"Behavioral and cell-based complementary screens to identify druggable targets modulating tau protein levels"

A key hallmark of Alzheimer's Disease, related dementias and Chronic traumatic encephalopathy is the progressive deposition of aggregates inside the neurons composed of the Microtubule Associated Protein Tau in what is known as "tangles". This Tau accumulation correlates very well with the onset and progression of disease symptoms and is known to be damaging from cell-based as well as mouse-based experiments. Interestingly, tests done in mouse models have shown that decreasing the levels of Tau even after neuronal dysfunction has begun can protect and, to some extent, revert the pathogenic effect of Tau. Therefore, identifying mechanisms involved in the regulation of Tau levels in neurons can provide us with potential therapeutic targets for the treatment of Alzheimer's Disease and related dementias.

With the support of the DKR Fund, we have screened the group of genes for which a drug could potentially be developed (called "druggable" genome) to identify which of them can modulate Tau levels. Since the druggable genome consists of thousands of genes, this initial screening phase cannot be carried out using mouse models, which are very costly and impractical. Therefore, we used a combinatorial screening strategy using *Drosophila* and cell-based models. The fruit-fly, *Drosophila* possesses a complex nervous system with similar biology to mammalian neurons but offers the high throughput capabilities that mice cannot. Using fruit-flies that express human Tau in their nervous system, we identified 222 genes that when inhibited could improve the neuronal dysfunction caused by Tau in neurons. Next, we inhibited these 222 genes one by one in human cells and found 25 genes that could also decrease Tau levels in human cells. Of these, 4 were able to decrease Tau levels in both *Drosophila* neurons and human cells and therefore we selected them for further characterization.

Autophagy is a process that cells, including neurons, use to degrade protein aggregates and prevent them from building up. As we age, neurons progressively lose their autophagic capabilities, and it has been described that in Alzheimer's disease and related dementias, autophagy can be severely defective. This may underlie protein aggregation, for example in the form of Tau tangles. In fact, it is well established that Tau can be degraded via autophagy. Interestingly, 2 of our most robust hits are able to promote autophagy when their levels are modulated, and this has been the focus of our current funding period.

We have confirmed that these two hits indeed induce autophagy activation. In addition, we obtained drug modulators of these genes and have seen both autophagy activation as well as decreased Tau deposition. Using primary neurons from mouse Tauopathy models, we have proven that both genetic as well as chemical manipulation of these genes results in Tau reduction and we are now in the process of validating these genes directly in mouse Tauopathy models by using viral delivery. We are also further characterizing the chemical inhibitors, to identify one that would be able to enter the brain and target these genes in neurons. We are very excited about the potential that these compounds may offer for clinical intervention or as tool compounds for preclinical trials.