The Fisher Center Lab at The Rockefeller University

Over the years, a number of hallmarks strongly associated with Alzheimer's disease (AD) have been discovered. The two most prominent ones being the amyloid precursor protein (APP) and Tau. Other important aspects of the work involve the identification of the molecular mechanisms underlying vulnerability and resistance of neurons. Neurons are crucial for all cognitive functions.

One of the latest lines of research is centered on the use and development of a unique type of cell derived from Alzheimer's patients. These cells can be grown in culture to study the importance of various genes and signaling pathways, with the ultimate goal of building a much better tool for drug discovery.

New lab space has been upgraded and equipped with state-of-the-art equipment. The main activity of this new lab extension is to create an entirely novel drug discovery platform, one that is based on technology called DNA-Encoded Library or DEL. This presents many advantages compared to regular approaches.

Nine manuscripts were prepared, submitted or published this year and are at varying levels of advancement. A brief summary of the most recent findings (including the status of each manuscript) is presented below.

An APP cleavage product called C99 affects neurons of Alzheimer's patients

In a new study, the Fisher scientists provide evidence that C99 (a product of APP) could be responsible for the toxicity that leads to Alzheimer's, and are working on tools to better detect C99. If successful, this approach could bring a very important diagnostic tool to the clinic and should considerably help clinical trials and clinical developments, as well as drug efficacy evaluation. This study has been accepted for publication in the journal *Alzheimer's and Dementia* and was available online in September 2019.

Screening chemical derivatives of Gleevec

Fisher scientists have previously demonstrated that the cancer drug Gleevec, that was known to target certain proteins, has the capacity to lower beta-amyloid, the toxic component thought to lead to Alzheimer's. The original version of Gleevec was not extremely potent and was inefficient at accumulating in the brain. In order to optimize these key aspects, different pharmacological programs were put into place. Several publications have described this work in detail. This work was linked to other families of molecules, one called the "DV Program"

and another one focusing on the testing of natural compounds found in traditional Chinese medicine.

A manuscript related to this work was published in the *Journal of Medicinal Chemistry* (March 2019), and another manuscript about Chinese natural compounds has been prepared and submitted for publication.

Characterization of GSAP function

A few years ago, our scientists identified a protein, Gamma-Secretase Activating Protein (GSAP), that could bind Gleevec, making it more effective. Fisher scientists investigated the role of GSAP in three different ways:

1. The mechanism by which GSAP regulates activity has not been discovered. While removal of GSAP in cultured cells directly reduces activity for Abeta production, it does not affect other important areas. This year, this work has been published in the journal *Proceedings of the National Academy of Sciences (P.N.A.S.)*.
2. Another part of the work is dedicated to understanding the mechanism by which GSAP regulates APP.
3. Biochemical, cellular, pathogenic and human genetic data consistently demonstrate that GSAP plays essential roles in the development of Alzheimer's. Fisher scientists identified all of the proteins interacting with GSAP using global approaches, and report that GSAP regulates multiple Alzheimer's disease pathways. Two manuscripts were produced by the end of 2019, one for each of these last two points.

Understanding the vulnerability of specific neurons

The role of nerve cells (neurons) is important when talking about Alzheimer's disease, because of the way neurons communicate in the brain. The pathways that are important for learning and memory are made up of specific cells, some of which die off early in patients with Alzheimer's disease. Understanding why some cells die off early and others do not is critical to finding a cure. To address this problem, Fisher scientists are using a unique set of tools and technologies that they have developed over the past decade.

This very ambitious and unique body of work has been published partially in 2018 in *BioRxiv*. A more definitive manuscript has been prepared and submitted for publication to the journal *Neuron*. A number of experiments requested by the reviewers are being performed while the manuscript is being updated and should be resubmitted to *Neuron* in the first half of the year 2020.

Regulatory role of accessory cells in the context of Alzheimer's disease

Accessory cells (non-neuronal cells) in the brain play a crucial role in protecting the neurons, feeding them (astrocytes) and also cleaning and removing debris (microglia). The Fisher scientists are actively working on these two cell types, especially in the context of inflammation. Microglia cells (also known as scavengers) seek out damaged areas. Once activated, the microglia cells will engulf and digest anything that is dysfunctional, misshaped or dead, such as dead cells and neuronal debris, and also amyloid plaques.

The Fisher scientists studied the possibility of manipulating microglial Presenilin 1 (the main active component of an enzyme related to APP), targeting cells that lead to Alzheimer's disease.

Two manuscripts were prepared and submitted for publication; we are currently working on requested experiments and revising the manuscripts based on the reviewers' comments. One study is under revision for the journal *Molecular Psychiatry* and the other for *PLoS One*.

The construction of a novel drug discovery platform

Significant progress has been made in several directions. This effort is closely supervised by Dr. Marc Flajolet, a neuro-molecular biologist, and is centered on the revolutionary technology called DNA-Encoded Library (DEL).

This technology is revolutionary contrary to the regular approach (HTS) that typically test on average 500,000 molecules per screen over a period of several months using important resources (both human and financial) and real estate. The DEL approach can easily test 100 million compounds all at once in one tube and in just weeks. This effort should greatly accelerate the drug discovery rate and significantly increase the number of therapeutic targets that can be tested at the Fisher Center as well as in collaboration with other labs and institutions.