drug in patients with amnesic mild cognitive impairment (aMCI), the pre-dementia phase of Alzheimer’s disease in which memory is worse than expected for a person’s age. Most aMCI patients progress to Alzheimer’s dementia within 7 to 10 years.

AGB101 is a proprietary formulation of low-dose levetiracetam, an FDA-approved treatment for epilepsy. In the upcoming study, patients with aMCI will receive just one-twelfth of the regularly prescribed dose of the drug given once a day.

Dr. Gallagher is hopeful that, if results are positive, AGB101 will be available to patients soon after. “It has the advantage of a relatively fast clinical pathway because the safety of the drug is known, and allows us to focus on demonstrating the potential for AGB101 to slow progression of aMCI and delay onset of Alzheimer’s dementia,” she says.



MICHELA GALLAGHER, PHD
JOHNS HOPKINS UNIVERSITY
AND AGENEBIO

“The ADDF’s funding was so beautiful because it gave us the resources we needed to get [this project] going and ultimately allowed us to get funding from the NIH.”

COGNITIVE ENHANCING

Alzheimer’s disease is characterized by the loss of memory, abstract thinking and judgment, language and other cognitive deficits. Scientists are investigating cognitive enhancing drugs that improve cognitive performance, including memory, problem solving and daily function.

NEUROINFLAMMATION

Chronic inflammation in the brain can accelerate Alzheimer's disease and may be a trigger of the disease. Scientists are investigating drugs that protect against disease- and injury-induced inflammation while preserving normal inflammatory responses.

THOTA GANESH, PHD EMORY UNIVERSITY

Thota Ganesh, PhD, believes Alzheimer's researchers need to shift their attention. "The majority of drug discovery efforts are based on only one hypothesis—that an effective Alzheimer's drug must target amyloid plaques. We need to focus on testing new hypotheses," he says.

Dr. Ganesh, an Alzheimer's researcher and assistant professor of pharmacology, is working on neuroinflammation. "The goal of my research is to find a compound that targets the EP2 receptor [which appears to drive inflammation in Alzheimer's disease] and works as an anti-inflammatory and neuro-protective agent on patients," he explains.

With funding from the ADDF, Dr. Ganesh is in the early stages of testing one of his leading drug candidates in animal models. If this preclinical trial is successful, he and the team at Emory University will begin to develop a clinically useful drug for humans.



PAOLO PEVARELLO, PHD AXXAM SPA

Paolo Pevarello, PhD, knows what Alzheimer's can do to families and caregivers. He's experienced the effects of the devastating disease within his own family. But as the principal investigator of Axxam SpA, an Italian biotechnology company, Dr. Pevarello is also uniquely positioned to fight it.

With continued support from the Alzheimer's Drug Discovery Foundation, Dr. Pevarello is making tremendous strides on that front. Since 2011, the ADDF has awarded Axxam three grants to further the company's research to identify drugs that selectively block the purinergic receptor, P2X7, which is involved in inflammation in the brain.

"In the last five years, there has been an increasing appreciation of the role that neuroinflammation plays in Alzheimer's disease," Dr. Pevarello explains. "The P2X7 receptor is pathologically over-activated with Alzheimer's."

That's why Dr. Pevarello is investigating drugs that selectively block the receptor and may be able to minimize brain inflammation. It's an area of research that, by and large, has remained largely unexplored.

Dr. Pevarello and the Axxam team are currently optimizing leading drug candidates. As he explains, "We're close to providing a proof-of-concept for our leading drug candidates, which will allow progression through the preclinical path to a clinical candidate."

Ultimately, Dr. Pevarello hopes that one of his drugs will be part of the solution to the Alzheimer's crisis. "Alzheimer's disease is a complex pathology and it's hard to think that a single 'magic bullet' will resolve it," he says. "Combining two or more complementary approaches, which are currently under evaluation, may speed up the pace toward its cure."

“We know so much about Alzheimer’s disease—the opportunity to develop a drug is there.”



GARY GIBSON, PHD
BURKE REHABILITATION CENTER

What if a treatment for Alzheimer’s disease was already in your medicine cabinet? If Gary Gibson, PhD, is right about his drug—which is a close cousin to vitamin B₁ (also known as thiamine)—that might not be far from the truth.

Dr. Gibson’s compound, benofotiamine, works by raising and maintaining thiamine levels. Developed in Japan just after World War II, benofotiamine is more effective than traditional vitamin B₁ supplements at increasing thiamine levels.

All patients with Alzheimer’s experience a reduction in their glucose metabolism, a process that is dependent on vitamin B₁. Dr. Gibson believes thiamine therapy may “have a large impact on Alzheimer’s disease.”

The evidence for his hypothesis is mounting. benofotiamine has already proven effective in animal models of Alzheimer’s disease and safe in a double-blind clinical trial in Germany.

Next up: a Phase 2 clinical trial of benofotiamine in patients with early-stage Alzheimer’s disease funded by a partnership between the Alzheimer’s Drug Discovery Foundation, Burke Rehabilitation Hospital and the National Institutes of Health (NIH).

If the results of this study are promising, the formulation—which is already being manufactured by a safe and well-regarded facility in Canada—could be available to patients rapidly.


ENERGY UTILIZATION

All cells need energy to maintain healthy function, and brain cells are among the highest energy users. Because energy inefficiency and loss in neurons is a hallmark of Alzheimer’s disease, scientists are working to develop drugs that enhance the function of the energy powerhouses of cells, known as mitochondria.

HOW WE'RE DIFFERENT

The ADDF is the only venture philanthropy focused on funding drug discovery. The path to a cure for Alzheimer's starts with basic science into how the disease works. This information helps create tests to diagnose and assess Alzheimer's and gives us the targets for drug discovery and development to treat and cure the disease.

% FUNDING BY AREA

- 
Drug Discovery, Development & Clinical Trials
Finding a cure
- 
Molecular Pathogenesis
How the disease works
- 
Diagnosis & Assessment
How to test for the disease and its progress
- 
Epidemiology
Describing the impact of the disease on distinct populations
- 
Care & Support
How the disease affects patients, caregivers and society

**2012–2014 data from The International Alzheimer's Disease Research Portfolio, a database developed through a collaboration between the National Institute on Aging, which is part of the NIH and the Alzheimer's Association.*



Alzheimer's Drug Discovery Foundation



Alzheimer's Research UK



National Institutes of Health (NIH)



Alzheimer's Association



Cure Alzheimer's Fund



United States Army Medical Research and Materiel Command



Alzheimer's Society UK



Centers for Disease Control and Prevention (CDC)



United States Department of Veterans Affairs (VA)

PARTNERS IN THE DEVELOPMENT OF A CURE

The Alzheimer's Drug Discovery Foundation puts a premium on partnerships. And we're proud to work with more than a dozen foundations, businesses and government entities worldwide, including our newest partner, the Harrington Discovery Institute.

Over 10 years ago, we began a relationship with the Association for Frontotemporal Degeneration (AFTD), one of our closest allies in the fight against Alzheimer's. After a decade of collaboration, the ADDF and the AFTD have jointly funded 24 unique drug discovery programs through grants totaling over \$2.7 million. In 2014, the AFTD and the ADDF awarded new grants to Charlotte Teunissen, PhD, VU University Medical Center Amsterdam, and Matthew Disney, PhD, of Scripps Research Institute. Dr. Teunissen is tackling one of the greatest challenges facing frontotemporal degeneration research—differentiating the two most common subtypes of the disease in patients. Dr. Disney is working to design a drug-like compound that prevents a toxic chain of events caused by a

genetic mutation, C9ORF72, which is responsible for the majority of familial cases of FTD and ALS.

"We're very proud of our long-standing collaboration with the ADDF," says Susan Dickinson, Founding Executive Director, AFTD. "By combining our resources, we have provided the scientific community with a deeper understanding of this understudied disease and given patients and caregivers hope for potential treatments." Nadine Tatton, PhD, Scientific Director, AFTD, adds, "This is really cutting-edge science, and I believe that we're supporting truly innovative approaches to drug discovery for Alzheimer's, FTD and related diseases."

The ADDF values all of our 2014 partners. We know that when we team up with other forward-thinking organizations, we increase our funding power and our collective expertise—ultimately ensuring that we find a cure for Alzheimer's and related dementias faster.



CELEBRATIONS OF HOPE

From fashion shows to science symposia, the Alzheimer's Drug Discovery Foundation's 2014 lineup of special events made one thing clear: there is hope on the horizon. Throughout the year, more than 1,000 ADDF supporters came together for 13 events that together raised more than \$5 million. Our allies gathered to learn more about Alzheimer's research, meet people grappling with Alzheimer's, honor advocates and scientists working toward a cure ... and celebrate our progress!



Heidi and Tom McWilliams

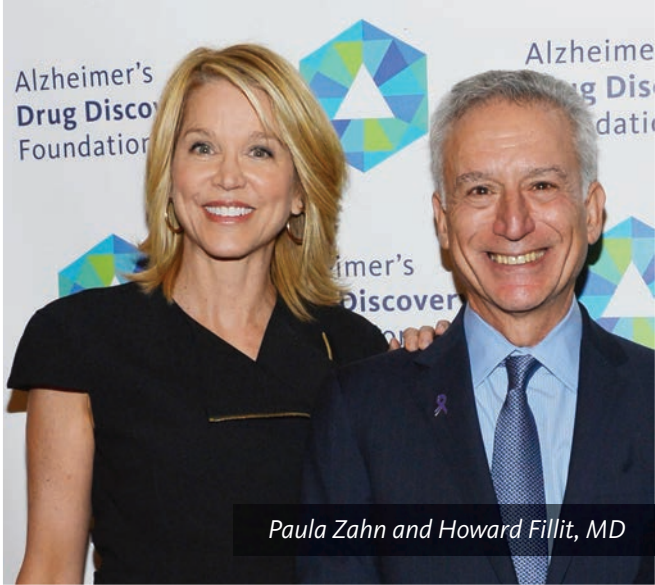
EIGHTH ANNUAL CONNOISSEUR'S DINNER

Honoring Leonard A. Lauder
Sotheby's, New York City | May 1, 2014



Robert and Renée Belfer

Leonard A. Lauder and Norah O'Donnell



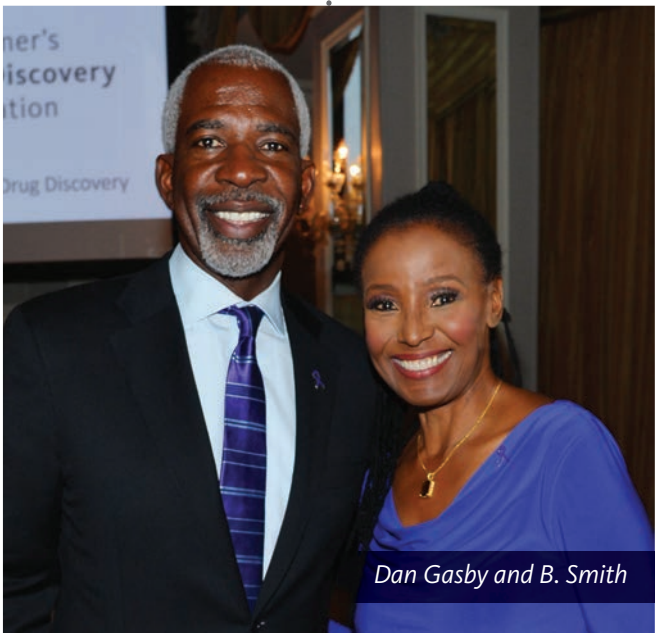
Paula Zahn and Howard Fillit, MD

FOURTH ANNUAL GREAT LADIES LUNCHEON & FASHION SHOW

Honoring Pat Summitt
The Ritz-Carlton, Washington, DC | April 1, 2014



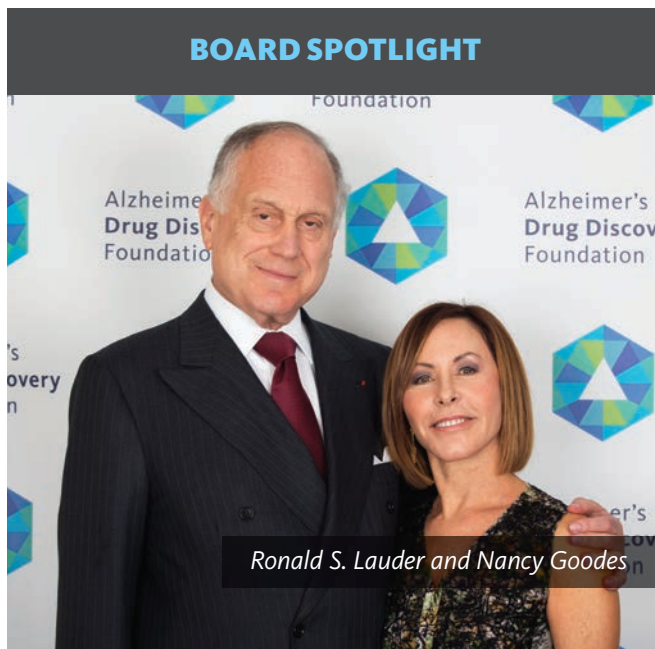
Andrea Mitchell, Leonard A. Lauder and Elise Lefkowitz



Dan Gasby and B. Smith

FIFTH ANNUAL FALL SYMPOSIUM & LUNCHEON

Honoring B. Smith
The Pierre, New York City | November 3, 2014



Ronald S. Lauder and Nancy Goodes



DONOR SPOTLIGHT: ROBERT J. APPEL

Andrew Carnegie famously said, "The man who dies rich, dies disgraced." Robert J. Appel is guided by this same spirit of philanthropy. Mr. Appel explains, "It's not just about giving back, but about being active and involved."

Mr. Appel, who joined the ADDF's Board in 2015, is a leader in supporting medical research. He chaired his alma mater Cornell University's immensely successful campaign for Weill Cornell Medical College. And he and his wife recently established the Helen & Robert Appel Alzheimer's Disease Research Institute there. Though the disease hasn't affected their family, the Appels have lost close friends to Alzheimer's. He chose to get involved with the ADDF because: "The problem is complex, and the solution is going to come from research into new drugs. We have to approach the search for a cure from as many ways as we can."

Mr. Appel's charitable endeavors go beyond medicine. His love of early American music led him to become Chairman of the Board of Jazz at Lincoln Center. He also serves as Trustee Emeritus and Presidential Councillor for Cornell University. His generosity and hard work in support of nonprofit organizations is a wonderful example of the power of philanthropy.

THANK YOU FOR MAKING IT ALL POSSIBLE!

We are deeply grateful to all those who supported our work in 2014.
Your generosity gives us hope for a future without Alzheimer's disease.

\$500,000 and above

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IN MEMORY

We remember all those taken by Alzheimer's in 2014 by continuing to fight for a cure.

Margaret Louise Ashburner	Chauncey Lufkin, Jr.
Jacques Boulanger	Jack Mausner
Marie Hunan Brennan	Charles Minichiello
Edward Carney	Eloise Mondau
Melvin R. Clayman	Jose A. Nessim
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IN HONOR

In 2014, many generous gifts were made to the Alzheimer's Drug Discovery Foundation in honor of friends and loved ones.

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Sharon Anderson
Shelley Banks
Jerald Barnett
Isabelle Black
Rochelle and Bernard Bloom
Faith Bobrow
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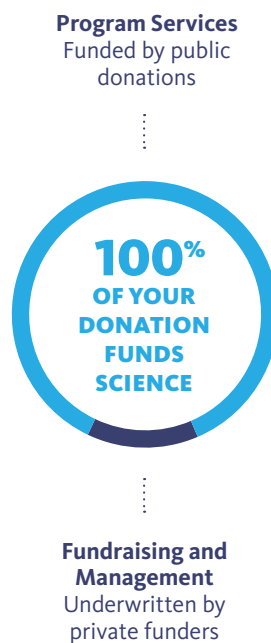
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2014 FINANCIAL OVERVIEW

STATEMENT OF FINANCIAL POSITION

ASSETS	12/31/14
Cash and cash equivalents	
<i>Operating</i>	\$ 4,633,217
<i>Restricted</i>	274,468
<i>Cash held by related party</i>	15,640
Total cash and cash equivalents	4,923,325
Investments, at fair value	10,809,963
Contributions receivable	4,059,717
Due from Institute for the Study of Aging	133,215
Other assets	26,103
Total assets	\$ 19,952,323
<hr/>	
LIABILITIES AND NET ASSETS	
Liabilities	
<i>Accounts payable and accrued liabilities</i>	\$ 49,324
<i>Grants payable</i>	11,513,136
<i>Deferred revenue</i>	61,350
Total liabilities	11,623,810
Net assets	
<i>Unrestricted</i>	8,054,045
<i>Temporarily restricted</i>	274,468
Total net assets	8,328,513
Total liabilities and net assets	\$ 19,952,323

Full audited 2014 financials available upon request



STATEMENT OF ACTIVITIES

CHANGE IN NET ASSETS	12/31/14
Support and Revenues	
Support	
<i>Contributions and grants</i>	\$ 6,514,722
<i>In-kind contributions from the Institute for the Study of Aging, Inc.</i>	2,832,504
<i>Proceeds from special events, net of direct expenses</i>	2,818,092
Revenues	
<i>Grant Returns</i>	1,799,905
<i>Conference registration fees and other income</i>	226,173
<i>Investment and other income</i>	1,574
<i>Foreign exchange gain</i>	105,048
Total support and revenues	14,298,018
Expenses	
<i>Program services</i>	10,850,140
<i>Fundraising</i>	1,236,175
<i>Management and general</i>	493,156
Subtotal	12,579,471
<i>Expense for uncollected pledge</i>	925,000
Total expenses	13,504,471
Change In net assets	793,547
Net assets, beginning of year	7,534,966
Net assets, end of period	\$ 8,328,513

RESOURCES

The Alzheimer's Drug Discovery Foundation is committed to providing researchers with the tools they need—from research funding to connections with drug discovery experts—to further their drug discovery efforts and advance the global search for an effective treatment, and a cure. While we continue our work toward ending Alzheimer's, the team at the ADDF is also evaluating the science behind prevention strategies to help you lower your risk.



SCIENTIFIC CONFERENCES

Our scientific conferences promote the exchange of ideas, the sharing of research results and the formulation of strategic alliances to further drug discovery and development goals. In 2014, we hosted two conferences, bringing together nearly 500 scientists, and co-sponsored and exhibited at many more. In addition to the conferences, we organized several advisory councils to identify solutions to specific challenges slowing the discovery and development of drugs to prevent and treat Alzheimer's, shared findings from these in white papers.

alzdiscovery.org/events/conferences



ADDF ACCESS

Drug discovery is a team effort, requiring collaboration between biologists, chemists, pharmacologists and many others. In 2014, ADDF ACCESS launched an enhanced online platform to help our research community of more than 4,500 scientists connect with a virtual network of consultants and contract research organizations (CROs)—connections that are critical to advancing their drug discovery work.

addfaccess.ondeckbiotech.com



PREVENTION

It's impossible to make educated decisions about brain health without access to the scientific evidence for and against potential strategies and treatments to prevent dementia. That's why this year our scientists launched Cognitive Vitality, a site designed to empower people to make smart, science-backed choices about brain health. The team behind Cognitive Vitality has conducted in-depth evaluations of 32 potential treatments to protect from dementia, ranging from FDA-approved drugs to natural products and supplements.

CognitiveVitality.org





Alzheimer's
Drug Discovery
Foundation

“TOGETHER WE CAN CONQUER ALZHEIMER’S DISEASE”

— Leonard A. Lauder & Ronald S. Lauder, Co-Founders & Co-Chairmen,
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