



FISHER CENTER FOR
ALZHEIMER'S
RESEARCH FOUNDATION

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**Zachary and Elizabeth M. Fisher Center for
Alzheimer's Research Foundation**

**Annual Report
2016**



MISSION STATEMENT

To support national and international projects devoted to medical research and education into the cause of, care for and cure for Alzheimer's disease.

ABOUT THE FOUNDATION

The Fisher Center for Alzheimer's Research Foundation prides itself in giving over 85% of the contributions received directly to programs in the quest to find a cure. The Foundation is the proud recipient of Charity Navigator's coveted 4-star rating for the sixth year in a row for its excellence in financial management and adherence to the best standards of accountability and transparency for a charitable organization.

Since 1995, the Fisher Center for Alzheimer's Research Foundation, a 501(c)(3) not-for-profit organization, has led the battle against Alzheimer's disease by developing innovative programs in research, education and caregiver support services. These programs focus on the cause, care and cure of Alzheimer's disease and are designed to make significant, positive differences in the lives of Alzheimer's patients, their families and the ability of caregivers and health providers to assist them.

The Foundation primarily funds scientific research into the cause and cure of Alzheimer's disease at the Fisher Center for Alzheimer's Research laboratory at The Rockefeller University. The 10,000-square-foot lab, housed at The Rockefeller University, one of the most advanced facilities of its kind in the country, is outfitted with the latest equipment necessary to undertake an interdisciplinary assault on this disease. The laboratory is under the direction of Paul Greengard, Ph.D., winner of the 2000 Nobel Prize in Medicine or Physiology. His seminal findings have been the basis for many modern day Alzheimer's investigations. Dr. Greengard and his team of over 50 world renowned scientists have published several major new findings that have led to a potential paradigm shift in how Alzheimer's is studied worldwide and treated in the future.

The Fisher Center Foundation also supports clinical research through the Fisher Alzheimer's Disease Education and Research Program at NYU Langone Medical Center. Led by pioneering researcher Barry Reisberg, MD, the program focuses on improving the care options and quality of life for Alzheimer's patients and their caregivers. The thrust of the program is to translate the advanced knowledge of the clinical symptomatology of Alzheimer's into improved caregiving. Through the program, Dr. Reisberg's team developed tools and scales for evaluating research and managing the disease in care settings around the world.



In 2001, the Fisher Center created its Alzheimer's Information Program. The program promotes public awareness and education about Alzheimer's disease. The core of the program is the Foundation's website, www.ALZinfo.org. It provides in-depth information on the most current research studies, treatments and disease management approaches. The site was recently redesigned to make it easier for visitors to navigate and find the information they need. The website is complemented by a web 2.0 social network site, ALZtalk.org, and a 1-800-ALZINFO that provides services to those who do not have access to the internet. The program uses both online and traditional media conduits to keep the public up to date with comprehensive and reliable information on recent developments in Alzheimer's disease research and treatment. The Foundation also publishes its nationally distributed magazine, *Preserving Your Memory: the Magazine of Health and Hope*, and a bi-monthly e-newsletter, both of which provide information on research developments and caregiver tips.

In 2016, the Fisher Center also published a book, "Why Can't Grandma Remember My Name?" written by the Foundation's President Kent L. Karosen and co-authored by Chana Stiefel. Written as a meaningful and creative way to explain the disease to children, the book features a series of illustrations created by children juxtaposed to people with Alzheimer's.

FOUNDATION HIGHLIGHTS 2016

Biomedical Research and Findings

1) COPI-dependent trafficking is essential for A β (Abeta) peptide accumulation

Amyloid plaques, one of the two major hallmarks of Alzheimer's disease (AD), are composed of aggregated A β peptides that result from the sequential cleavage of the amyloid precursor protein (APP). APP is cleaved by a protein (or protease) called beta-secretase, and then by the protein complex called gamma-secretase, releasing the toxic A β peptides. Those cleavages occur while APP is trafficking inside the cell, mainly from the plasma membrane to late endosomes. These multi-step biochemical reactions affect a range of biological processes, such as protein maturation and protein trafficking and involve various cellular compartments. Interestingly, little attention has been paid to the early secretory pathway, involving the coatamer protein complexes called COPI and COPII, and how these complexes affect APP maturation.

Fisher scientists investigated the possibility that an early trafficking step, involving COPI-dependent trafficking, could be relevant for APP maturation and therefore for AD. Our latest studies, using a complex set of imaging technologies coupled to biochemical experiments, demonstrate that the COPI complex, and one subunit especially (delta-COP), indeed regulates APP intracellular trafficking, controlling its subcellular



localization, cell surface expression, maturation and thus the production of A β peptides. While AD studies typically focus on the efficiency of the proteases involved in APP cleavages, this contrarian study indicates that the modification of APP itself, that occurs in early trafficking steps, could be at the origin of the problem. Altogether, these findings demonstrate the physiological relevance of delta-COP in AD pathogenesis. This study has been submitted, revised and published this year in the *Proceedings of the National Academy of Sciences*.

Fisher scientists further confirmed the biochemical results described above and assessed *in vivo* the relevance of these results for the pathophysiology of AD. By crossing a mouse model deficient in delta-COPI function with an AD mouse model well characterized in the laboratory, they investigated the role of delta-COP on APP localization and metabolism *in vivo* in the context of an intact brain. Here, they demonstrate that delta-COP regulates APP intracellular trafficking rather selectively when compared to three other proteins important for APP metabolism. More importantly, the reduction of delta-COP function significantly decreased amyloid plaque load and led to an improvement in some memory impairments observed in these mice. Fisher scientists, in collaboration with a team of geneticists, also identified genetic markers (SNPs) and mutations in COPI genes linked with an increased AD risk. These results demonstrate *in vivo* the importance of COPI and early trafficking steps in AD. This study has been submitted, revised and published this year in the *Proceedings of the National Academy of Sciences*.

2) Development of novel imaging tools to study amyloid plaques and tau neurofibrillary tangles in 3D

Amyloidosis, the formation of amyloid structures or plaques, is clearly at the epicenter of AD. More broadly, amyloidosis is a major health problem linked to aging in over one hundred diseases. Over the last three years, Fisher Center scientists have been developing new ways and optimizing new tools to study amyloid plaques in 3D. Indeed, the scientists believe that understanding how plaques are developing over time in their three-dimensional context will have profound medical and scientific consequences. Using a new methodology called iDISCO, a visualization method involving targeted molecular labeling, tissue clearing and light-sheet microscopy, the scientists gained unprecedented access to the intact AD mouse brain and studied plaque formation in animals up to thirty months of age. They are now able to visualize not only amyloid plaques, but also and simultaneously two other parameters such as tau, microglia cells and vasculature. This is the first time ever that it is possible to follow three parameters at once in 3D and in a full mouse brain. This study has been submitted, revised and published this year in the journal *Cell Reports*.



3) Screening chemical derivatives of Gleevec

Fisher scientists continue their effort to synthesize derivatives (chemically altered forms) of Gleevec and screen the derivatives for more potent beta-amyloid lowering activity and the ability to accumulate in the brain without being pumped out by the blood-brain-barrier. The main limitation of Gleevec to date is that it cannot be used *in vivo* because of its inability to accumulate in the brain. We now have designed, generated and purified over 130 Gleevec derivatives. Several of these present a better brain penetration than Gleevec. We also have derivatives that inhibit beta-amyloid accumulation more potently than Gleevec and have other improved properties, based on cellular experiments. We are currently concluding a large set of experiments to test the beneficial effects of long-term treatment for two of these compounds in mice.

Independent of this drug-based effort, a mutation that protects the elderly from developing AD was recently discovered. The cellular process responsible for the mutation's protective effect was also identified, suggesting that drugs targeting this process or pathway might also provide protection against the development of AD. In the present study, Fisher scientists discovered that Gleevec and a related compound mimic the effects of the protective mutation and thus can act as models for the development of effective drugs to fight AD. This study has been submitted, revised and published this year in the *Proceedings of the National Academy of Sciences*.

Another aim of the research program on Gleevec has been to identify how Gleevec works at the molecular level and the target protein(s) responsible for reducing beta-amyloid production. The main protein target that Fisher Center scientists identified and named - "gamma-secretase activating protein" (GSAP), based on its function - corresponds to an uncharacterized protein. This work has been previously published in the journal *Nature*. To investigate the biological functions of GSAP, and uncover its role in AD, several projects using an elaborate set of technologies ranging from molecular biology, biochemistry, cellular biology, imaging and *in vivo* experiments were initiated. The latest results confirmed the results described last year and seem to indicate that GSAP might in fact harbor several functions beneficial for AD. Indeed, recent imaging data indicate that GSAP might also act in different cell compartments and might therefore modify APP metabolism using several routes. We are finalizing several sets of experiments regarding this aspect of the work and we anticipate submitting a manuscript for publication within the next twelve months.

4) Regulation of Abeta peptide by autophagy using various chemical and biological tools

In a study previously published in the *Journal of Federation of American Societies for Experimental Biology (FASEB)*, Fisher Center scientists succeeded in accelerating the breakdown of beta-amyloid. The cellular process involved is called autophagy, a system responsible for removing debris from the cells, including unwanted materials such as the protein aggregates that are hallmarks of Alzheimer's disease. Fisher scientists discovered



a compound called SMER28 which lowers the level of beta-amyloid found in nerve cells by stimulating autophagy.

Along those lines, and following up on earlier work from the Fisher Center, Fisher scientists have identified a completely novel signaling network within neurons that regulates beta-amyloid degradation and metabolism. This work has progressed significantly over the last 12 months, and two manuscripts were submitted. As previously mentioned, A β originates from sequential cleavage of the Amyloid Precursor Protein (APP). The APP first cleavage is by BACE and yields β CTF. In turn, β CTF is cleaved by Presenilin 1 (PS1) to produce A β . In this paper, we show that PS1, in addition to synthesizing A β , can also decrease A β levels by directing β CTF degradation through autophagy. This previously unrecognized mechanism of regulation of A β by Presenilin 1 could provide an attractive target for potential Alzheimer's disease therapies. Furthermore, we demonstrated that the phosphorylation of PS1 by the protein kinase CK1 participates in the degradation of intracellular material. Lack of phosphorylation on Presenilin 1 causes accumulation of partially fused autophagosomes-lysosomes in mouse brain and reduced autophagic flux. The disturbance in autophagy leads to decreased β CTF degradation and resultant accumulation of toxic A β peptide in the brain.

5) Understanding the vulnerability of some specific neurons that causes them to disappear early on in the disease

Selective neuronal vulnerability corresponds to the concept that specific types of nerve cells (neurons) will be more susceptible to a pathological process. In the case of AD, it is well known that based on human post mortem studies that specific neuronal types disappear before others, while some other types seem to be resistant to the disease process. Understanding why some cells are vulnerable and others are resistant to the disease process will certainly bring new clues on the underlying causes of the disease and help design entirely new therapeutic strategies. Fisher scientists are pursuing their efforts to understand selective neuronal vulnerability in AD using a unique set of tools and technologies that they have developed over the years. A brain region called the entorhinal cortex is the region of the brain that is the most vulnerable to degeneration, where cell death happens very early on, but it is not known why. Fisher scientists discovered a protein which they named ADV1 (for AD vulnerability 1) that is present in much larger quantity in the entorhinal cortex and that might make this part of the brain more fragile. A world-class geneticist has identified a mutation in this gene that increases the susceptibility to the disease for people who carry this mutation. They are now trying to understand how the protein could cause vulnerability. They showed that ADV1 was interacting physically and functionally with constituents of axon terminations, at the synapse, regulating axon excitability. ADV1 seems to prevent axon terminations by excessively stimulating electrically the synapse they are forming. It remains to be shown why entorhinal cortex neurons seem to have a special mechanism for the regulation of axon excitability compared to other neurons. Their role in the formation of new memories



probably requires specific electrical properties. Fisher scientists also obtained data suggesting that an improper regulation of axon excitability might be critically linked to neurodegeneration, using state of the art bioinformatics techniques. Mutations in ADV1 might cause this dysregulation of axon excitability and thus cause irreversible damage to entorhinal cortex neurons. Fisher scientists are trying to confirm ADV1 function in neuronal cells cultivated *in vitro* but also in mice that do not have ADV1. ADV1, along with other genes shown to be acting in concert with ADV1, could represent an entirely new therapeutic strategy to specifically prevent entorhinal cortex neurons degeneration

Clinical Research and Findings

In 2016, the researchers at the Fisher Alzheimer Disease Education and Resources Program at the NYU School of Medicine completed a new statistical analysis of the data for the Comprehensive Individualized Person-Centered Management Program (CI-PCM). The prior statistician had left NYULMC and went back to China and was not active in the study subsequently. The new data analysis was completed and included an additional revised CIBIC- plus analysis. These new statistical analyses were used in the preparation and eventual publication of the research findings in a paper entitled, “Comprehensive, Individualized, Person-Centered Management of Community-Residing Persons with Moderate-to-Severe Alzheimer’s Disease: A Randomized Controlled Trial.”

In this publication, Fisher Center researchers at NYU describe the methodology of the CI-PCM management program and the research findings. An effect with the management program, globally, was about 10 times that usually observed in both prior “successful” nonpharmacologic trials, as well as the “successful” pharmacologic trials that have resulted in medication approvals. The detailed findings in this publication, which went into press in 2016, indicated very strong effects in terms of improvements in behavioral disturbances and in functioning in the AD subjects treated with the management program.

In 2016, the Fisher Center researchers at NYU published an important seminal paper entitled, “Ecopsychosocial Interventions in Cognitive Decline and Dementia: A New Terminology and a New Paradigm.” This publication is very important and will hopefully benefit the entire field of Alzheimer’s disease management and treatment. Prior to this publication, Alzheimer’s disease treatments and therapies, apart from medications, have been described as “nonpharmacologic treatments.” This is a problem because it relegates the importance of all other therapies, apart from medications, to an inferior status rather than describing these treatments for AD in terms of their true nature. Fisher Center researchers coined a new term, which comprehensively encompasses these treatments, i.e. ecopsychosocial treatments. This new terminology was published in the *American Journal of Alzheimer’s Disease & Other Dementias*. This new terminology is becoming the state of the art. The result should be an improved recognition of the true importance of psychosocial therapies for AD. This improved recognition should benefit AD persons



and their family members directly as well as help to form a stronger basis for research support for treatments that make a difference to Alzheimer's patients and their families which are not pharmacologic treatments.

In 2016, the Fisher Center researchers at NYU wrote a 59-page chapter entitled Alzheimer's disease, which will be published in January 2017. This chapter will be published in the 5th edition of the textbook "Medical Aspects of Disability." The chapter comprehensively describes the nature and the symptoms of Alzheimer's disease as well as the science of management, which the researchers developed with the support of the Fisher Center Foundation. At the conclusion of the chapter, there are case histories of people living with Alzheimer's disease who have been treated by Fisher Center scientists. One of these patients, S.M., was treated over a period of nearly 14 years. Her progression was about 50% of the rate which is usually seen in Alzheimer's disease. The excellent care provided to this woman - as a result of our treatment, advice and intervention - are extensively described. These case histories, for the first time, concretize the principles of our science of AD management.

The results of the research, including the latest findings described above, were presented in the following venues:

Department of Psychiatry, Nassau University Medical Center, Grand Rounds presentation, "Life's Mirror: New Ways of Understanding and Treating Alzheimer's Disease," East Meadow, New York, March 30, 2016.

Alzheimer's Disease Resource Center, "Life's Mirror: New Ways of Understanding and Treating Alzheimer's Disease," sponsored by the Fisher Center for Alzheimer's Research Foundation, Melville, Suffolk County, New York, April 7, 2016.

"Life's Mirror: New Ways of Understanding, Diagnosing, and Treating Alzheimer's Disease," sponsored by Zicharon, Inc., Brooklyn, New York, June 1, 2016.

Alzheimer's Disease Resource Center, "Comprehensive, Individualized, Person-Centered Care: Research Study Findings," sponsored by the Fisher Center for Alzheimer's Research Foundation, Melville, Suffolk County, New York, April 7, 2016.

The Fisher Alzheimer's Education and Resources Program at NYU Langone Medical Center accomplished basic research foundational work on the health outcomes study, including the creation of red cap accounts for primary study personnel and all regulatory work for 2016. They maintained compliance with good clinical practice standards. Additionally they updated the CI-PCM study clinicaltrials.gov account and registered the health outcomes study creating a new clinicaltrials.gov account.



In summary, the program has made significant advances in demonstrating the value of scientifically based AD management and care in 2016. Dr. Reisberg and his team have been publicizing our advances in the scientific media. They believe they are justified in the belief and their hope that these advances will continue to be translated into improved care and improved health and wellbeing for persons living with AD and those who share their burden.

Alzheimer's Information Programs

The Fisher Center Foundation's Alzheimer's Information Program is designed to provide education and disease awareness to the public. It combines traditional media conduits with the internet and social networking to expand its outreach to the public.

The Alzheimer's Information Program primarily educates the public through its website ALZinfo.org, with a complimentary 1-800-ALZINFO and its social networking site, ALZTalk.org. ALZTalk.org provides a fun, personal environment for families, friends, and medical professionals to share messages, forums, blogs, pictures, videos, chats, favorite links, etc., and allows users to stay connected with others in the Alzheimer's community.

The ALZinfo.org website is regularly updated with fresh content and coding which enhances the viewer's experience and makes it more prominent on internet searches, such as Google.com. 735,518 unique visitors viewed our site in 2016. We also send out an e-newsletter on a regular basis to over 16,500 subscribers. It features current studies and findings in Alzheimer's research that have been reviewed prior to publication by experts in the field. This is complemented by social media outreach efforts, where we have 411,000 supporters on our Facebook Causes page and 30,400 followers on Twitter.

Our updated website offers a wealth of resources for all those affected by Alzheimer's. It allows visitors to follow our research progress in developing new treatment protocols and ultimately finding a cure for this debilitating disease. One of the unique features of the site is the Resource Locator, which features a national database of over 97,000 resources for locating appropriate services in the viewer's area. The database includes nursing homes and skilled nursing facilities, home health agencies, elder law attorneys and much more. The new site also highlights a more streamlined navigation and more interactive elements. It is both smartphone and tablet friendly.

In 2016, the Fisher Center for Alzheimer's Research Foundation published a book, "Why Can't Grandma Remember My Name?" Foundation President Kent L. Karosen and Chana Stiefel wrote the book to explain the disease to children. It features a series of illustrations created by children as well as people with Alzheimer's. The juxtaposition of



the artwork provides a unique view into how the mind interprets the world and serves as an inspiring platform for parents to enlighten their children.

The Foundation's magazine, *Preserving Your Memory: the Magazine of Health and Hope*, is published three times a year. It has been in existence since 2007 and has a circulation of 60,000 copies per issue distributed at no cost to high prescribing doctors' offices and caregiving facilities in the U.S. The magazine reaches an estimated 2.8 million Americans per year, based on Mediamark Research's analysis. The magazine provides readers with information about Alzheimer's and what to do if they or a loved one fall victim to the disease. Each issue includes advice for dealing with everyday challenges, features on the latest in disease research, tips on maintaining a healthy lifestyle and more. Recent issues have featured interviews with Julianne Moore, Candy Crowley, Owen Wilson, B. Smith, and more who have been touched by Alzheimer's. The publication is also available for free download online.

Karolinska Institute, Stockholm, Sweden

The Fisher Center awarded a grant to the Karolinska Institute in Stockholm Sweden to support the research of Dr. Per Svenningsson. Dr. Svenningsson and his colleagues at the Department of Clinical Neuroscience at Karolinska continue to elucidate, through their findings, the molecular mechanisms of action in the brain relating to the cause and possible treatment of neurological disorders such as Alzheimer's disease.



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