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