



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 2018

Mission Statement

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

About the Foundation

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 eighth consecutive year for its excellence in financial management and adherence to the best standards of accountability and transparency for a charitable organization.

In addition, the Foundation was awarded the 2018 Gold Digital Health Awards by the Health Information Resources Center (HIRC) for its website content. The awards recognize high-quality digital health resources for consumers and health professionals.

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 causes, 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 causes and cure of Alzheimer's disease at the Fisher Center for Alzheimer's Research laboratory housed at The Rockefeller University. 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 Medicine or Physiology, his seminal findings have been the basis for many modern-day Alzheimer's investigations. Dr. Greengard and his team of 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.

The Foundation funded 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 drive 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.

The Foundation also funded the Department of Clinical Neuroscience at Karolinska Institute in Stockholm, Sweden where research continues to clarify their findings regarding the molecular mechanisms of action in the brain relating to the cause and possible treatment of neurological disorders such as Alzheimer's disease.

Finally, the Foundation supported the Weizmann Institute of Science, where Professor Michal Schwartz and colleagues suggest new ways to penetrate the blood-brain-barrier to deliver effective treatment of Alzheimer's disease (AD).

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. The website has 540,000 unique visitors. Our social platforms have a combined reach of over 45,000 followers. The website is updated regularly with fresh content on Alzheimer's, caregiving and research. Our 1-800-ALZINFO telephone line is complimentary to its social networking site, ALZTalk.org, which provides a 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 Alzheimer's Information Program promotes public awareness and education about Alzheimer's and information on caregiving. The program uses both online and traditional media conduits to keep the public informed with comprehensive information about Alzheimer's, recent research studies, treatments and disease management approaches through its publication, *Preserving Your Memory Magazine* (Circulation: 49,944; published three times a year, with an estimated readership of almost one million annually), which is distributed to health care and community organizations nationwide.

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 Sebastian Maniscalco, Pat Bowlen, Kim Cattrall, and more who have been touched by Alzheimer's. Each publication is archived on the website and is available for download at no cost.

The Alzheimer's Information Program distributes biweekly *Alzheimer's Research News You Can Use* e-newsletters of expert-reviewed Alzheimer's news and research to over 27,000 subscribers.

The Alzheimer's Information Program also distributed a book, *Why Can't Grandma Remember My Name*, written by Foundation President Kent L. Karosen and co-authored by Chana Stiefel. The book explains Alzheimer's disease by integrating artwork created by children, juxtaposed with art created by Alzheimer's patients, demonstrating the power of art therapy for all ages. The book allows parents and family to share with a younger audience what is happening to their loved ones.

Foundation Research Highlights

A grant was made to the Fisher Center for Alzheimer's Research at The Rockefeller University for neurological research into the causes and progression of Alzheimer's and potential new pharmacological treatment options. The Fisher Center for Alzheimer's Research team at the Rockefeller University has multiple competences ranging from molecular biology, electrophysiology, cellular biology, behavioral analysis, to organic chemistry. Furthermore, the scientists are studying the disease at various levels ranging from fundamental research (deciphering the causes of disease) to translational research (identifying new drug targets and drug-like compounds), moving more and more into drug design and testing candidate compounds on humanized systems.

Foundation Research Highlights (continued)

The Fisher scientists are continuing their effort researching the two main hallmarks of the disease and their related pathways: 1) the toxic beta-amyloid peptide that leads to amyloid plaque formation, and 2) the mechanisms underlying the tau pathology. They are also developing other fields of research such as inflammation, selective neuronal vulnerability and drug discovery. Some of the key developments are summarized below.

An important concept has been emerging in the field of Alzheimer's Disease (AD) within the last few years, the notion of selective neuronal vulnerability. This concept implicates that specific types of nerve cells (neurons) will be more susceptible to a pathological process, they will be affected and disappear sooner than others and thus be called resistant neurons. In the case of AD, it is well known 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 neurons 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.

To pursue their effort in that direction, Fisher scientists are using a unique set of tools and powerful technologies that they developed meticulously over the last ten years. They discovered dozens of new genes that are linked to the vulnerability and they are currently characterizing these genes, giving a special emphasis on genes that could be targeted therapeutically, that could help in designing drugs to cure the disease. Remarkably, a number of genes directly related to the protein tau have been found. Another new avenue that is emerging from these large-scale studies seems to highlight the importance of the cytoskeleton (structure located inside a cell and responsible for its shape) of the neurons. The neurons being quite complex with extremely long processes depend heavily on the shape and integrity of their cytoskeleton.

The Fisher scientists are testing the possibility to recreate, in a petri dish, neurons that are vulnerable using skin cells obtained from Alzheimer's patients called iPS cells (for Induced Pluripotent Stem cells). The goal is to generate in a petri dish the precious neurons that are the most vulnerable in the disease by reprogramming the skin cells into neurons; this process takes 4-6 weeks. The next step will be to use these patient reprogrammed neurons to identify ways to make them more resistant to insults relevant for Alzheimer's disease. One possibility is to perform gene therapy in a petri dish. By manipulating the genes identified previously, the researcher measures their impact (positive and negative) on vulnerable neurons. Another possibility is to use drug-like compounds to test putative drug-treatments that could increase the lifespan of these specific neurons.

In other research, the scientists accelerated the breakdown of the toxic beta-amyloid component by targeting a cellular process called autophagy. In the context of the amyloid hypothesis, it is believed today that the amyloid plaques might not be as toxic as initially thought, and instead smaller aggregates of beta-amyloid might be really deleterious. These toxic beta-amyloid peptides and small aggregates are being generated inside the cells. One field of research consists in identifying cellular pathways that regulate the formation of these small aggregates inside the cells. The Fisher scientists have linked the cellular process called autophagy to this phenomenon. The biological function called autophagy is responsible for removing debris from inside the cells, including unwanted materials such as protein aggregates and beta-amyloid peptides in particular. The scientists identified a novel signaling network within neurons that

Foundation Research Highlights (continued)

regulates beta-amyloid degradation and demonstrated that the phosphorylation of PS1 (a key component for the production of the toxic beta-amyloid peptide) by the protein kinase CK1 participates in the degradation of intracellular material. They are currently using several approaches to identify drug-like compounds that could activate CK1 and therefore be used as a drug to reduce the amount of beta-amyloid before they are released.

Fisher scientists continued to characterize and optimize derivatives (chemically altered forms) of Gleevec, testing the newly optimized derivatives for more potent beta-amyloid lowering activity. The new compounds were also tested for their ability to accumulate in the brain without being pumped out by the blood-brain-barrier, a weakness of the original Gleevec molecule. Interestingly, mutations that protect people from developing AD have been described in the literature. Mechanistically, some of the Gleevec derivatives synthesized seem to mimic the effect of one such protective mutation called A673T. The Fisher scientists have now studied in great detail the cellular process underlying the protective effect of this mutation. This recent work is also suggesting that drugs targeting this pathway might provide protection against the development of AD.

The Fisher scientists are studying a type of cell called Microglia often considered accessory because they are not neurons. These cells function, in the central nervous system, as scavengers. Microglia contributes to AD pathogenesis and seems to have various roles, several of them related to inflammation, but the mechanisms by which microglia, and inflammation in general, become dysfunctional in AD remain obscure. The Fisher scientists have shown that they can modulate AD-like hallmarks by manipulating *in vivo* the activity of Presenilin 1.

More recently, the scientists initiated a new line of research studying another type of accessory cells called astrocytes or astroglia. They are very abundant in the brain and have important roles. They are closely associated with neurons and they are well known for supporting the metabolic functions (feeding) of the neurons (they provide neurons with various key nutrients). The interrelationship between neurons and astrocytes is evidently very complex, but it is believed to be out of balance in the case of Alzheimer's disease. We are currently performing large scale experiments to analyze all the genes and identify those that are altered in pathological conditions relevant to Alzheimer's disease. To confirm the importance of these genes, viral vectors are then used to target these genes in rodent brains using a type of gene therapy delivery method.

This year the Fisher Center increased its size and acquired a lab space at The Rockefeller University to build a novel drug discovery platform to speed up the process. The team has been working on that technology for years and after several successful proof-of-concept experiments, it was decided that more space and more power was needed to significantly and forcefully move into that space. While typically 1 million molecules are tested using 1 million tubes or wells, this novel technology will allow the Fisher scientists to test over 100 million molecules in a single tube, possibly speeding up the drug discovery process 100 times.

Clinical Research and Findings

The Foundation supported The Zachary and Elizabeth M. Fisher Alzheimer's Disease Education and Resources Program at the New York University School of Medicine (NYUSOM) where Drs. Reisberg and Kenowsky completed significant research on the health outcomes of a Comprehensive, Individualized, Person-Centered Management Program (CI-PCM) for persons with advanced Alzheimer's disease.

Dr. Reisberg chaired a Featured Research Session at the Alzheimer's Association International Conference in Chicago, Illinois in July entitled, "Ecopsychosocial Treatments of Dementia: New Findings and Advances in Community and Institutional Settings". Dr. Reisberg presented findings that participants who received the management program for 28-weeks significantly improved in terms of their mood and behavior, while requiring less anti-anxiety medication, such as Valium or lorazepam, to treat agitation, anxiety and insomnia. The serious side effects of these medications in persons living with AD may include: increased risk of falls, paradoxical agitation, increased confusion, delirium, accelerated cognitive decline, pneumonia, stroke and death. According to a recent report in the *International Journal of Geriatric Psychiatry*, the risk of dying increases 40% for Alzheimer's disease patients who are prescribed these medications (benzodiazepines) for symptoms such as agitation, insomnia and anxiety.

These findings highlight the importance of using successful non-pharmacologic management techniques to treat these symptoms. Additionally, persons living with Alzheimer's who had been randomly assigned to the management program were found to have significantly fewer behavioral and psychological disturbances such as hitting their caregivers, being agitated, and experiencing nighttime wakefulness, as measured by two different behavioral assessment tests. In contrast, the group which did not receive the management program experienced more behavioral and psychological symptoms.

Dr. Kenowsky reported that the CI-PCM program also decreased the risk of hospitalization by 67%, and emergency room visits by 50%, in community-residing persons with advanced Alzheimer's. These findings were published in the prestigious journal, *Alzheimer's and Dementia*. Dr. Reisberg also presented findings at the American College of Neuropsychopharmacology showing that cognitive decline on tests precedes the advent of subjective cognitive decline in the course leading to the eventual dementia of Alzheimer's disease. This initial stage of, "psychometric cognitive decline," is the first new stage of eventual Alzheimer's disease to be described in 33 years.

Dr. Reisberg described the 2-year outcomes and markers of decline in normal older persons with subjective cognitive decline in a complete report in the *Journal of Alzheimer's Disease*. Dr. Reisberg and colleagues published additional results on the nature of subjective cognitive decline in AD in the journal, *International Psychogeriatrics*, as well as in the journal, *Alzheimer's and Dementia*. Furthermore, with colleagues, Dr. Reisberg published novel genetic risk factors for Alzheimer's disease related pathology in the journal, *Nature Genetics*. Dr. Kenowsky presented several community lectures, which are listed below:

- "How to Manage Persons Living with Dementia," Rockefeller University, May 2, 2018.
- "The Link between Cardiovascular Health and AD," NYU Tisch Hospital, May 22, 2018.
- "How to be a Successful Long Distance Caregiver," Credit Suisse, November 7, 2018.

Clinical Research and Findings (continued)

In addition, Dr. Kenowsky did an interview on Doctor Radio entitled, “Healthy Lifestyle Changes to Decrease the Risk of AD & Cardiovascular Disease,” May 16, 2018.

Dr. Reisberg also reported in the Newark *Star Ledger* and other New Jersey news outlets on the management program which Dr. Kenowsky developed or could say the Fisher Foundation supported, and its implications for persons with Alzheimer’s and their care providers.

In conclusion, Drs. Reisberg and Kenowsky have demonstrated important additional positive effects and advantages of their Comprehensive Management Program. They have also been describing new discoveries with respect to the origins and nature of Alzheimer’s disease, which are of relevance for the prevention and also treatment of this prevalent and costly illness.

International Clinical Research and Findings

Karolinska Institute

The Foundation 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.

p11 is an intracellular adaptor protein for transmembrane receptors which was discovered as key protein linked to the pathophysiology of major depressive disorder in the Greengard Laboratory at the Fisher Center by Doctors Svenningsson and Flajolet in 2006. Researchers have recently also found an unexpected role for p11 relevant for some forms of neurodegeneration.

In work supported by the Fisher Foundation, researchers found low levels of p11 in several brain regions in patients with movement disorders. Researchers have also found that mice completely lacking p11 have a lower response to L-dopa, the precursor of dopamine. The researchers are excited about the possibility that p11 may be implicated in processes leading to some degree to neurodegeneration and also modulate dopamine function.

The researchers have generated unique mice which lack p11 specifically in dopamine neurons and are studying how the physiology of dopamine cells are altered. More clinically relevant, they are also studying how dopamine neurons lacking p11 respond to environmental toxins, like rotenone, known to induce Parkinsonism in mice and humans.

If researchers can confirm the anticipated increased vulnerability of dopamine cells lacking p11 to experimental Parkinsonism, they will devise gene therapy approaches to overexpress p11 and cure p11 dependent deficits in dopamine neurons. This gene therapy approach could in principle be translated to other disorders involving p11.

Since 80% of the patients presenting motor symptoms and lower levels of dopamine develop dementia at later disease stages, researchers believe that changes in p11 may also correlate to cognitive status.

International Clinical Research and Findings (continued)

Weizmann Institute

The Foundation awarded a grant to the Weizmann Institute of Science in Rehovot, Israel where Professor Michal Schwartz and colleagues explore new ways to penetrate the blood-brain-barrier to deliver effective treatment of Alzheimer's disease (AD).

For 20 years, Professor Schwartz and her team at the Weizmann Institute have been working on understanding how the immune system supports the brain in health and disease. Four years ago, they observed in animal models of Alzheimer's disease, that when this support is most needed, its levels are insufficient. They showed, however, that boosting the systemic immune system by blocking inhibitory immune checkpoints, PD-1/PD-L1 pathways, you could restore immune activity needed for modifying the disease process. However, they were left with the key question of whether and how the brain's pathology accelerates immune aging/exhaustion, and identifying the key aspects of immune exhaustion that contribute to disease escalation.

Alzheimer's disease is a devastating age-related neurodegenerative disorder, and the most frequent cause of senile dementia. The appearance of cognitive decline is associated with accumulation of misfolded proteins, as well as the presence of several additional toxic processes. Among the common neuropathological features found in AD are synaptic and neuronal loss, intracellular neurofibrillary tangles, elevated levels of the toxic form of amyloid beta ($A\beta$), and the accumulation of extracellular senile plaques containing misfolded $A\beta$ peptide. Local inflammatory responses, as well as overwhelming astrocyte reactivity, are often observed in the brains of AD patients and in rodent models; these processes are not necessarily the primary causes of the disease, but are considered to be key factors in disease progression and escalation. The accumulated misfolded proteins and the neuro-inflammatory component have led to numerous attempts over the years to arrest disease progression, either using treatments that are directed against the misfolded proteins to arrest plaque burden, or using systemic anti-inflammatory drugs to arrest the brain inflammation.

Inconsistent and even conflicting results were reported, and none of the drugs tested thus far have proven effective in reversing or arresting cognitive loss in patients. The failure of treatments directed at $A\beta$ to arrest cognitive loss or to reverse it could reflect the fact that by the time $A\beta$ plaque burden is high, removal of plaques, while still important, may be insufficient to modify disease because of numerous collateral disease-escalating factors that enter into a vicious cycle, which continues even after the plaques are removed. Such factors might include those whose mitigation is dependent directly or indirectly on the immune system. In apparent support of such a model are the results suggesting that resolution of inflammation requires an active mechanism mediated by circulating immune cell recruitment to sites of brain pathology.

For decades, it was commonly believed that the brain, and the CNS in general, is unable to tolerate immune cell entry, mainly due to the understanding that the brain is a tissue behind barriers, and is viewed as an immune privileged site. In animal models of acute CNS injuries, both monocyte derived macrophages and CD4+ T cells recognizing brain antigens, are needed for coping with and helping heal parenchymal damage. Moreover, T cells present in the periphery facilitate recruitment of the monocyte-derived macrophages to the CNS, and such macrophages play a role in supporting neuronal survival and



International Clinical Research and Findings (continued)

facilitating axonal growth by resolving the local inflammatory response through their production of IL-10, and degradation of the local scar by metalloproteinase secretion.

Additional studies revealed that systemic T cells not only participate in CNS repair, but are also needed for life-long brain plasticity. In investigating how T cells support healthy brain plasticity while they are excluded from the brain parenchyma, how they facilitate recruitment of monocyte-derived macrophages, and how such monocytes can gain access to the CNS without breaching the blood-brain-barrier (BBB), it was demonstrated that the brain's barriers, including the meningeal barrier and the epithelial cell layer (CP) within the BCSFB, can serve as key compartments for immune-brain crosstalk in health and disease. This finding, coupled with unique epithelial composition of the BCSFB relative to other CNS barriers, comprised of endothelial tight junctions, and the accumulated evidence that immune cells are needed for brain maintenance and repair, led us to discover that the blood-CSF-barrier is a physiological restrictive gate that enables selective immune cell access, depending on the needs of the CNS.



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