



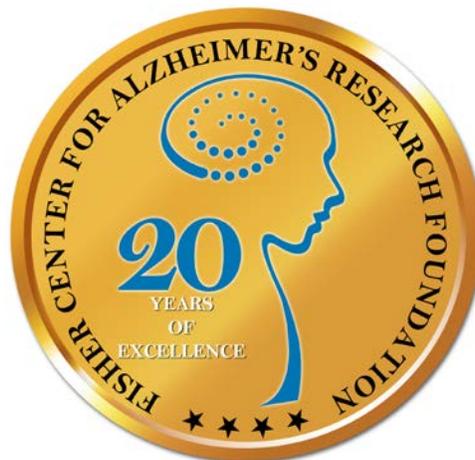
FISHER CENTER FOR  
**ALZHEIMER'S**  
RESEARCH FOUNDATION

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## **Fisher Center for Alzheimer's Research Foundation**



[www.alzinfo.org](http://www.alzinfo.org)

***20 YEARS OF EXCELLENCE***

**Annual Progress Report  
2015**



## **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.*

## **20 YEARS OF EXCELLENCE**

**The Fisher Center Foundation prides itself in giving over 85% of the contributions received directly to research in the quest to find a cure. The Foundation is the proud recipient of Charity Navigator's coveted 4-star rating for the fifth 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, is one of the most advanced facilities of its kind in the country outfitted with the latest in 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. Paul 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 will possibly be treated in the future.

Fisher Center Foundation also supports clinical research through the Fisher Alzheimer's Education and Resources 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 work of this program, tools and scales for research evaluation and a science of disease management for Alzheimer's were developed that are used in care settings around the world.

In 2001, the Fisher Center created its Alzheimer's Information Program (AIP). The program promotes public awareness and education about Alzheimer's disease. The core



of the program is the Foundation's website, [www.ALZinfo.org](http://www.ALZinfo.org). The website provides in-depth information on the most current research studies, treatments, and disease management approaches. The site just went through a revamp with a completely new look and usability to make it easier for visitors to navigate to find the information they need. The website is complemented by a web 2.0 social network site, ALZtalk.org, and a 1-800-ALZINFO phone system that provides the same 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.

## **FOUNDATION HIGHLIGHTS 2015**

### **Biomedical Research and Findings**

#### **1) The early trafficking step COPI-dependent is crucial for Abeta peptide production**

Alzheimer's disease (AD) is a complex condition that involves various cellular compartments, and affects a range of biological processes such as protein maturation and protein trafficking. The presence of amyloid plaques composed of aggregated A $\beta$  peptides that result from the sequential cleavage of the amyloid precursor protein (APP) constitutes the main hallmark of the disease. APP is first cleaved by a protein called beta-secretase, and then by the protein complex called gamma-secretase to finally release the toxic A $\beta$  peptides. Those cleavages occur while APP is trafficking inside the cell, mainly from the plasma membrane to late endosomes. However, little attention has been given to how APP maturation might be affected by its trafficking through the early secretory pathway, involving the coatamer protein complexes called COPI and COPII.

Fisher scientists investigated the relevance of an early trafficking step in APP maturation, involving COPI-dependent trafficking. Results demonstrate that one COPI subunit (delta-COP) regulates APP intracellular trafficking, controlling its maturation and thus the production of A $\beta$  peptides. Altogether, these findings demonstrate the physiological relevance of delta-COP in AD pathogenesis. Furthermore, while AD studies focus mostly on the efficiency and/or accessibility of the proteases involved in APP cleavages, this study suggests that the origin of the problem might be the modification of APP itself that occurs in early trafficking steps. This study has been submitted for publication to the *Proceedings of the National Academy of Sciences*.

After showing the involvement at the biochemical level of early trafficking steps COPI-dependent on APP maturation and consequently A $\beta$  production, Fisher scientists next further confirmed those results and assessed *in vivo* the relevance of these results. Using a



mouse model presenting impairment in delta-COPI function crossed with an AD mouse model, they investigated the role of delta-COP on APP localization and metabolism. Here, we demonstrate that delta-COP regulates APP intracellular trafficking rather selectively when compared to three other proteins important for APP metabolism. Moreover, the amount of APP present at the cell surface is significantly decreased after delta-COP. More importantly the reduction of delta-COP function significantly decreased amyloid plaque load and improved memory impairments.

Furthermore, in collaboration with a team of geneticists, the Fisher scientists identified twelve Single Nucleotide Polymorphisms (SNPs) located in COPI genes that are genetically associated with AD risk. This study has also been submitted for publication to the *Proceedings of the National Academy of Sciences*.

## **2) APP intracellular domain-WAVE1 pathway reduces amyloid-beta production**

As mentioned above, an increase in A $\beta$  production is a major pathogenic mechanism associated with AD. Fisher scientists reported recently that a portion of the protein APP (the intracellular domain called AICD) downregulates the protein WAVE1 as part of a novel mechanism to limit A $\beta$  production. The AICD binds to regulatory elements of the WAVE1 gene and negatively regulates its expression. WAVE1 also interacts and colocalizes with APP in the Golgi apparatus. Experimentally reducing WAVE1 in cultured cells reduced cell-surface APP, thereby reducing the production of A $\beta$ . WAVE1 downregulation was observed in mouse models of AD. Reduction of WAVE1 gene expression dramatically reduced A $\beta$  levels and restored memory deficits in a mouse model of AD. Remarkably, a decrease in amounts of in the messenger RNA of WAVE1, called WASF1, was also observed in human AD brains, suggesting clinical relevance of the negative feedback circuit involved in homeostatic regulation of A $\beta$  production. This work was published in the journal *Nature Medicine*. This study has also been well received worldwide.

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

Amyloidosis, the formation of amyloid structures or plaques, is a major health problem linked to aging in over one hundred diseases and the most alarming one is clearly Alzheimer's disease. Understanding its genesis in a three-dimensional context will have profound medical and scientific consequences. Over the last two years the Fisher scientists have been developing new ways and optimizing new tools to study amyloid plaques in 3D. Using the iDISCO visualization method involving targeted molecular labeling, tissue clearing and light-sheet microscopy, the researchers at the foundation gained unprecedented access to the intact AD mouse brain and studied plaque formation in animals up to twenty seven months of age. They can now visualize simultaneously amyloid plaques in 3D together with tau, microglia cells and vasculature. This is the first time ever that following three parameters at once in 3D and in a full mouse brain was



possible. Furthermore, this methodology allows the researchers to perform volume imaging followed by direct quantification of plaque characteristics like volume and inter-plaque distance. More importantly, the methodology employed is also applicable to analysis of frozen human brain samples without specialized preservation. This work progressed greatly over the last twelve months and due to its highly competitive nature, the scientists at the Fisher Center hope to be able to submit it for publication as soon as possible.

#### **4) Understanding the cellular functions of GSAP (Gamma-Secretase Activating Protein)**

Previously, Fisher Center scientists demonstrated that the anti-cancer drug Gleevec lowers beta-amyloid production by inhibiting  $\gamma$ -secretase activity but does not inhibit Notch-1 cleavage (as do other  $\gamma$ -secretase inhibitors). One of the aims of this research has been to identify the Gleevec target protein(s) responsible for reducing beta-amyloid production. One protein they identified was named, "gamma-secretase activating protein," or GSAP, based on its function. This work has been previously published in the journal *Nature*.

GSAP is a protein corresponding to a new gene and none of its functions within the cells are known at this time. To investigate the biological functions of GSAP, and better understand its role in AD, they initiated several projects using an elaborate set of technologies ranging from molecular biology, biochemistry, cellular biology, imaging and *in vivo* experiments. Recently, a highly sophisticated imaging technology has been applied to this system and has yielded exciting results pertaining to the cell biology of beta-amyloid regulation. These new results seem to indicate that GSAP has a function elsewhere in the cell, and could possibly modify APP metabolism using several routes.

#### **5) Understanding the vulnerability of some specific neurons to disappear early on in the disease**

Fisher scientists are pursuing their efforts to understand selective neuronal vulnerability in AD. The entorhinal cortex is the region of the brain that is the most vulnerable to degeneration, but it is not known why. Fisher scientists discovered a protein that they named ADV1 (for AD vulnerability 1) that is present in a much larger quantity in the entorhinal cortex and that might make this part of the brain more fragile. A world-class geneticist has found the mutation in this gene that increases the susceptibility to the disease for people that carry this mutation. Fisher Scientists are now trying to understand how the protein could cause vulnerability. This might reveal the mechanisms at play during early degeneration of entorhinal cortex cells. A possible explanation is that ADV1 might fine tune the capability for entorhinal cortex neurons to take up glucose from the extracellular milieu. It is possible that entorhinal cortex neurons, for reasons still unknown, have an increased need for glucose compared to other neurons. Mutations in ADV1, if they prevent ADV1 from fulfilling its normal function, might decrease the



amount of glucose that entorhinal cortex neurons can obtain. This is what is observed in AD patients: one of the first symptoms that can be seen is that entorhinal cortex neurons take up less glucose than in control individuals. Fisher scientists are not only trying to confirm ADV1 function in neuronal cells cultivated *in vitro* but also in mice that do not have ADV1. They have access to MRI and PET scanners from the Weill Cornell Medical Center and can monitor entorhinal cortex metabolism in mice that do not have ADV1. If that role of ADV1 is confirmed, this would highlight the importance of correcting metabolism defect in entorhinal cortex neurons at early stages of the disease.

## **6) 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)*, scientists from the Fisher Center 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.

The scientists discovered that a compound called SMER28 lowers the level of beta-amyloid found in nerve cells by stimulating autophagy. Fisher scientists continue their effort to develop chemical compounds that act like SMER28 to stimulate autophagy. Several dozen new compounds have been generated using medicinal chemistry and are currently being tested in various biological systems ranging from cultured cells to mice. Unlike drugs that attempt to inhibit the formation of beta-amyloid, these drugs are designed to stimulate the destruction, or degradation, of beta-amyloid that has been produced. Ideally, to be most effective, AD could be treated with a drug combination consisting of a beta-amyloid-inhibiting drug and a beta-amyloid degrading drug, most likely increasing the efficacy of the putative combined treatment.

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 represents another interesting lead to explore, but more work is required. Various tools have been made successfully such as molecular constructs, antibodies and even animal models.

## **7) 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 100 Gleevec derivatives. Several of these derivatives 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 initiating a large set of experiments to test one of these compounds in mice. Our ultimate goal is to produce a first generation drug, derived from Gleevec, to effectively treat the progression of AD by targeting Abeta peptide formation and/or stability.

## **Clinical Research and Findings**

### **Comprehensive, Alzheimer's Person Centered Individualized Care Program**

In 2015, the researchers at the Fisher Education and Resources Program at NYU Langone Medical School presented and published additional results from their study, "Memantine and Comprehensive, Individualized, Person Centered Management (CIPCM) of Alzheimer's Disease: A Randomized Controlled Trial," at the Alzheimer's International Conference in Washington DC. They found that participants who received the management treatment program for 28 weeks as well as the medication memantine, improved in their ability to independently perform activities of daily living such as bathing, dressing and toileting themselves, on two different test measures. Persons living with Alzheimer's in the group that only received memantine declined in these same abilities. Additionally, persons living with Alzheimer's in the management group were found to be happier and to have significantly fewer behavioral and psychological disturbances, such as, hitting their caregivers, being agitated, and experiencing night time wakefulness, than the other group, who received only the memantine treatment. These positive results with the management treatment were observed on two separate behavioral tests.

The Fisher Center researchers at NYU also completed a very comprehensive chapter entitled, "Alzheimer's Disease," for a widely used textbook of physical medicine, **Medical Aspects of Disability, 5<sup>th</sup> edition**. This chapter by Reisberg et al., will be published by Springer (New York). The chapter contains a description of the principles which were incorporated in the science of AD management used in their CIPCM studies. The chapter also contains a scientific update on the worldwide findings with respect to retrogenesis, the process by which degenerative mechanisms in Alzheimer's disease reverse normal human developmental patterns. The retrogenesis process is a fundamental mechanism of disease discovered by the Fisher Center researchers, and the term "retrogenesis" was "coined" by them (Reisberg, et al., 1999). This process has been very widely validated in worldwide studies over the past fifteen years, and these studies are summarized in this chapter for the first time. The chapter also contains two illustrated case histories of persons with Alzheimer's disease. In one case, the subject's history of the disease over a 14 year period is described and in the other case a 6 year history of progressive dementia is described. The continuing creative abilities and the continued meaning of life into the final stages and substages of AD are described and illustrated with photographs and drawings. Consequently, this chapter should be an excellent, "companion piece," to their continuing publications of the results of our CIPCM studies.



Another accomplishment in 2015 was the preparation of their 2 CIPCM studies, “Memantine and Comprehensive, Individualized, Person Centered Management of AD: A Randomized Controlled Trial” and “A 24 Week Extension Study of Memantine and Comprehensive, Individualized, Person Centered Management of AD: A Randomized Controlled Trial,” for a rigorous audit and review called a Quality Assurance and Good Clinical Practice Compliance Review. The review was performed by the Biomedical Research Alliance of New York, a group independent of the New York University School of Medicine (NYUSOM). Our studies were found to be fully compliant with the gold standard of the International Conference of Harmonization/Good Clinical Practice Guidelines.

Additionally, Fisher Center researchers at NYU completed the design of two new studies entitled, “Health Outcomes of a 28 Week Comprehensive, Individualized, Patient Centered Management Program (CIPCM) in Moderately Severe Alzheimer’s Patients on Memantine” and “Health Outcomes of a 24 Week Extended Comprehensive, Individualized, Patient Centered Management Program in Moderately Severe Alzheimer’s Patients on Memantine.” These studies will examine the Health Outcomes of their CIPCM studies including medication usage, illness incidence and outcome, hospitalization incidence and outcome, and incidence of death. These outcomes will be studied and compared in the management treatment subject group plus memantine treatment, in comparison to the nonintervention group treated with memantine alone. They created two new protocols, and submitted the new protocols to the NYUSOM Institutional Review Board for review and approval. Furthermore, they revised their new protocol application and successfully completed all regulatory work. Subsequently, the new studies and protocols received approval from the NYUSOM Institutional Review Board.

The goals of the work at NYU supported by the Fisher Center for Alzheimer’s Research Foundation are to improve the lives of persons with AD, and concomitantly of those who love, care for, and share the burdens of persons with AD. Towards these ends, there has been a nomenclature and conceptual problem which needed to be addressed. The most common designation of the treatments is “nonpharmacologic treatments.” As previously reported, they have been getting approximately 10 times the effects of AD medications with our CIPCM management approach. Under these circumstances, describing their approach by what it is not, i.e., “nonpharmacological,” rather than by what it is, for example, a “comprehensive, person centered management program,” seemed wrong and misleading. Therefore, in collaboration with an international group, they are proposing a new comprehensive, positive terminology for programs such as CIPCM program. The term is “ecopsychosocial” treatment. This term encompasses working on the AD person’s environment, psychological state, and social milieu. They presently have a publication in press in the *American Journal of Alzheimer’s Disease and Related Disorders*, proposing this new terminology (Zeisel, Reisberg, Whitehouse, et al., in press).



In 2016, Fisher Center researchers at NYU are in the process of preparing another more detailed manuscript for publication of their complete, comprehensive 28 Week CIPCM study findings.

### **Alzheimer's Information Programs**

The aim of the Fisher Center Foundation's Alzheimer's Information Program is to provide education and disease awareness to the public at large. 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](http://ALZinfo.org) with a complimentary 1-800-ALZINFO phone system and its web 2.0 social networking site, [ALZTalk.org](http://ALZTalk.org). [ALZTalk.org](http://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 the ability to stay connected with others in the Alzheimer's community.

The [ALZinfo](http://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](http://Google.com). 620,000 unique visitors viewed our site in 2015. We also send out an e-newsletter on a regular basis to over 15,000 subscribers which 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 as well where we have 411,000 supporters on our Facebook Causes page and 24,500 followers on Twitter.

In 2015, the site was re-launched due to the pro-bono services of [MRM](#), a top global digital and direct agency within McCann Worldgroup. Our reinvigorated website now offers a wealth of resources for all those affected by Alzheimer's, and 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 with 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, more interactive elements and is both smartphone and tablet friendly.

The Foundation's magazine, *Preserving Your Memory: the Magazine of Health and Hope*, is published three times year. It has been in existence since 2007 and has a circulation of 100,000 copies per issue distributed at no cost to high prescribing doctors' offices and caregiving facilities in the U.S. *Preserving Your Memory* magazine reaches an estimated 2.8 million Americans per year, based on Mediamark Research Inc.'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 of the magazine have featured interviews with Glenn Campbell, Judy Collins, Seth Rogan and Jim Nantz, 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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