



CIRCUITS:

A Consortium Approach to Understanding the Epigenetics of Alzheimer's

In December, Cure Alzheimer's kicked off one of the most ambitious projects it has funded—the **Collaboration to Infer Regulatory Circuits and to Uncover Innovative Therapeutic Strategies**, or CIRCUITS. Following in the footsteps of the 3-D Drug Screen Consortium (3DDS), CIRCUITS tasks nine renowned researchers and their labs from six world-class institutions to address the many unanswered questions about epigenetics and Alzheimer's disease, and to create a vast, analyzed repository of epigenetic data tied to biological and health data from patients. To meet the ambitious goals of the CIRCUITS research plan, Cure Alzheimer's Fund will support the group with \$4 million over two years.

The researchers involved in CIRCUITS are:

- **Lars Bertram, M.D.**, University of Lübeck (Germany)
- **Joseph Ecker, Ph.D.**, Salk Institute for Biological Studies
- **Winston Hide, Ph.D.**, University of Sheffield (United Kingdom)
- **Brad Hyman, M.D., Ph.D.**, Harvard Medical School/Massachusetts General Hospital
- **Manolis Kellis, Ph.D.**, Broad Institute/Massachusetts Institute of Technology
- **Rudolf Jaenisch, M.D.**, Massachusetts Institute of Technology
- **Andreas Pfenning, Ph.D.**, Carnegie Mellon University
- **Rudy Tanzi, Ph.D.**, Harvard Medical School/Massachusetts General Hospital
- **Li-Huei Tsai, Ph.D.**, Massachusetts Institute of Technology

CIRCUITS has its foundations in the Alzheimer's Genome Project™ (AGP), headed by Rudy Tanzi, Ph.D., at Massachusetts General Hospital, and supported by Cure Alzheimer's Fund since 2005. The AGP scanned the entire human genome from a large cohort of Alzheimer's families for genes associated with risk for or protection against Alzheimer's disease. The project identified dozens of risk genes, many of which currently are being investigated for therapeutic potential by CureAlz researchers.

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“The AGP provided us with a wealth of genetic data,” explains Tanzi, “but to really understand how these genes are functioning in the disease, we need epigenetic data as well. That’s where CIRCUITS comes in.”

CIRCUITS: A Consortium Approach to Understanding the Epigenetics of Alzheimer's

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From Genetics to Epigenetics

Genes are sections of DNA that code for specific proteins. The APP gene, for instance, codes for the amyloid precursor protein. Mutations in these sections of code can lead to gain or loss of function as the mutated proteins perform differently than the typical version. Such changes can lead to dysfunction and disease in ways that, in many instances, scientists have been able to trace.

But recently, geneticists have found that genes themselves don't tell the whole story. In addition to the genes in our DNA, there are vast sections of code that we are only just beginning to parse. Much of this DNA, which once was considered "junk," is now thought to regulate whether and at what level genes are decoded into proteins.

"APP, APOE and other AD genes carry mutations that directly influence susceptibility to Alzheimer's," Tanzi explains, "but another section of DNA in the human genome might be responsible for regulating that gene. It's just as important to understand this regulatory activity as it is to understand the gene defects themselves."

These regulatory changes often take place through a process called DNA methylation. Molecules called methyl groups attach themselves to genes in DNA. The number and location of these groups will affect whether and how that section of DNA is made into proteins and used by the cell.

Epigenetics introduces new levels of complexity in our understanding of DNA, but also explains a great deal that our earlier concept of genetics could not. For instance, while an organism has the same DNA in each cell of its body, the location of methyl groups on the DNA can differ by cell type. This means that a neuron and a blood cell, for example, might have different patterns of methyl groups, and therefore identical genes produce different protein output in the different cell types. Additionally, evidence suggests that an organism's life experience affects methylation, meaning how DNA is expressed can change over the course of an organism's lifetime. As a result, two individuals born with the same gene variant impacting risk of disease still might face different levels of risk from that variant, depending on how their life experiences affect the methylation of that gene.

New Levels of Specificity

Manolis Kellis, Ph.D., of the Broad Institute and Massachusetts Institute of Technology (MIT), and Li-Huei Tsai, Ph.D., of MIT and a member of the Cure Alzheimer's Fund Research Consortium, are leading a CIRCUITS project aimed at understanding these differences among cell types. "In the past, when researchers have looked at brain tissue for evidence of DNA changes linked to Alzheimer's, they haven't distinguished among cell types," Kellis explains. "My project with Dr. Tsai will provide data specific to different cell types, so we'll know whether the abnormal encoding is happening in neurons, glial cells or somewhere else."

Other researchers are generating data from a variety of sources to build a comprehensive picture of changes seen in the disease. For example, Brad Hyman, M.D., Ph.D., of Harvard Medical School and Massachusetts General Hospital, will be comparing neurons grown from stem cells to actual brain tissue from the same patients. "With current stem cell technology," explains Hyman, "we can take a patient's skin cells, convert them back into stem cells, and then grow them into a new

cell type, such as a neuron." Hyman will be able to compare these lab-grown neurons with actual brain cells from the same patient upon autopsy. "No one has ever had the opportunity to compare stem cell models to brain cells from the very same individual," says Hyman. "This experiment will be invaluable in telling us about possible limits of stem cell models, and if these newly generated cells differ from cells in tissue that has already lived many years."

Analyzing and Disseminating Data

While researchers like Kellis, Tsai and Hyman are performing experiments to generate new data, other CIRCUITS researchers are working on ways to analyze that data. Winston Hide, Ph.D., of the University of Sheffield, brings his expertise as a computational biologist to the CIRCUITS team. Hide is working on the algorithms and database design needed to make sense of the volume and complexity of the experimental data produced by the other members of the consortium. Hide and Andreas Pfenning, Ph.D., of Carnegie Mellon, will employ "big data" computing and advanced biostatistics to reveal patterns and connections among the data inputs that would have gone unseen without such sophisticated tools. The end result will be a ranking of genes and epigenetic regulatory pathways based on their likely impact on Alzheimer's disease, as well as their profile for potential drug intervention.

This data will be of vital importance to CureAlz researchers for future studies, but it also will be of great value to the Alzheimer's field as a whole. "One of the primary goals of CIRCUITS," Kellis explains, "is to generate data that can be widely distributed and used by any researcher. We don't want to keep anything proprietary. We want this



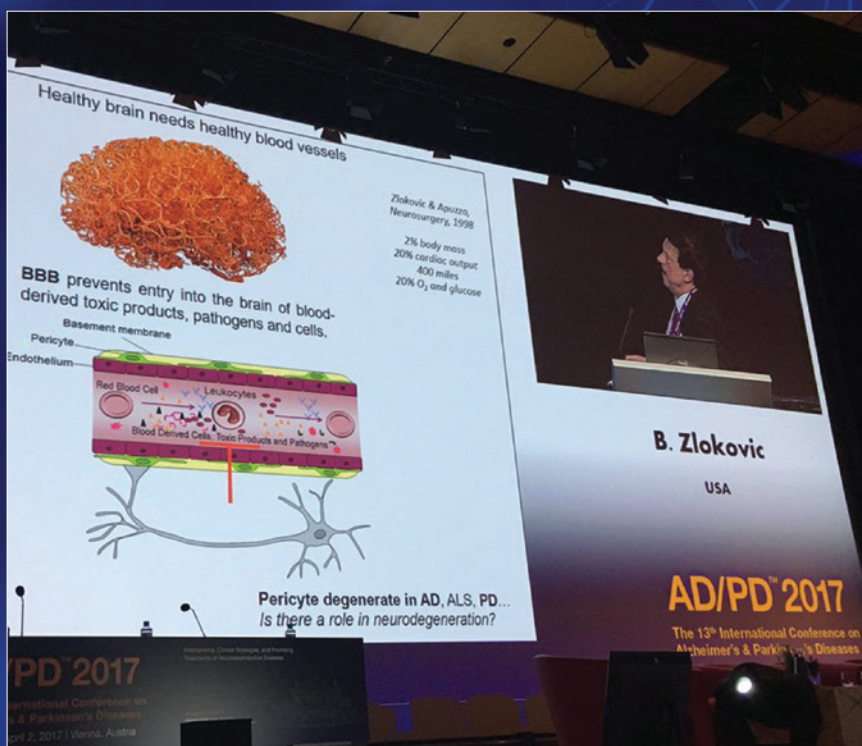
information to be used to get us to a cure as fast as possible.”

The Consortium Approach

While Cure Alzheimer’s Fund historically has supported smaller-scale research projects—one or two researchers working together and grants at the \$100,000–\$300,000 level—it was clear a different approach was needed for CIRCUITS. Generating many different types of data and analyzing that data requires expertise across several fields and a strong collaborative approach. Having seen solid results from the 3-D Drug Screening Consortium established in 2015, CureAlz wanted to apply the model in other circumstances where separate projects may never accomplish as much as a planned, coordinated effort.

“CIRCUITS has been designed very thoughtfully as a multilab consortium,” says Tim Armour, President and CEO of Cure Alzheimer’s Fund. “We have always encouraged and even required our funded researchers to share ideas and collaborate. CIRCUITS epitomizes a model where collaboration is built into the very structure of the research. The funding CureAlz provides, thanks to our donors, not only encourages, but actually enables, this kind of organized team research across institutions. We are committed to establishing additional consortia on topics vital to finding a cure.”

A consortium on APOE, the gene whose variants have the greatest impact on risk of late-onset or sporadic Alzheimer’s, is expected to launch this year. Meanwhile, Cure Alzheimer’s Fund also will continue to support individual researchers working on innovative stand-alone projects exploring promising topics in Alzheimer’s research.



AD/PD 2017 Conference

In early April, Cure Alzheimer’s Fund sponsored the “Modeling Neurodegenerative Disease in Neuron Culture Systems” panel at the Alzheimer’s Disease/Parkinson’s Disease (AD/PD) Congress in Vienna, Austria.

More than 1,000 scientists attended the panel, which featured researchers Doo Yeon Kim, Ph.D., of Massachusetts General Hospital, Li-Huei Tsai, Ph.D., of Massachusetts Institute of Technology, Andrew Yoo, Ph.D., of Washington University School of Medicine in St. Louis and Stephen Wong, Ph.D., of Houston Methodist Research Institute, all funded by Cure Alzheimer’s Fund.

Rudy Tanzi, Ph.D., of MGH and Research Consortium Chair for Cure Alzheimer’s Fund, moderated the discussion, which featured Alzheimer’s in a Dish and its use both for investigating Alzheimer’s disease pathways and for high-throughput drug screening. Each of the featured scientists mentioned their research projects would not have been possible without funding from CureAlz.

The AD/PD conference attracted 3,400 scientists from around the world who focus on Alzheimer’s disease, Parkinson’s and other neurodegenerative diseases.

STATE OF THE MIND EVENTS

State of the Mind research presentations are private gatherings of donors and prospective donors who come together to hear from a researcher about Alzheimer's disease and the role Cure Alzheimer's Fund is playing in eradicating it—funding research that leads to preventing, slowing or reversing the disease's progression. These events highlight insights into the disease pathology and allow guests to ask questions and hear directly from a researcher. This past quarter, there were five different such receptions—two each in California and Florida, and one in New York.

In Florida, an event hosted by Northern Trust Bank in Miami and arranged by CureAlz Co-Chair and Co-Founder Jeff Morby featured Rudy Tanzi, Ph.D., Chairman of the Cure Alzheimer's Fund Research Consortium. Another event in Jupiter, Florida, also featuring Tanzi, was arranged by Co-Founder and Director

Phyllis Rappaport and hosted by Mary Ann and Robb Peglar. In New York City, a State of the Mind presentation was hosted by Patty Tobin and featured Sam Gandy, M.D., Ph.D., of the Icahn School of Medicine at Mount Sinai. Two other presentations were held in California, one in Beverly Hills featuring Berislav Zlokovic, M.D., Ph.D., of the University of Southern California, hosted by Rozann Newman, while the other featured Tony Wyss-Coray, Ph.D., of Stanford University, and was held in Menlo Park. "Without the generosity of our donors, we would not have made as much progress as we have today," said Tim Armour, President and CEO, Cure Alzheimer's Fund.



L to R: CureAlz Co-Founders Jeff and Jacqui Morby, Mary Ann Peglar, Rudy Tanzi, CureAlz Co-Founder Phyllis Rappaport, Jerry Rappaport and Robb Peglar at the Loxahatchee Golf Club in Jupiter, Florida.



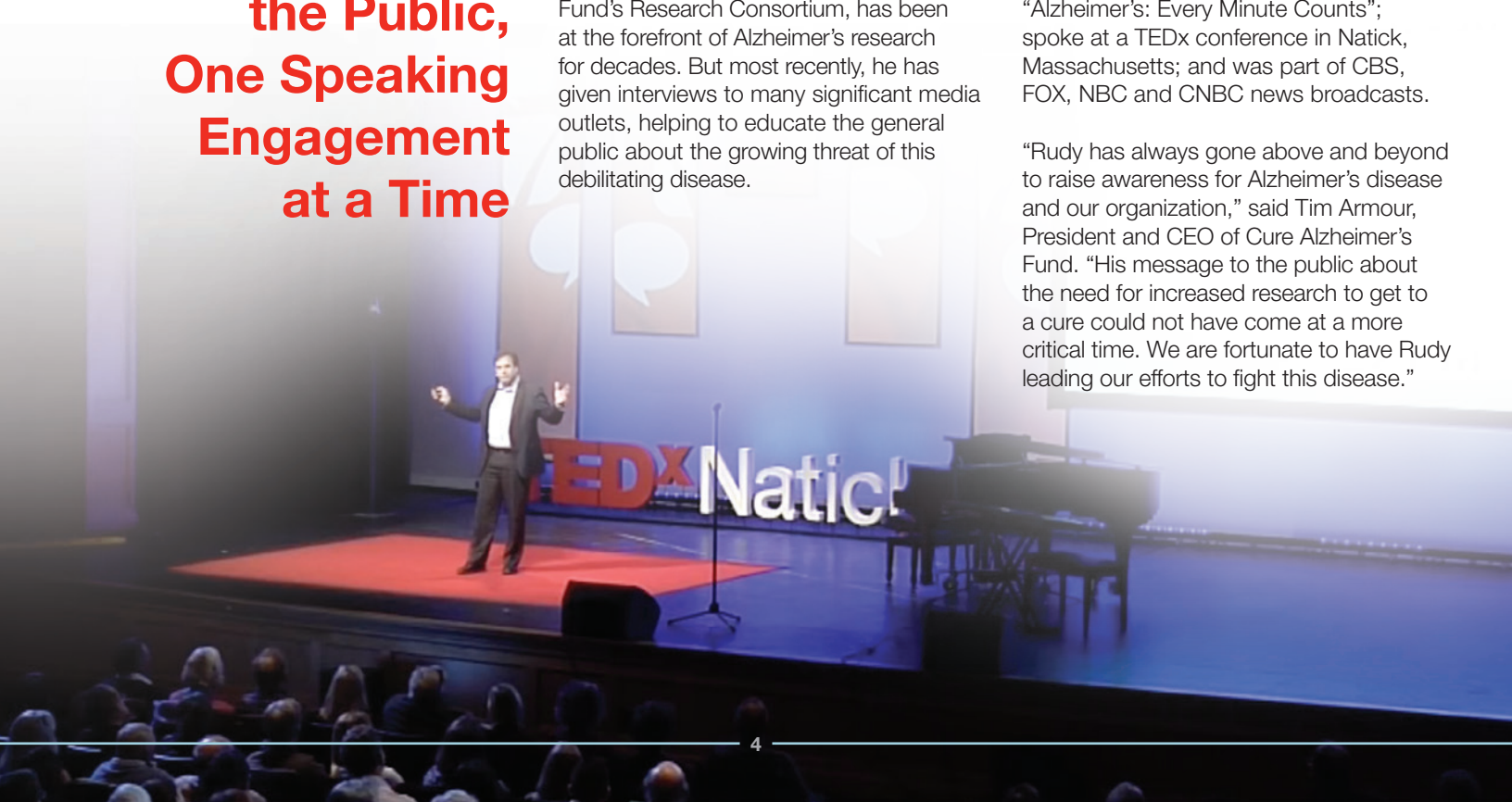
Rudy Tanzi, Ph.D., presents to Northern Trust Bank in Miami.

Educating the Public, One Speaking Engagement at a Time

Massachusetts General Hospital's Dr. Rudy Tanzi, Ph.D., Chair of Cure Alzheimer's Fund's Research Consortium, has been at the forefront of Alzheimer's research for decades. But most recently, he has given interviews to many significant media outlets, helping to educate the general public about the growing threat of this debilitating disease.

During the past few months, Tanzi was featured in a PBS documentary "Alzheimer's: Every Minute Counts"; spoke at a TEDx conference in Natick, Massachusetts; and was part of CBS, FOX, NBC and CNBC news broadcasts.

"Rudy has always gone above and beyond to raise awareness for Alzheimer's disease and our organization," said Tim Armour, President and CEO of Cure Alzheimer's Fund. "His message to the public about the need for increased research to get to a cure could not have come at a more critical time. We are fortunate to have Rudy leading our efforts to fight this disease."



Research Consortium Meeting Recap

The annual meeting of the Cure Alzheimer's Fund Research Consortium was held in February in San Diego. Eighteen members of the consortium attended, as well as key staff and board members of Cure Alzheimer's Fund. The two-day session provided the researchers with an opportunity to share their work, including insights and findings.

Beth Stevens, Ph.D., of Boston Children's Hospital reviewed how the complement pathway, which "prunes" synapses in normally developing brains, also may be involved in early synapse loss in the Alzheimer's brain. In addition, Tony Wyss-Coray, Ph.D., of Stanford University discussed the impact of young blood plasma on memory, while Karen Duff, Ph.D., of Columbia University shared her findings

on the damage to brains from excess tau protein. Finally, David Holtzman, M.D., of Washington University in St. Louis, provided an update regarding the influence of the APOE gene on Alzheimer's.

"One of our founding principles is to have open collaboration among our researchers," said Tim Armour, President and CEO of Cure Alzheimer's Fund. "This meeting provides an in-person forum where the scientists can share publicly available and confidential information fostering open discussion about the progress being made in Alzheimer's research, as well as the challenges that may be impeding that progress. The meeting is dynamic and extremely valuable for advancing the understanding of the science."

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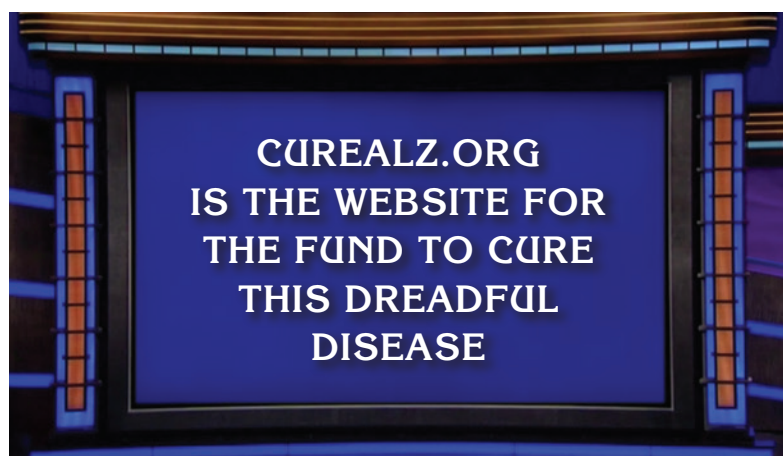
Memory Café

Three years ago, Jewish Family and Children's Services opened the first intergenerational Memory Café in Waltham, Massachusetts, designed to help people living with dementia feel comfortable and successful. The café hosts free monthly social gatherings for those living with dementia, and their family and friends. At the gatherings, community members and Brandeis University students serve as volunteer co-hosts, and a guest artist facilitates a creative exploration activity. For

care partners, the café is a much-needed break and a chance to have fun together without focusing on the disease. One spouse of a man with Alzheimer's said, "We can't wait to come back. This is the first positive activity we've had in months!" As one of Massachusetts' largest social service providers, JF&CS is able to offer the Memory Café free of charge because of generous support from individuals and organizations, including the board of Cure Alzheimer's Fund.

Making the Big Time

Did you happen to catch us on "Jeopardy!" in February? "What is Alzheimer's?" was the question for the answer, "Curealz.org is the website for the fund to cure this dreadful disease."



"Your donations make a big difference in our progress toward finding a cure for Alzheimer's disease. Your passion, your energy and your generosity are an inspiration to all of us to work even harder to end this terrible disease. Thank you all for your leadership and support."

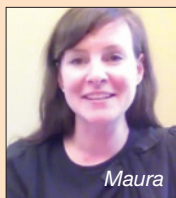
—Tim Armour, President and CEO, Cure Alzheimer's Fund

Wendy Hinden, 64, of Provincetown, Massachusetts, created a "Facebook Memory Challenge" on March 3, the 5th anniversary of her mother, Ruthi's, death. She asked friends to donate to CureAlz in Ruthi's honor.



Ruthi, left, and Wendy

Every time residential real estate broker **Maura Neill** of Atlanta closes a deal, she asks her clients to choose a charity and makes a donation out of her commission. This year, she virtually presented a check to CureAlz over Skype.



Maura

High school senior and dancer **Gabrielle de Weck** from Natick, Massachusetts, organized a dance show by The Greater Boston School of Dance in February to benefit Cure Alzheimer's Fund and honor her grandmother, who suffers from the disease.



Gabrielle

For the second year in a row, **Lt. Ralph Blight** and **Quincy (Massachusetts) Fire Fighters Local 792** held a bowling tournament in February to raise money for research.

"Alzheimer's affects so many families...guys on our job, friends, the people in our community. This bowling night, sponsored by Quincy Fire Fighters Local 792, is our way of pulling the community together for a fun night of fundraising and giving back. Any dollar, any penny raised, that can get us closer to a cure...well, 'nuff said."

—Lt. Ralph Blight



The Quincy Fire Fighters present a check.

The Deer Creek Chorale in Baltimore chose to spotlight Cure Alzheimer's Fund at its annual a capella showcase this past March to raise awareness for the disease and the organization.



Headline group The Chromatics performs at the showcase.



Stiletta, national champions, perform at SingStrong's A Cappella Festival.

For the 14th time, **Jonathan Minkoff**, 46, of New York City, produced the SingStrong International A Cappella Festival—this time at Adelphi University in Garden City, New York. All profits went, once again, to support music and Cure Alzheimer's Fund.

For the second time, the **Fraternal Order of Eagles** from Riverside, California, held a festive fundraiser with balloon tosses, raffles, bingo and a homemade cake auction, and donated all the proceeds to Alzheimer's research.



The 4th annual **Aine's Boutique fashion show** fundraiser for Alzheimer's research, a 600-person sold-out event, was held in March in Reading, Massachusetts. **Julie Centrella**, owner of the boutique named for her mother, co-sponsored the show, along with the **DKJ Foundation**, founded by brothers **Gregg** and **Bruce Johnson** in their father's honor.



L to R: MC Doug Meehan, organizer Jen Cote, Bruce Johnson, Gregg Johnson and John Slattery

Cure Alzheimer's FUND

34 Washington St.
Suite 200
Wellesley Hills, MA 02481
p: 877-CURE-ALZ (287-3259)
f: 781-658-2399
curealz.org

Centre City Tower
650 Smithfield St.
Suite 2015
Pittsburgh, PA 15222
p: 412-261-2785

Mission

Fund research
with the highest probability
of preventing, slowing
or reversing
Alzheimer's disease.

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CHARITY DESIGNATION

Cure Alzheimer's Fund®
is a "doing business as"
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tax ID #52-2396428.

Contributing Writer: Patty Bovie
Copy Editor: Colleen O'Neill
Design: Winking Fish

Financial Update

	This Quarter	YTD	Inception to Date
Fundraising	\$3.3M	\$3.3M	\$79.0M
Expenses paid for by the board	\$0.8M	\$0.8M	\$15.9M
Funded research	\$2.0M	\$2.0M	\$53.4M

Numbers shown are preliminary for the period and are rounded to the nearest \$100,000.

Research Update (Research funded during the first quarter of 2017)

Project/Researcher	Distribution Amount
Role of ATXN1 in Regulating BACE1 Activity – Jaehong Suh, Ph.D., Massachusetts General Hospital	\$287,500
Molecular and Cellular Mechanisms of ACE1 Variant in Alzheimer's Disease – Robert Vassar, Ph.D., Northwestern University	\$250,000
ABCA7 in Brain Homeostasis and Alzheimer's Disease – Guojun Bu, Ph.D., and Takahisa Kanekiyo, M.D., Ph.D., Mayo Clinic Jacksonville	\$200,000
Tau Missorting in AD—Causes and Consequences – Eva-Maria Mandelkow, M.D., Ph.D., and Eckhard Mandelkow, Ph.D., German Center for Neurodegenerative Diseases (DZNE)	\$172,500
Propagation of Tauopathy and Ubiquitin Proteasome System Dysfunction: Impact and Rescue with a UPS Activator – Karen Duff, Ph.D., and Natura Myeku, Ph.D., Columbia University	\$320,106
Genetic Targets to Block Tau Propagation: Test Knockdown of Heparan Sulfate Proteoglycan Genes <i>in Vivo</i> – Marc Diamond, M.D., University of Texas Southwestern	\$150,000
The Role of PICALM Mutations in Alzheimer's Disease – Berislav Zlokovic, M.D., Ph.D., and Zhen Zhao, Ph.D., University of Southern California	\$200,000
G2T™ Research Models and Materials – Taconic Biosciences	\$492,757
Total Distributed to Research for Q1 2017	\$2,072,863

For full abstracts of all funded projects, visit curealz.org/research/funded-research.

100 percent of every donation goes directly to research.

Help us fund research with the highest probability of preventing, slowing or reversing Alzheimer's disease.
Donations can be made through our website, curealz.org/donate, or sent directly to our office.

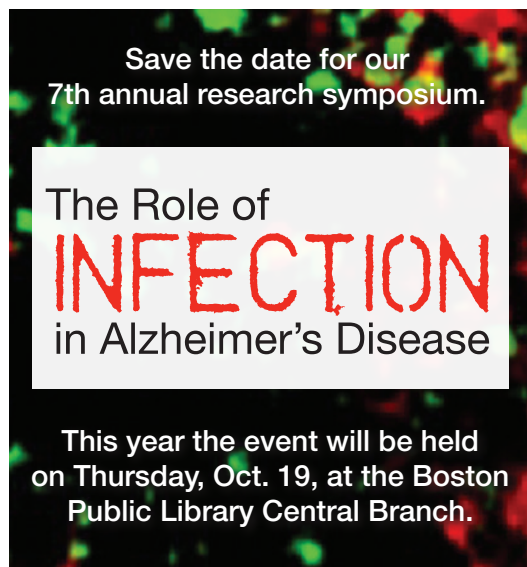
For gifts of securities or direct wire transfers, please contact Tim Armour
at **877-CURE-ALZ (287-3259)** for further information.



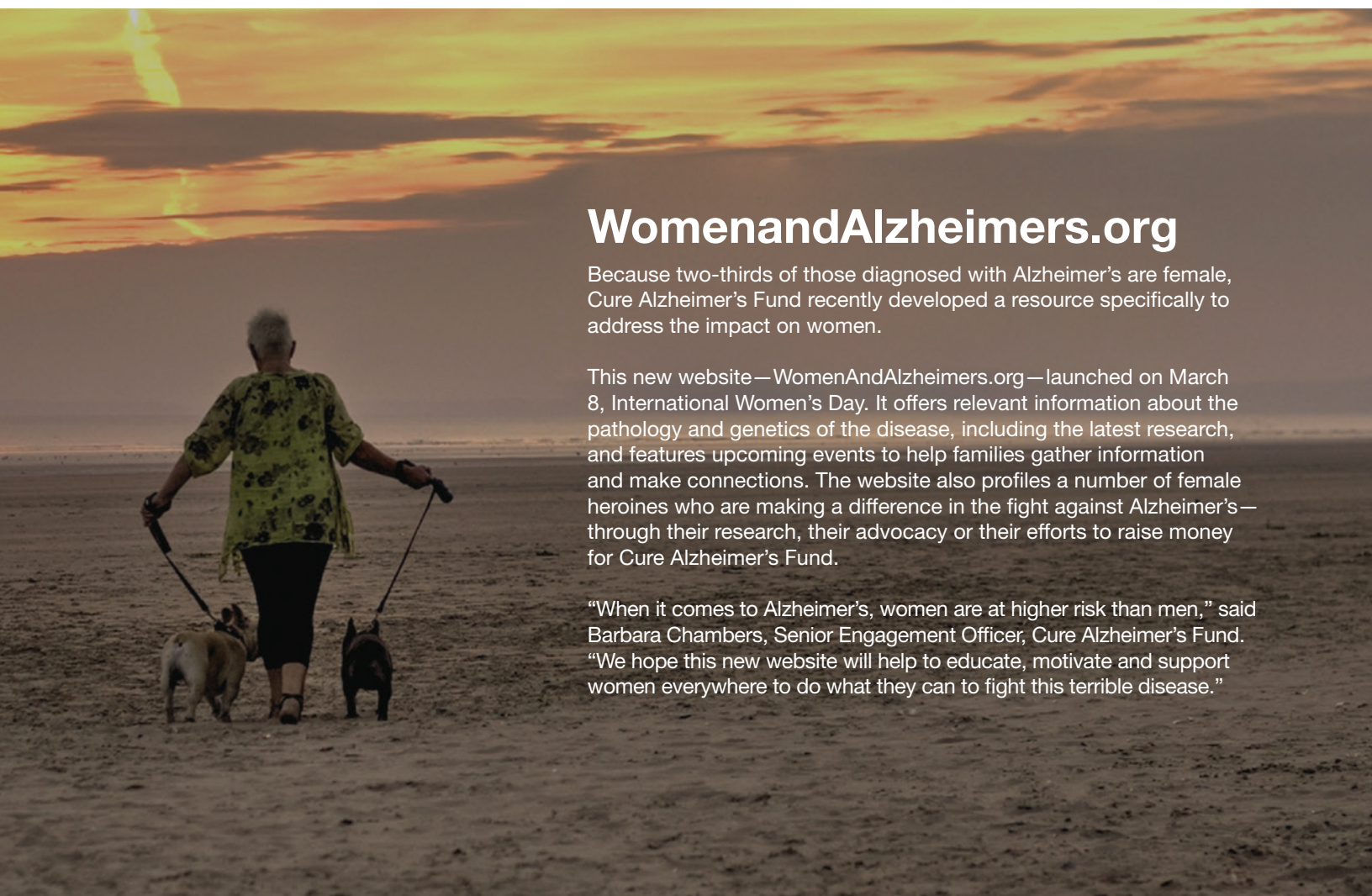
34 Washington St., Suite 200
Wellesley Hills, MA 02481

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Check out our Facebook page for our most recent posts, photos, videos and more! Go to facebook.com/CureAlzheimers.



WomenandAlzheimers.org

Because two-thirds of those diagnosed with Alzheimer's are female, Cure Alzheimer's Fund recently developed a resource specifically to address the impact on women.

This new website—WomenAndAlzheimers.org—launched on March 8, International Women's Day. It offers relevant information about the pathology and genetics of the disease, including the latest research, and features upcoming events to help families gather information and make connections. The website also profiles a number of female heroines who are making a difference in the fight against Alzheimer's—through their research, their advocacy or their efforts to raise money for Cure Alzheimer's Fund.

"When it comes to Alzheimer's, women are at higher risk than men," said Barbara Chambers, Senior Engagement Officer, Cure Alzheimer's Fund. "We hope this new website will help to educate, motivate and support women everywhere to do what they can to fight this terrible disease."