HISTORY OF THE FISHER CENTER ON ALZHEIMER'S RESEARCH LABORATORY: 25 YEARS OF MILESTONES

DR. ALOYSIUS (ALOÏS) ALZHEIMER

The history of Alzheimer's Disease dates back to 1906 with the discovery by Dr. Aloïs Alzheimer of abnormal structures in the brain of one of his patients. In 1901, when Dr. Alzheimer was working in the city mental asylum in Frankfurt, Germany, he met a 51-year-old patient named Auguste Deter, who had developed strange symptoms, including loss of short-term memory. Dr. Alzheimer was fascinated by the patient, even intervening at one point to refuse her transfer to another facility so that he could continue to observe her. Upon her death in 1906, Dr. Alzheimer had her medical records and brain brought to his laboratory where he discovered substantial shrinkage and abnormal accumulations throughout the nerve cells. These were signs that would eventually become the identifying markers for Alzheimer's disease.

For several decades, the majority of studies on Alzheimer's disease focused on these structures, known as amyloid plaques. Scientists spent these early years exploring the relationships between physical aspects of the brain and related cognitive abilities, but nothing was known about how amyloid plaques affected the brain, and every answer they uncovered led to more questions.

NOBEL LAUREATE

DR. PAUL GREENGARD

(1925-2019)

The Man Behind the Research Center

Fifty years later, Paul Greengard would earn his Ph.D. from Johns Hopkins and start his scientific research career, leading him to Vanderbilt, Yale University, and ultimately The Rockefeller University in 1983, where his work focused on how cells in the brain transmit signals between one another. Greengard credits a lecture at Johns Hopkins on enzymes and their effect on hormones with the idea that sparked his long career. In an interview in 2016, Greengard spoke about how it had occurred to him that the way hormones transmitted information could be the same way neurotransmitters worked in the brain: "If there was one single thought I had that caused the foundation of my…later work, that was it."

Over the course of his long career, Dr. Greengard, the Vincent Astor Professor at The Rockefeller University, was known for his pioneering work as an expert in neuroscience, receiving numerous prestigious awards, including the Dickson Prize and the NAS Award in the Neurosciences. In 2000, Greengard was recognized at the highest level by his award of the Nobel Prize in Physiology or Medicine. Using the proceeds, he and his wife, sculptor Ursula von Rydingsvard, established the Pearl Meister Greengard Prize for outstanding women in biomedical research. The award was not only created to honor his mother (who died giving birth to him), but to combat the distressing discrimination he witnessed towards women in the scientific community.

When he died on April 13, 2019 at the age of 93, Dr. Greengard was still actively running the Fisher Center Research on Alzheimer's Laboratory and working in various fields of research with a team comprised of 60 people, including 30 promising young scientists. He was skilled at generating funding for his research and did so until his final days.

ZACHARY FISHER

(1910-1999)

In the 1990s, Zachary Fisher, a philanthropist and prominent figure in the New York real estate world, found himself in conversation with David Rockefeller. Fisher confided that his wife, Elizabeth, had recently been diagnosed with Alzheimer's, a progressive and deadly disease with no known cure. Rockefeller was no stranger to the disease, as his sister-in-law, Blanchette Rockefeller, had passed from Alzheimer's complications. The two men formed a partnership to create The Zachary and Elizabeth M. Fisher Center on Alzheimer's Research Laboratory (The Fisher Center Lab) that would be funded by The Zachary and Elizabeth M. Fisher Center for Alzheimer's Research Foundation (The Fisher Center Foundation). At the time, Dr. Paul Greengard, an expert in neuroscience, was already well versed in Alzheimer's disease, and so they brought him on board. Greengard served as the Lab's first and only Director until his death in 2019.

Zachary and Elizabeth M. Fisher in front of one of the Fisher Houses, which serves military personnel in need of medical care.

Photo courtesy of the Fisher House Foundation

Alzheimer's Disease

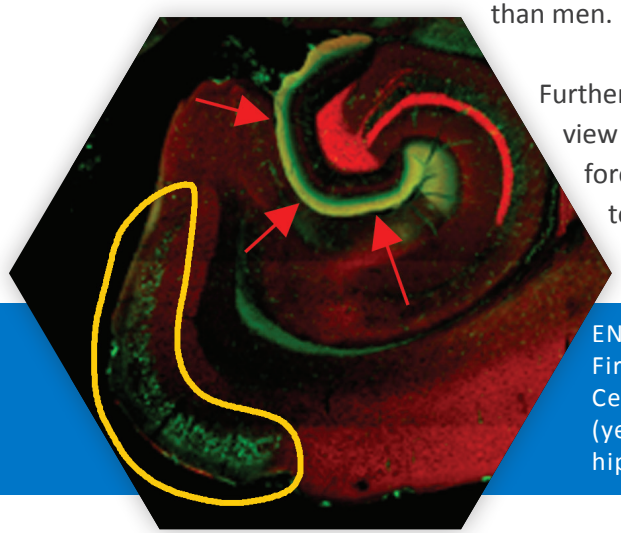
Over the last 25 years, under the direction of Dr. Greengard, scientists at the Fisher Center Lab at The Rockefeller University have had a number of breakthroughs, and have made seminal discoveries in several fields relevant to Alzheimer's disease, including novel technological advances.

Our focus has evolved over the years to encompass even more research fields, and the techniques have advanced as well. While initially, the main goal of the Fisher Center was to understand what goes wrong in the brain, over the years the focus has become more therapeutically oriented, putting significantly more weight on identifying drug targets and therapeutic approaches. The Fisher Center recently acquired more lab space to develop new drugs. Our network of collaborators has grown enormously, ranging from biologists to neuro-surgeons, human geneticists, and organic chemists.

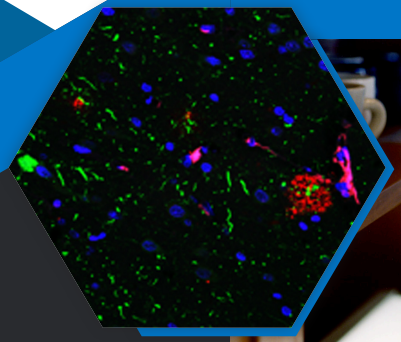
1990s

Throughout the 1990s, our scientists released important studies on their findings, including one published in the journal *Nature Medicine*. Studies that connected enzymes responsible for brain function, and breakthrough research connecting Alzheimer's disease to hormonal regulation (specifically estrogen), were particularly relevant as the scientific community had already realized that women were at higher risk of developing Alzheimer's disease than men.

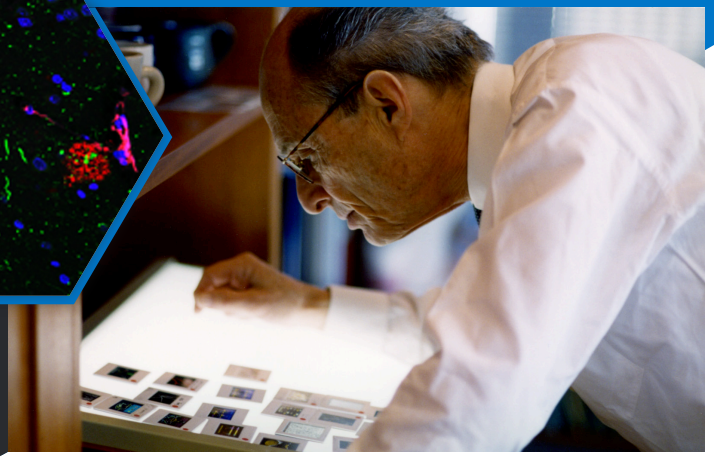
Further findings unveiled a more dynamic view of the problem and brought to the forefront the notion that events leading to certain brain functions might be more complex.



ENTORHINAL CORTEX
First region that degenerates in AD. Cellular bodies of entorhinal neurons (yellow) and their projections to the hippocampus (red arrows).



Human Tau in green - with Abeta in red



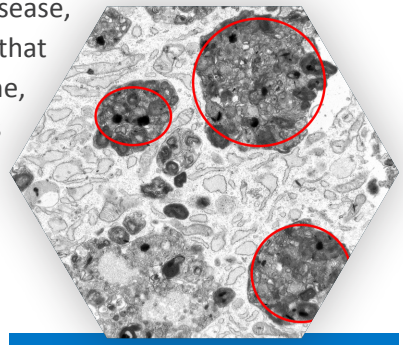
Dr. Greengard reviewing slides for an oral presentation.

Until then, the scientific community had a more static view of the problem, focusing mostly on the cell surface.

2000s

The 2000s marked a clear acceleration in the progress of the Fisher Center compared to the previous decade. This is one of the crucial pivotal periods during which we extended our field of expertise and ventured into novel scientific directions.

Pursuing our effort to understand the impact of hormones on the brain in the context of Alzheimer's disease, our researchers demonstrated that testosterone, the male hormone this time, reduced neuronal secretion of Alzheimer's beta-amyloid peptides.



Autophagic Vesicles

Scientists demonstrated a very clear correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. It is important to remember that for the longest time, only post-mortem studies were able to confirm the presence of amyloid in a patient's brain. Later on, it became clear that the correlative factor between the two was not always obvious, and that many exceptions exist for which the correlation is rather poor.

In addition, diabetes had been associated relatively early on with Alzheimer's disease, so our scientists tackled the role of insulin and in April 2001 published a study on their findings in *The Journal of Neuroscience*.

In 2005, an important breakthrough initiated a shift in the field of Alzheimer's research. Until then, the scientific community was convinced that the amyloid plaques first described by Aloïs Alzheimer were the reason for the disease. With a study published in the journal *Nature Neuroscience*, scientists demonstrated that the beta-amyloid peptide was interfering with the function of an important neuronal receptor. In other words, after this study, the world started to realize that beta-amyloid is like a sticky substance that covers the neurons, physically impairing neuronal communication, leading to vast cognitive problems, and possibly to massive neuronal death.

In 2007, while our team was looking for drug-like compounds that could regulate amyloid precursor protein (APP) to generate less beta-amyloid without affecting other functions of the brain, our scientists made several discoveries that later led to the development of better drug-like compounds. This is still a very active program today.

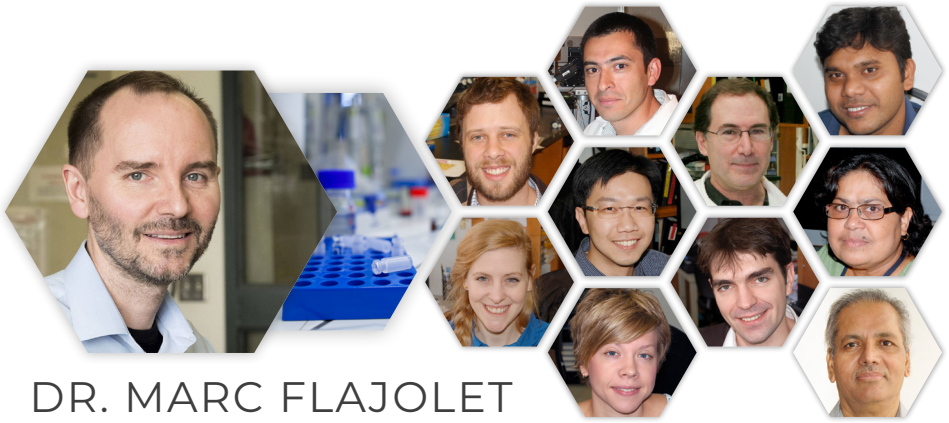
The years between 2010 and 2019 were marked by a strong push to work progressively with human samples and data, and to further develop programs to identify novel therapeutic targets as well as drug-like compounds.

In 2013, the Fisher Center lab made its debut into the world of autophagy, a kind of “cellular cleanup system,” where our scientists evaluated the possibility of boosting cell clearance to remove the toxic amyloid peptide before it is released into the brain. During this time, they published a number of studies on various cellular structures and biological systems and their relation to Alzheimer’s disease.

In September 2016, a study published by Cell Reports by our scientists received a lot of attention and praise. A technique was developed to observe inside a brain in 3D, thereby seeing firsthand the hallmarks of Alzheimer’s disease. The method works on fixed brain tissue and allows for the tissue to be cleared, as it becomes literally transparent. Using special dyes on this now transparent brain tissue, one can detect various Alzheimer’s markers.

During the past several years, our scientists have continued their efforts to further study gene therapy, research other brain cells and their various roles, develop therapeutic approaches, and to build a novel platform for drug discovery applications, including research into drugs currently used for other diseases (such as those for cancer treatment), that could be useful for Alzheimer’s. In 2020, this novel drug discovery platform was used — in conjunction with other scientists — to research drugs that could block the virus responsible for COVID-19.

Since Dr. Aloïs Alzheimer’s initial discovery in 1906, Alzheimer’s disease research has evolved and progressed. Over the years, our scientists have developed a unique set of tools and technologies that have brought us ever closer to finding the causes of this disease. The Fisher Center for Alzheimer’s Research Foundation is more determined than ever to continue raising funds for this research, and to provide information and resources to the public. We will find a cure for Alzheimer’s, and by doing so we will change the lives of millions and their loved ones.

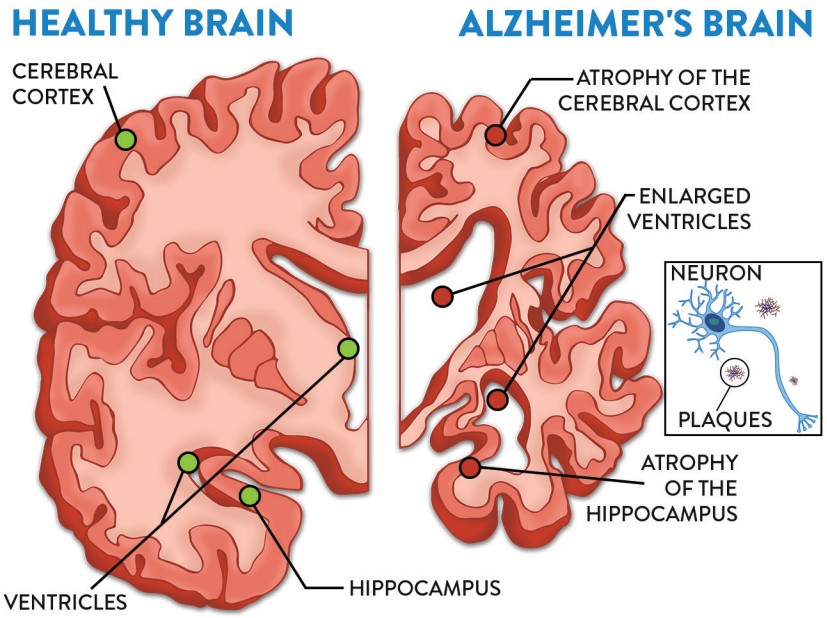


DR. MARC FLAJOLET

Interim Head of the Fisher Center Lab at The Rockefeller University
Dr. Flajolet’s research led to the discovery that a protein called CK1 regulates the production of beta-amyloid in the brain, suggesting that inhibitors of this protein might be useful in treating Alzheimer’s disease.

A TOUR OF YOUR BRAIN

Your brain is the most powerful organ in your body, and Alzheimer's disease has a devastating effect on its ability to function. This side-by-side comparison shows exactly how Alzheimer's disease destroys a healthy brain.



HEALTHY BRAIN

CEREBRUM: The main part of the brain filling most of the skull and consisting of two hemispheres. It is crucial for remembering, problem solving, thinking, feeling and movement.

CEREBELLUM: Controls coordination and balance.

CEREBRAL CORTEX (outer layer of the cerebrum): Interprets sensations, generates thoughts, participates in learning and memory, and controls movement.

BRAIN STEM: Connects the brain to the spinal cord and controls breathing, digestion, heart rate and more.

ALZHEIMER'S BRAIN

CEREBRAL CORTEX: Due to widespread cell death, the cortex shrivels up, and individuals lose their ability to communicate, recognize family and friends, and care for themselves.

NERVE CELLS AND BRAIN TISSUES: Progressive cell and tissue death causes the brain to shrink dramatically and over time affects nearly all of a person's functions. The brain cell death causes thinking and reasoning problems, followed by difficulty in walking and loss of bladder control.

HIPPOCAMPUS: Severe shrinking impairs the ability to form new memories.

VENTRICLES: Fluid-filled spaces grow larger due to brain cell death and brain shrinkage, leading to the expansion of the ventricles.

TANGLES: Abnormal, twisted clusters of proteins (Tau) that slowly prevent cells from functioning, which ultimately lead to cell death and can cause serious brain malfunctions.

PLAQUES: Abnormal aggregates of protein fragments (Abeta peptide) that accumulate between cells, slowly diminishing brain functionality.

16.1 million Americans provide unpaid care to people with Alzheimer's disease.

The estimated cost of caring for people with Alzheimer's disease and other forms of dementia is $277 billion this year. The cost could soar to more than $1.1 trillion annually by 2050.

MORE THAN 5 MILLION AMERICANS ARE LIVING WITH ALZHEIMER'S

Visit ALZinfo.org/brain to learn more

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