



FISHER CENTER FOR
ALZHEIMER'S
RESEARCH FOUNDATION

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

**Annual Progress Report
FY 2013**



MISSION STATEMENT

To attack the scourge of Alzheimer's disease through a 3-pronged assault focused on understanding the Causes of Alzheimer's disease; improving the Care of people living with Alzheimer's to enhance their quality of life; and finding a Cure for this devastating disease.

ABOUT THE FOUNDATION

The Fisher Center for Alzheimer's Research Foundation, a 501(c)(3) not for profit organization, founded in 1995, leads 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 Disease Research laboratory. The 10,000 square foot lab 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 under the direction of Paul Greengard, Ph.D., winner of the 2000 Nobel Prize in Physiology or Medicine. His seminal findings have been the basis for many modern day Alzheimer's investigations. In 2010, Dr. Paul Greengard's team of scientists published a major finding that has been lauded as a potential paradigm shift in how Alzheimer's will be studied worldwide, and possibly treated, in the future.

Fisher Center Foundation also supports clinical research through the Fisher Alzheimer's Disease Education and Resources Program. 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 heart of which is the Foundation's website, www.ALZinfo.org. The website provides in depth information on the most current research studies, treatments, and disease management approaches. It incorporates the latest in scientific and social research with a unique Resource Locator feature for locating appropriate services in local areas. 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 informed with comprehensive and reliable information on recent developments in Alzheimer's disease research and treatment through its nationally distributed publication, *Preserving Your Memory: the Magazine of Health and Hope*, and a bi-monthly e-newsletter.

FOUNDATION HIGHLIGHTS 2013

Biomedical Research and Findings:

1) GSAP (Gamma-Secretase Activating Protein)

Previously, Fisher Center scientists demonstrated that the anti-cancer drug Gleevec lowers b-amyloid production by inhibiting γ -secretase activity but does not inhibit Notch-1 cleavage (as do other γ -secretase inhibitors). Furthermore, Gleevec was shown to inhibit γ -secretase by competing with ATP for binding to an, as then, unidentified protein. One of the aims of this research has been to identify the Gleevec target protein(s) responsible for reducing b-amyloid production. They have been successful in fulfilling this aim and this work was published in *Nature* in September 2010.

The protein they identified was named, "gamma-secretase activating protein," or GSAP based on its function as an activator of gamma-secretase. They furthermore showed that GSAP is a selective activator of gamma-secretase. In other words, it activates the gamma-secretase cleavage of amyloid precursor protein (APP) metabolites that are precursors of b-amyloid, while not affecting Notch cleavage.

GSAP is a protein encoded by a novel gene and the biological function of GSAP is unknown. To investigate the biological function of GSAP, they initiated a project designed to identify proteins physically interacting with GSAP to better understand the role of GSAP in AD. They succeeded in identifying several GSAP-interacting proteins, suggesting additional unique layers of regulation of b-amyloid metabolism and potential additional Alzheimer's drug targets. They identified twenty five GSAP interacting proteins and thirteen candidates that could be grouped into categories of proteins relevant for AD. Seven of these candidates showed an effect on A β production in cells. Following an in depth study, we chose to further study one of the seven candidates, a candidate that seems to be highly relevant for GSAP biology, called protein trafficking protein 1 (TP1).

Recently, Fisher Center scientists discovered a novel signaling pathway within cells involving at least two of the GSAP interacting proteins. This pathway determines how



proteins within the cell are relocated to specific sites or cellular organelles by being packaged into structures called cargo vesicles. This turns out to be critically important for regulating the amount of b-amyloid made by the cell. In addition to having a list of GSAP-interacting proteins that are potential drug targets for regulating amyloid metabolism, our researchers now have an understanding of how some of these proteins regulate b-amyloid, as well as new assays for measuring the effects of drug candidates targeting Alzheimer's disease.

2) **Why certain brain cells die in AD and why others are spared**

Brain cell death is believed to underlie most of the severe symptoms of AD. Brain cells die in a very distinct pattern in humans suffering from AD. Cells in the entorhinal cortex die at an early stage of the disease, and then, cells in other parts of the cerebral cortex die, progressing from one area to the next as the disease worsens. Fisher Center scientists have come up with a novel idea. They hypothesize that brain cells differ in their sensitivities to the damaging effects of factors, such as b-amyloid and tau accumulation, that initiate AD pathogenesis. They are identifying and comparing genes that function in different regions of the cortex corresponding to the pattern of cell death in AD. To do this they have successfully used a revolutionary technology that was developed at the Fisher Center called TRAP that makes it possible to resolve differences in gene function between closely associated cells in the brain, a feat that was not previously feasible. By understanding differences in gene function, Fisher Center scientists expect to be able to tell why certain brain cells and not others are sensitive to death in AD. Panels of genes have been identified that distinguish susceptible vs. resistant cells. These must now be studied to determine whether manipulation of these genes affects cellular susceptibility to neurodegeneration. This information is expected to lead to the development of drugs that would prevent brain cell death, and thus prevent or reduce AD symptoms.

Recently, Fisher scientists discovered a gene that is expressed preferentially in the entorhinal cortex, a region of the brain that is particularly susceptible to early neurodegeneration in AD. Working with a world-class geneticist, Fisher scientists then discovered that mutations in this gene are associated with an increased risk of developing AD. This important discovery will help us to determine whether the protein expressed by this gene contributes to the spreading pattern of AD in the brain and whether manipulation of this protein by drugs could prevent the spreading process and thus, slow or stop the progression of AD.

3) **Ridding cells of b-amyloid**

In 2011, Fisher Center scientists discovered that a small molecule enhancer of autophagy (the process through which a cell degrades its own components in order to regenerate itself), Smer28, reduced levels of b-amyloid in an Alzheimer's model. In a study, published in the March 7, 2011 issue of the *Journal of Federation of American Societies for Experimental*



Biology (FASEB), they succeeded in accelerating the breakdown of beta-amyloid. They discovered that a process called autophagy reduces the buildup of beta-amyloid in isolated cells and might be utilized to eliminate the buildup of beta-amyloid in the brains of Alzheimer's patients. Autophagy is a process cells use to "clean out" the debris from their interiors, 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. This occurs because SMER28 stimulates autophagy, which then rids the cell of beta-amyloid.

Recently, Fisher scientists have synthesized chemical compounds that act like Smer 28 to stimulate autophagy and rid cells of b-amyloid. By comparing the structures of these compounds, we are discovering ways of making more potent drugs that stimulate autophagy. Unlike drugs that attempt to inhibit formation of b-amyloid, these drugs are designed to stimulate the destruction, or degradation, of b-amyloid that has already been produced. In this way, AD could be treated with a drug combination consisting of a b-amyloid-inhibiting drug and a b-amyloid degrading drug. Such drug combinations are expected to be much more efficient at ridding the brain of b-amyloid than drugs that target either production or degradation of b-amyloid alone.

Clinical Research and Findings:

Comprehensive, Patient Centered, Individualized Care

The Fisher Education and Resources Center at NYU Langone Medical Center conducted a study of the effects of an individualized patient care management approach, in combination with memantine, on moderately severe stage Alzheimer's patients. The individualized, comprehensive care management program, developed by the Fisher Education and Resources Center, consisted of caregiver training that included Dr. Reisberg's *Clinical Stages of Alzheimer's* and the theory of retrogenesis, Memory Coaching, a technique also developed by the Center to re-learn basic functions lost during the course of the disease, and other information from the National Institutes of Health on the nature of Alzheimer's.

The subjects were divided into 2 groups, both received memantine, caregiver support group sessions, and comprehensive home evaluations at regular intervals throughout the course of the study. In addition to this, the caregivers in one group received the individualized care management training.

What Dr. Reisberg and his research staff saw in the group of patients whose caregivers received the individualized care management training were tremendous changes in behavior and



functionality. These patients improved in their ability to dress and bathe and toilet properly. Some even regained some of their previously lost functionality. There was also improvement in behavior, the patients exhibiting less aggression, distress, and agitation. The group whose caregivers did not receive the training, on the other hand, worsened and continued to lose functionality in their activities of daily living.

As Dr. Sunnie Kenowsky of the Fisher Education and Resources Center and the Study Director who developed and conducted this project said, "Persons with Alzheimer's still have all the needs, desires and emotions we, as human beings, share, but they gradually lose the ability to express and fulfill their needs. When [they] are loved, taught, guided, treated and supported appropriately, they can learn new ways to express themselves, find joy, meet their needs and live meaningful lives."

The results of this study are in the process of being quantified and written up, and the results will be presented for publication in the near future.

Alzheimer's Information Programs:

The Fisher Center Foundation's Alzheimer's Information Program's aim 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 with a complementary 1-800-ALZINFO phone system and its web 2.0 social networking site, ALZTalk.org. ALZTalk.org provides a fun, personal environment for families, friends, and medical professionals to post messages, forums, blogs, pictures, videos, chat, favorite links and gives the ability to stay connected with those in the Alzheimer's community. As of 2013, it enjoyed 2,879 members.

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. The number of views on the site reached 41,300 unique visitors per month. ALZinfo.org sends out an e-newsletter on a regular basis to 9,195 members (a 10% increase from last year) which contains current studies and findings in Alzheimer's research that have been reviewed prior to publication by experts in the field. The site is undergoing an extensive overhaul provided by the pro-bono services of MRM, a top global digital and direct agency within McCann Worldgroup. By March, 2014, the refreshed site will feature a more streamlined navigation, more interactive features and will be 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 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. According to a readership survey recently conducted, 100% found that the magazine gave them a better understanding of the disease. 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. This past year has featured interviews with Diane Keaton, Penny Marshall, Joan Lunden 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 granted \$25,000 to 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 will elucidate the molecular mechanisms of action in the brain relating to the cause and treatment of neurological disorders such as Alzheimer's disease

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