FUNDING

INNOVATIVE RESEARCH
WORKING TOWARD A CURE
OFFERING HOPE

ALZHEIMER'S FOUNDATION OF AMERICA
WE NEVER GIVE UP
A Message from Our President and Chief Executive Officer

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16 Mission and Background
At AFA, we never give up, and we’re actively doing all we can to advance the field of Alzheimer’s research. A key aspect of AFA’s commitment to improving the lives of those with dementia and their families is not only to ensure optimal support and resources—but to identify and help fund vital research endeavors.

To best support finding an Alzheimer’s cure or prevention—or, at least, an effective treatment to slow progression—AFA has embarked on an ambitious program to fund some of the most novel translational research initiatives, from basic science to projects that already have clinical applications.

As you will see from the pages that follow, AFA-funded research studies are innovative—and have the potential to be transformative. Many of these initiatives touch upon areas that have been identified as the most important in the field. These include projects that take advantage of the most sophisticated imaging tools to identify biomarkers that will enable diagnosis of Alzheimer’s in its earliest stages, when scientists say it is most likely to be amenable to treatment.

This focus fits nicely with the FDA’s recent proposal to fast-track the process to test drugs in people who haven’t yet shown outward clinical symptoms of Alzheimer’s, but who have a biomarker of the disease. The draft guidance, which has drawn a great deal of interest in the research community, suggests that the FDA is willing to approve therapies based on subtle biological signs, rather than proof that they alleviate symptoms—a significant change from clinical trials in the past.

Still other critical AFA-funded research initiatives, like that of Peter Davies, PhD, of The Feinstein Institute for Medical Research in New York, are testing a variety of new, more targeted drugs with minimal side effects as potential treatments for some of the most insidious aspects of the disease—such as hallucinations. It is these psychoses that frequently drive families to the difficult decision to move their loved ones to residential care facilities.

It is also of paramount importance to address the needs of those who are clinically underserved, as well as underrepresented in Alzheimer’s research, and to work toward reducing such disparities. Epidemiologists suggest that rates of Alzheimer’s and other forms of dementia among African-Americans are as much as twice those of whites.

The goals of Atlanta’s Emory University—to provide education, screening, and research information to help reduce these racial disparities—have been supported by AFA with great success and could potentially serve as a model across the country. In 2016, African-American participation in Emory’s Alzheimer’s clinical trials increased to 32 percent, up from two percent in 2008.

Whether AFA-funded research leads to a cure, dramatically improves quality of life, or simply deepens our understanding of Alzheimer’s—AFA is doing everything it can to help push the field forward.

We hope that you can help us further invest in research. Every dollar from your donation will have an impact: 100 percent of all contributions designated for research go exclusively to funding research.

Make your contribution online today at www.alzfdn.org/donate, or complete and return the enclosed form by mail to AFA.

Thank you for your past support of AFA and for continuing to make a difference for the 5 million Americans living with Alzheimer’s disease and their families.

Charles J. Fuschillo, Jr.
President & CEO
Alzheimer’s Foundation of America
cfuschillo@alzfdn.org
AFA is committed to providing optimal care and services to individuals confronting dementia, and to their caregivers and families—through member organizations dedicated to improving quality of life. As a part of its mission, AFA also funds translational scientific research toward improved treatments and a cure.
Families living with Alzheimer’s disease (AD) know all too well the paranoia, hallucinations, agitation, and aggressive behaviors that often present in the course of the illness—symptoms that frequently drive families to the heart-wrenching decision to move their loved ones to residential care facilities.

Peter Davies, PhD, Director of the Litwin-Zucker Center for the Study of Alzheimer’s Disease and Memory Disorders at The Feinstein Institute for Medical Research in New York, and his colleagues have identified a series of changes, including an accumulation of tau in the brain’s frontal cortex, as potential causes of the psychosis seen in AD.

The researchers have developed a new mouse model to study psychosis in AD and to test a variety of new drugs, including tau antibodies, as potentially more targeted treatments and without the dangerous side effects of currently used drugs.

Dr. Davies is also a Professor of Pathology and Neuroscience at the Donald and Barbara Zucker School of Medicine at Hofstra University and Northwell Health.

“Currently, the only medications available for treating the behavioral symptoms of Alzheimer’s are the powerful antipsychotics used to treat schizophrenia, but these drugs have been known to cause adverse side effects, including an increased risk of cardiovascular issues and stroke,” says Davies.

Dr. Davies hopes that their findings from the mouse studies will lead to the emergence of a few compounds to be tested in clinical trials in the coming years.

“We are trying to address an enormous need,” he says. “Our work has implications for more targeted and effective remedying of some of the most insidious aspects of the disease, which offers hope.”
Tangles in the brain’s frontal lobe may be associated with psychosis in Alzheimer’s.

Purified neurofibrillary tangles from a case of Alzheimer’s disease.
PLATELET-RICH PLASMA in the Study of Alzheimer’s Disease in a Model for the Human Brain
Amyloid is made naturally in platelets, which are cell fragments without a nucleus found in large numbers in blood, and are involved in clotting. However, in elevated levels in the brain or the blood, the presence of amyloid may suggest a disease state.

Allison B. Reiss, MD, and her team are investigating the platelet-rich plasma of patients with and without AD, as well as interactions of this plasma with neural progenitor cells (manufactured cells that behave like neurons from a person's brain). The study aims to help predict who is at risk for AD and aid in developing treatments.

Dr. Reiss is Head of the Inflammation Laboratory of the NYU Winthrop Research Institute and Associate Professor of Medicine at Stony Brook University in New York. Her interdisciplinary team includes: geriatrician Irving Gomolin, MD; neurologist Aaron Pinkhasov, MD; cardiologist Joshua De Leon, MD; and neurobiologist Lora Kasselman, PhD.

According to the researchers, there are a number of advantages to this model. First, it uses all human cells and allows for a personalized approach, since each platelet-rich plasma sample comes from an individual blood sample (and is currently widely used to accelerate healing from sports injuries). Second, the model examines neurons and their behavior without the need for a brain biopsy, which would be difficult and invasive.

Beyond accumulating in the brains of individuals with AD, studies have shown high levels of secreted amyloid in the blood of persons with only mild cognitive impairment. “If you have faulty machinery for amyloid in the brain, you most likely have faulty machinery in your platelets, since both carry your unique genetic material,” says Reiss.

“Our study is based on the hypothesis that there are significant systemic abnormalities in people with Alzheimer’s. It’s not just going on in the brain; it is a whole body disease,” she says.

The research has potential in both biomarker development—diagnosing early on who is at risk for AD—and developing drug therapies to treat it. The testing of compounds, according to the researchers, is similar in principle to what is being done now in the field of oncology as far as identifying the most optimal and targeted treatment regimens for breast and other cancers.

Dr. Reiss adds, “Our work may have important implications for predicting who may be predisposed to Alzheimer’s disease and for testing new drugs. Development of new medications has been far too slow; we want to move the field forward.”

Human immune cells stained for lipids under conditions of low inflammation (figure 1 / top of page 6) and high inflammation (figure 2 / top of page 7). High inflammation can contribute to the production of toxic amyloid and the accumulation of lipids in immune cells.

Human astrocytes unstained in quiescent state. These brain cells are extremely important in maintaining neuronal health.
Understanding the Experience of Learning an Alzheimer’s Biomarker Result
As more high-resolution diagnostic imaging tools emerge that measure amyloid and tau, understanding the impact of learning one is at heightened risk of developing Alzheimer’s dementia—a largely unstudied area—has become more urgent.

In an effort to better align communications in clinical trials—the language of researchers with the language of research subjects and clinicians—Jason Karlawish, MD, and his team are exploring how learning the results of an amyloid scan impacts participants’ daily lives and relationships.

“Understanding how people react to learning about the risk of developing Alzheimer’s dementia is as important as understanding their response to a drug,” says Karlawish.

Dr. Karlawish is Professor of Medicine, Medical Ethics and Health Policy, and Neurology at the University of Pennsylvania in Philadelphia.

Known as SOKRATES, the research is rooted in the A4 study, which is a prevention trial whereby cognitively normal adults, ages 65 to 80, undergo a PET scan to measure brain amyloid levels. The other protein implicated in Alzheimer’s is tau, and researchers are working on imaging tools to measure this, as well.

(SOKRATES stands for The Study of Knowledge and Reactions to Amyloid Testing; A4 is the Anti-Amyloid in Asymptomatic Alzheimer’s Study; and PET is short for Positron Emission Tomography).

SOKRATES will also examine individuals whose age places them far closer to the age of onset of Alzheimer’s.

“For now, the results of SOKRATES are telling investigators they need to master skills in communicating ambiguity to explain how they arrive at either a ‘not elevated’ or ‘elevated’ amyloid result,” says Dr. Karlawish.

“Alzheimer’s is a disease of the brain. What we’re finding is that it’s also a problem of the mind. As researchers discover ways to diagnose and treat it in people, they’ll need to assure them, as well, that the examined mind is worth living with.”
The aspect of brain functioning that allows us to assess where we are in space, time, and relation to others is called orientation. According to neuropsychiatrist Shahar Arzy, MD, PhD, disorientation is the core cognitive disturbance in AD. His work builds on the research of 2014 Nobel Prize in Physiology or Medicine winners John O’Keefe, May-Britt Moser, and Edvard I. Moser,¹ for their discovery of this positioning system—an “inner GPS” in the brain that makes it possible to create “cognitive maps” of the environment around us, demonstrating a cellular basis for this high cognitive function.

Dr. Arzy, Director of the Computational Neuropsychiatry Lab at Hadassah Medical Center in Israel, and his team are researching the ability to orient oneself relative to places and events, and how this mental orientation system is compromised in people with AD.

“We hypothesized that Alzheimer’s disease is a disorder of orientation, where people lose their way on the cognitive maps of memory, places, and later, people,” says Dr. Arzy. “Early on in the disorder, disorientation is compensated by memory functions, which in later stages fail as well. Early support of orientation may therefore protect memory in Alzheimer’s disease.”

At Hadassah’s Computational Neuropsychiatry Lab, Dr. Arzy’s study aims to characterize the mental orientation system and its disturbances in individuals with AD and mild cognitive impairment using a variety of high-resolution neuroimaging tools, including functional magnetic resonance imaging (fMRI), PET, and high-definition electroencephalogram (EEG), as well as by extrapolating “big-patient-data” from thousands of patients around the world.

In his diagnostic approach, Dr. Arzy begins by exploring what is
going on in the patient’s brain using personalized data regarding the patient’s own world taken from digital media, such as Facebook. Then, computational algorithms analyze the data and reveal, in real time, what is going on in the brain.

“We’re hopeful that our efforts may lead us to diagnose Alzheimer’s much earlier. It is at this earliest stage, when compensatory mechanisms still work, that the disease will be most amenable to treatment,” adds Arzy.

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Mental-orientation and standard-orientation contrast.
The investigators used fMRI to record neural activity and compare the newly developed mental-orientation task and standard-orientation tests [in the domains of time, space and person]. The contrast revealed mental-orientation to preferentially activate brain regions known as the precuneus, parieto-occipital sulcus, posterior cingulate cortices, parahippocampus and hippocampus (purple cluster). As these regions are the loci of the earliest Alzheimer’s-related pathological processes, their preferential recruitment by the mental-orientation task underlies its increased sensitivity to early manifestations of Alzheimer’s-related neurodegenerative processes.
Although AD occurs in all racial and ethnic groups, research suggests that rates of AD and other forms of dementia among African-Americans are as much as twice those of whites. In addition, African-Americans are often diagnosed at later stages of the disease when neurological damage is more advanced. African-American communities, moreover, are underserved clinically and underrepresented in AD research.

With support from the AFA, Emory University’s Alzheimer’s Disease Research Center (ADRC) in Atlanta has developed an education and outreach program in recent years to build trust within local Atlanta African-American communities and provide the latest information on AD.

Under the direction of Emory ADRC’s Clinical Core Lead James Lah, MD, PhD; Minority Engagement Core Lead Monica Parker, MD; and Education Core Lead Ken Hepburn, PhD—the ADRC has been working to help connect the African-American community with AD-related programs and services, as well as to increase engagement with research initiatives.

Progress has already been made. In 2016, largely because of Dr. Parker’s efforts, African-American participation in Emory’s AD clinical
trials increased to 32 percent, up from two percent in 2008.

“Here at Emory’s ADRC, we are invested in stopping Alzheimer’s. A core component of our center is dedicated to African-Americans, who are disproportionately affected by this disease. The grant from AFA has supported our goals to provide education, screening, and research information to help reduce the racial disparities related to Alzheimer’s,” says Dr. Lah.
The most commonly used medications to improve memory in neurodegenerative diseases target a set of neurons critical for memory called cholinergic neurons. But the drugs, known as cholinesterase inhibitors, are not very effective.

In an effort to develop treatments that more specifically target the damage, Christine DeLorenzo, PhD, and her colleagues—from the Departments of Neurobiology and Behavior of Stony Brook University and Pharmacological...
Sciences, Psychiatry and the Center of Excellence for Alzheimer’s Disease of Stony Brook Medicine in New York—are comparing the cholinergic system in healthy brains with those in AD to determine what goes wrong in AD.

Dr. DeLorenzo is Associate Professor of Psychiatry and Biomedical Engineering and Electrical and Computer Engineering. Her co-investigators include: Ramin Parsey, MD, PhD; Lorna Role, PhD; David Talmage, PhD; Nikhil Palekar, MD; and Mala Ananth. “We believe that we may be able to improve the efficacy of current treatments by gaining a better understanding of the structure and function of cholinergic neurons in healthy controls and comparing how these neurons are damaged in Alzheimer’s,” says DeLorenzo.

In the study, the investigators will use a translational approach—a parallel analysis in rodents and humans—to reveal such clues. To understand how disease-induced changes in the cholinergic system are related to memory, the investigators need to see the effects of these changes in both humans and mice.

First, using high-resolution microscopy, genetic techniques, and PET imaging, the researchers will visualize and quantify the cholinergic system in healthy mice and in a mouse model of AD. Parallel assessments using PET and MRI will be done in the humans. Memory assessments in the mouse models will then be compared to data generated from memory assessments of the human participants—again involving both healthy controls and those with AD.

It has been known for decades that the loss of cholinergic function is a hallmark of cognitive decline. Yet, says the researchers, medications that target the cholinergic system—the most widely used treatments to improve memory—have only a modest effect. “Determining why this is has been a challenge in the field,” says DeLorenzo. “The answer likely lies in our need for a more precise understanding of the cholinergic system in health to identify what is broken in Alzheimer’s. Such insight may lead to improved therapeutic strategies that are more personalized to the individual.”
Seizures in Individuals with Alzheimer’s

Epilepsy and AD frequently co-exist. The former may contribute to the progression and the more rapid decline of an individual living with AD, making early epilepsy identification and treatment critical.

What makes some people with acquired brain disorders go on to develop epilepsy, while others do not? To find out—potentially leading to more targeted epilepsy treatments—Orrin Devinsky, MD, and his team at NYU Langone Health in New York are currently investigating biomarkers of the disease.

Dr. Devinsky is Director of NYU Langone’s Comprehensive Epilepsy Center. He is also a Professor of Neurology, Neurosurgery, and Psychiatry at NYU School of Medicine.

“Interestingly, the process of developing epilepsy parallels Alzheimer’s in that in some cases, it involves the same two pathologies long thought of as the primary causes of Alzheimer’s—amyloid beta and tau,” says Devinsky.

In this prospective study, the information of tens of thousands of people living with AD over a number of years, including clinical, imaging, and cognitive function data, will be leveraged to identify these biomarkers. The available data come from two
large community-based groups—the Framingham Heart Study (FHS) and Rotterdam Study (RS).

Dr. Devinsky says, “Given our aging society, the incidence and prevalence of late-onset seizures is expected to rise substantially, making late-onset epilepsy a condition of significant public health importance—both when it coincides with and is independent of Alzheimer’s disease.

For people living with Alzheimer’s, eliminating or reducing seizures could slow Alzheimer’s progression and improve their quality of life, the ultimate goal of medicine until we can cure Alzheimer’s,” he adds.
THE ALZHEIMER’S FOUNDATION OF AMERICA (AFA) was founded in 2002 to fulfill a national need to ensure optimal care and services for individuals living with Alzheimer’s disease and related disorders, their families, and professional caregivers. Today, AFA unites a network of more than 2,600 member organizations nationwide dedicated to this mission. AFA’s services and programs include the following:

**HELPLINE**

AFA’s National Toll-Free Helpline is a resource for anyone who has questions about Alzheimer’s disease, needs emotional support, or is looking to find services. Staffed exclusively by licensed social workers, who are specifically trained in dementia care, the AFA helpline fields questions on everything from, “my loved one was just diagnosed, now what?” to more complex issues such as behavioral challenges. Helpline callers can also receive educational materials and referrals to local resources seven days a week and regardless of where they reside.

**EDUCATION AND RESOURCES**

AFA’s Education and Resource Center offers a variety of programs and services to individuals living with Alzheimer’s disease, their families, and professional caregivers, as well as the general public. Through its “Care Connection Series,” AFA provides services such as integrative therapeutic programming, educational classes, and wellness programs. The center also hosts free memory screenings and professional training workshops. Visit www.alzfdn.org/events to view upcoming events.

In addition, AFA offers free, educational webinars and materials for family caregivers. “Care Connection,” AFA’s monthly webinar series, is held on the second Thursday of each month and features guest experts highlighting topics such as paying for long-term care, managing grief, the importance of self-care, facilitating care transitions and more.
PROFESSIONAL TRAINING
AFA offers dementia-specific training to health care professionals of all levels and has trained more than 13,000 people nationwide to date. Our comprehensive and innovative training program, “AFA Partners in Care: Supporting Individuals Living with Dementia,” is rooted in the philosophy that relationships are at the core of high quality care. Training is offered regularly at AFA’s Education and Resource Center, as well as through a six-hour training DVD. AFA also conducts on-site corporate trainings that are customizable by size and topic.

PUBLIC POLICY
Advocating for increased funding for Alzheimer’s research and support services for caregivers on both a national and local scale is a necessity as the number of individuals with Alzheimer’s continues to grow. AFA has an active public policy team based in Washington, D.C. to help keep the needs of individuals with Alzheimer’s and their families top-of-mind with members of Congress and grassroots organizations.

MEMORY SCREENING
AFA believes that people should take a proactive approach to brain health and address memory concerns as early as possible. By way of its National Memory Screening Program, AFA offers free, confidential cognitive screenings across the country throughout the year. More than 4 million people have been screened since the program’s inception. Screenings take only five to 10 minutes and consist of a series of questions and tasks designed to gauge memory, analytical and language skills. While the results are not a diagnosis of any particular condition, a screening can suggest whether someone should follow up with a physician for further evaluation.

CAREGIVER SUPPORT GROUPS
AFA offers free, weekly telephone-based support groups for caregivers to help them stay connected and receive support. Groups are led by AFA’s licensed social workers and are designed to give caregivers a place to share personal experiences and best practices with one another. Call AFA’s National Toll-Free Helpline at 866-232-8484 and speak with one of our licensed social workers for more information.

DEVELOPMENT
In order to fund research, membership grants, youth scholarships, and educational conferences and programs—AFA has a robust development community. Our team helps community members organize fundraisers and cultivate relationships with donors who are as passionate about the mission as we are. AFA is a Better Business Bureau-accredited charity and prides itself on holding Charity Navigator’s highest rating of four stars.

RAISING ALZHEIMER’S AWARENESS
Each November, as part of Alzheimer’s Awareness Month, AFA holds a “Light the World in Teal” day, where landmarks around the world light up in teal to help raise Alzheimer’s awareness. Approximately 200 sites participated in the 2017 Light the World program, including: the Empire State Building and Madison Square Garden in New York; the Wrigley Building in Chicago; LAX Airport in Los Angeles; TD Garden in Boston; Trafalgar Square in London; and the Sichuan Tower in China.

YOUTH LEADERSHIP
AFA recognizes that, for a growing number of high school and college students, Alzheimer’s is a part of life. Through its youth leadership programs, AFA gives them a voice—an opportunity to raise awareness among their peers, and to receive college scholarships and emotional support.

FOR MORE INFORMATION ON ANY OF AFA’S PROGRAMS, VISIT WWW.ALZFDN.ORG.
NORMAL AGING
ALZHEIMER’S DISEASE

Using specialized software, the Computational Neuropsychiatry Lab of Shahar Arzy, MD, PhD, at Hadassah Medical Center in Israel, reconstructed anatomical MRI scans into 3D models of the brain’s cortex.

Here, the researchers demonstrate brain atrophy, or shrinkage, that occurs in Alzheimer’s disease. The brain typically shrinks to some degree in normal cognitive aging, though it does not lose neurons in large numbers. However, in Alzheimer’s disease, the damage is widespread. Many neurons cease functioning, lose connections with other neurons, and die. Alzheimer’s disrupts processes crucial to neurons and their networks, including communication, metabolism, and repair.

Special thanks to Gregory Peters-Founshtein, MD-PhD candidate in Dr. Arzy’s lab.
WE ARE HONORED the Alzheimer’s Foundation of America is supporting our study to better understand what causes the emergence of such troubling behaviors in previously gentle people. Through this research, we hope to develop antibody-based medications to treat tangles in the brain, helping reduce the effects of the disease and associated psychosis and aggression.

— PETER DAVIES, PHD
The Feinstein Institute for Medical Research in New York

HERE AT EMORY’S ADRC, we are invested in stopping Alzheimer’s. A core component of our center is dedicated to African-Americans, who are disproportionately affected by this disease. The grant from AFA has supported our goals to provide education, screening, and research information to help reduce the racial disparities related to Alzheimer’s. Progress has already been made. In 2016, largely because of the efforts of Monica Parker, MD, African-American participation in Emory’s Alzheimer’s clinical trials increased to 32 percent, up from two percent in 2008.

— JAMES LAH, MD, PHD
Emory University in Atlanta