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
2014

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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, 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 Research laboratory. 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 Physiology or Medicine. His seminal findings have been the basis for many modern day Alzheimer's investigations. Dr. Paul Greengard and his team of 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. The website provides in depth information on the most current research studies, treatments, and disease management approaches. 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

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through its nationally distributed publication, *Preserving Your Memory: the Magazine of Health and Hope*, and a bi-monthly e-newsletter.

FOUNDATION HIGHLIGHTS 2014

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, it appeared that Gleevec likely inhibited 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. Fisher scientists were successful in fulfilling this aim and the results of their work were published in the journal *Nature.*

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)-derived precursors of b-amyloid, while not affecting Notch cleavage.

GSAP is a protein encoded by a novel gene and is believed likely to serve several, as yet unknown, functions within cells. To investigate the biological functions of GSAP and better understand its role in AD, they initiated a project designed to identify proteins physically interacting with GSAP. 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 believed or demonstrated to be relevant for AD. Seven of these candidates showed an effect on Aβ production in cells. Following an in depth study, they chose to further investigate one of the seven candidates, a protein called trafficking protein 1 (TP1). This continues to be a focus of an active investigation.

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

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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. Most recently, a highly sophisticated imaging technology has been applied to this system and has yielded exciting results pertaining to the cell biology of b-amyloid regulation. Parts of this work were recently submitted for publication in a major journal.

2) <u>Why certain brain cells die in AD and why others are spared</u>

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.

Most recently, several additional genes have been identified and work is underway to determine how these genes effect the susceptibility of neurons to degeneration in the Alzheimer's brain.

3) <u>Ridding cells of b-amyloid</u>

In a study, published in the *Journal of Federation of American Societies for Experimental Biology* (FASEB), they succeeded in accelerating the breakdown of

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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.

Most recently, Fisher scientists have identified a completely novel signaling network within neurons that regulates b-amyloid degradation and metabolism. We believe that this network will provide an understanding of why most cases of AD occur at advanced age. Understanding these factors will provide the basis for discovering drugs that combat the most important risk for sporadic AD –advanced age.

Screening chemical derivatives of Gleevec

Fisher scientists have begun to synthesize derivatives (chemically mutated forms) of Gleevec and screen the derivatives for more potent b-amyloid lowering activity and the ability to accumulate in the brain without being pumped out by the blood-brain-barrier. The reason why Gleevec cannot be used to treat AD stems largely from its inability to accumulate in the brain in sufficiently high concentration. We now have several Gleevec derivatives whose brain penetration has been improved. We also have derivatives that inhibit b-amyloid accumulation more potently than Gleevec and have other improved properties. Our goal is to produce a first generation drug (derived from Gleevec) to effectively treat the progression of AD.

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Clinical Research and Findings:

Comprehensive, Alzheimer's Person Centered Individualized Care Program

Earlier, the initial results from the Comprehensive, Individualized, Person Centered Care Management Program, conducted by the Fisher Alzheimer's Education and Resources Program at the New York University Langone Medical Center. This Program consisted of caregiver education in the course of Alzheimer's disease, how to do cognitive stimulation, activities and exercises with subjects, and caregiver education in numerous skills, such as how to manage challenging behaviors and help Alzheimer's persons relearn activities they had forgotten. In this study, The Fisher Center at NYU worked with the most difficult to manage Alzheimer's persons who had lost the ability to do one or more basic life activities, such as dressing, bathing or toileting themselves. These Alzheimer's persons also have the greatest degree of behavioral disturbance, of all the stages of Alzheimer's disease. In the study, they divided the subjects into two groups, one group received the management program and the other group did not.

They looked previously at a comprehensive measure which included the measurement of Alzheimer's persons' abilities in terms of overall functioning, behavioral disturbances and thinking abilities. After 28 weeks of treatment, those in the management program did nine times better with this comprehensive program than the known effects of a standard medication used for the treatment of Alzheimer's disease. Hence, the program was "nine times as good as medication alone." Further analyses of the constituents of the comprehensive measure indicated that the improvements which were observed were in the areas of less behavioral disturbances in the patient as reported by the caregivers and in improvements in subject functioning. For example, patients were better able to perform activities such as dressing, bathing and toileting independently. There were no significant improvements observed in thinking abilities on this measure with the management program.

A remarkable aspect of this investigation is that an entirely different group of clinicians also assessed the study subjects and interviewed the subjects' caregivers on, for the most part, different clinical measures of behavioral disturbances, functional abilities, and thinking abilities. This second set of clinicians was entirely unaware of the findings and results which were being obtained by the first group of clinician investigators. Hence, it was possible to determine whether the findings obtained from the first group of clinicians (a geriatric psychiatrist and a neurologist) would also be observed by a second group of clinicians.

The results were very exciting and very supportive of the seemingly enormous benefits of the Comprehensive Individualized Person Centered Management Program, both for the AD persons themselves, as well as for their caregivers. The results obtained were recently analyzed from this second group of clinicians and the findings have been submitted and accepted for presentation at an international scientific meeting in 2015.

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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.

The ALZinfo 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. Over 576 ,000 unique visitors viewed our site in 2014. We also send out an e-newsletter on a regular basis to over 6,000 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 14,900 followers on Twitter.

In 2014, the site underwent an extensive overhaul provided by the pro-bono services of MRM, a top global digital and direct agency within McCann Worldgroup. Our reinvigorated website now offers a deep well 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 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

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have been touched by Alzheimer's. The publication is also available for free download online.

The Foundation was the proud recipient of Charity Navigator's coveted 4-star rating for the fourth year in a row for its excellence in financial management and adherence to the best standards of accountability and transparency for a charitable organization.

Karolinska Institute, Stockholm, Sweden:

The Fisher Center gave a grant 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 Karolinksa 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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