December 4th, 2017 – Andy Teich, MD, PhD, Assistant Professor of Pathology & Cell Biology, Columbia University/ Neuropathology Core Co-Lead, Columbia University ADRC/ Co-Director New York Brain Bank - *A Systems Biology Approach to Discovering Novel Drivers of Disease in AD.*

Dr. Andy Teich presented his research to determine which signaling molecules are responsible for aberrantly turning on or off large groups of genes. He thinks that these signaling molecules, "master regulators," may explain the disrupted gene function in AD, and ultimately hold promise as therapeutic targets. In an effort to better understand the molecular drivers of synaptic dysfunction in Alzheimer's disease (AD), his laboratory has analyzed neuronal gene expression data from human AD brain tissue to identify master regulators of synaptic gene expression. Analysis of this data recently identified ZCCHC17 as a top candidate master regulator predicted to normally support the expression of a network of synaptic genes, and whose dysfunction in AD leads to lower expression of these genes.

A summary of Teich's laboratory findings so far: ZCCHC17 is normally expressed in neurons and is reduced early in the course of AD pathology. A majority of the synaptic genes predicted to be driven by ZCCHC17 in human neurons are down regulated after ZCCHC17 knockdown in rat cortical cultures. The net effect on gene expression after ZCCHC17 knockdown preferentially affects oncology groups related to synaptic function, even when secondary changes in gene expression are included. The lab group also observed predicted alterations in potassium function, both physiologically and in terms of protein expression level.

In future work, Teich's group will continue to characterize the electrophysiology and synaptic consequences of ZCCHC17 knockdown in rat cortical cultures. They plan to express a ZCCHC17-flag protein in human iPSC-derived neurons and perform mass spectrometry after IP pull-down. This approach will allow them to catalog the proteins that directly interact with ZCCHC17 in neurons. This work will serve as a proof of concept for a high throughput screening of drugs for advancing precision medicine for AD. At Columbia University, High-Throughput Drug Screening with PLATE-seq is already being used successfully for oncology research and can easily be applied to AD research.

Teich also introduced a project to collect biopsies of brain tissue and CSF during routine surgery for normal pressure hydrocephalus**.** Often elderly, some of these patients show

biomarkers of early stage AD and provide a unique and uncommon opportunity to study tissue samples at this early stage of disease, before a person’s death. The project involves screening this brain tissue using advanced sequencing technologies to determine which genes are being abnormally turned on and off, and then correlating this with various biomarkers that relate to Alzheimer's disease progression. Another goal is to verify that CSF phosphor-tau levels are driving changes in gene expression in NPH biopsies, in hopes of understanding the mechanisms of pathological change in this biopsied tissue.