FIRST-IN-CLASS DRUG CANDIDATES WITH NEUROPROTECTIVE POTENTIAL FOR TREATING PD AND AD BY CLEARING MEMBRANE-ASSOCIATED A-SYNUCLEIN AND TAU

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Introduction: Neuronal degeneration in Alzheimer's and Parkinson's disease entails an elusive cascade of events comprising noxious aggregation of amyloidogenic proteins. Although the precise nature as to the harmful misformers inciting neuronal demise remains elusive, pharmacological inhibition of such anticipated toxic species would represent an effective strategy to decelerate disease progression.

Aims: Identifying therapeutically relevant TAU and α-synuclein (SYN) species involved in neuronal degeneration.

Methods: Chemo-genetic screening approaches - aimed to understand the mechanism by which previously identified drug candidates inhibit toxic SYN and TAU species - were performed. Studies using transgenic animal models of AD/PD were carried out to evaluate therapeutic potential of the toxicity inhibitors.

Results: Chemo-genetic screening demonstrated that decreasing SYN/TAU toxicity by the inhibitors required endosome-to-lysosome vesicle sorting and lysosomal proteolysis. In agreement with this observation in-vivo studies revealed that treated AD/PD animal models with the toxicity inhibitors displayed a strong decrease of SYN and phospho-TAU in the membrane fractions, but not in soluble or insoluble protein fractions. Treatment with the inhibitors also led to a strong reduction of oligomeric SYN, TAU tangles and CSF TAU. Moreover, neuronal integrity was found preserved and behavioral deficits were mitigated in treated animals.

Conclusions: Increasing lysosomal degradation of membrane-associated pathological TAU/SYN assemblies exerts neuroprotection. Pharmacological modulation of such lysosomal clearance pathway comprises a promising therapeutic avenue for treating PD and AD patients.