TCS/22/06 – Development and Application of a Drug Screen for Compounds Targeting Phenotypic Deficits Associated with Mutation of SORT1 in a Human Neuronal-based Model of Dementia.

The mechanisms that lead to neuronal (nerve cell) death in Alzheimer's Disease (AD) are not fully understood, but we know two key things. The first is that mutations (damaging changes) in certain genes, including the SORT1 gene, increase a person's risk for AD. The second is that a build-up of a toxic molecule, amyloid beta (Aβ), in the brain is important. Aβ is made by the splitting of a bigger protein, APP, into different sized fragments. How much Aβ is produced depends upon APP's location within the cell. APP's location within the cell is determined by its interaction with other proteins. One of these other proteins, sortilin (a protein produced by the SORT1 gene) interacts with APP, managing its location and processing. More Aβ is produced when sortilin is missing from mouse neurons, and when sortilin production is restored levels of Aβ are decreased. Given this evidence, we wish to identify the differences between human neurons with mutant and normal SORT1 and test thousands of drugs to identify those that restore neurons with mutant SORT1 to health. In the longer term, we hope that this work will lead to drugs that will reduce the risk for AD.