

**OC.14- THE MOLECULAR TWEEZER CLR01 INHIBITS AMYLOID AGGREGATION RELIEVING LYSOSOMAL PATHOLOGY AND PROTECTING AGAINST NEURODEGENERATION IN LYSOSOMAL STORAGE DISEASES**

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Lysosomal storage diseases (LSDs) are inherited metabolic disorders caused by either lysosomal or non-lysosomal proteins deficiencies and often showing a severe neurodegenerative course. No cure is currently available to slow neuropathology progression in these diseases. Neurodegeneration in LSDs is driven by a global dysfunction of the lysosomal system, in particular of autophagy pathway. Such lysosomal dysfunction is associated to progressive accumulation of several types of substrates, whose nature and pathogenic relevance remain, however, still unclear. Here we found that massive amyloid deposition characterizes brain pathology in several mouse models of LSDs. Brain amyloid deposits progressively build up as neurodegeneration proceeds as shown by analyzing a mouse model of neurodegenerative LSDs. Such amyloid inclusions contain  $\alpha$ -synuclein together with several other aggregate-prone proteins, such as prion protein, Tau and amyloid  $\beta$ -peptide. A major fraction of these amyloid deposits is localized to the lysosomal compartment where they act as main determinants of lysosomal dysfunction, thus boosting the development of neurodegenerative phenotype. Indeed, inhibiting amyloid deposition in MPS-IIIA mice by CLR01, a “molecular tweezer” molecule, which efficiently hamper self-assembly of multiple amyloidogenic proteins relieves lysosomal pathology, thus re-activating lysosomal-autophagic pathway and ameliorating neuropathological signs. Together, these data put more insights on mechanisms determining amyloid aggregation toxicity and identify LSDs as a new class of amyloid disorders. Moreover, our results identify CLR01 as a potent drug candidate for the treatment of brain lesions in LSDs.

