

Oligomers of Wild Type Transthyretin are Cytotoxic: Understanding the Pathology of Senile Systemic Amyloidosis

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Senile Systemic Amyloidosis (SSA) is a unique disease predominately affecting men over the age of 60 years. In SSA, the wild type (WT) human serum protein transthyretin (TTR) becomes destabilized, misfolds and precipitates as amyloid primarily in the heart; amyloid deposits lead to congestive heart failure, arrhythmias, and conduction defects. Previous studies have suggested that heart failure due to amyloidosis may be greatly unrecognized and under diagnosed. Furthermore, it has been shown that the amount of amyloid in the heart does not directly correlate to disease severity; thus, cytotoxicity may be a contributing factor in SSA pathology. The purpose of this study was to investigate whether non native WT TTR oligomers (pre fibrils) are cytotoxic to cells in culture. Recombinantly generated human WT TTR and two TTR mutants (V30A and V122I) associated with cardiac amyloidosis