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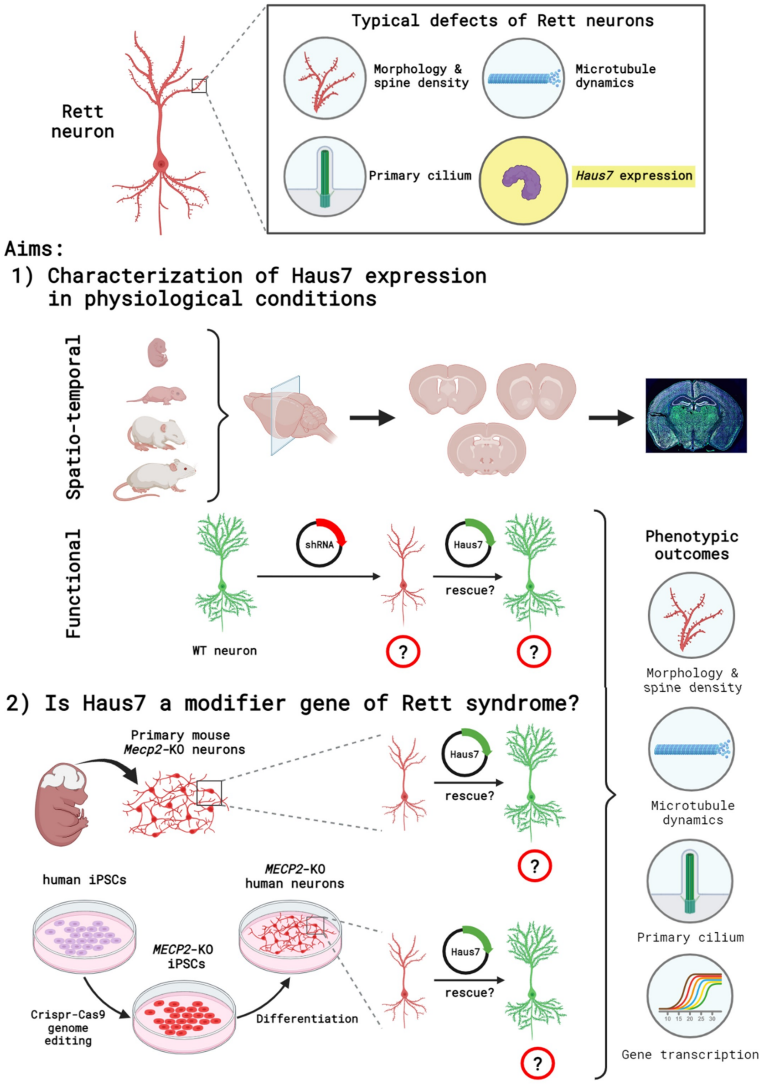
Molecular, cellular and functional characterization of Haus7 a new potential molecular determinant in neuronal maturation and neurodevelopmental disorders



Rett syndrome (RTT) is the leading cause of severe intellectual disability in females and is caused by mutations in MeCP2. Neurons represent the core targets of the pathology, and Mecp2 deficient neurons exhibit defective dendritic complexity and synaptogenesis, together with altered microtubule dynamics and microtubule dependent trafficking. We have recently identified the Haus7 gene as consistently downregulated in the brain of Mecp2 deficient mice.

HAUS7 is a member of the protein complex augmin, which regulates microtubule assembly and spindle formation in cycling cells. The protein is also expressed in neurons where its precise function remains undefined. To provide new insights in the comprehension of RTT syndrome and to disclose novel therapies, we will investigate the role that Haus7 plays in wild-type and RTT neurons. In particular, we will define the spatio-temporal expression of Haus7 in the WT and Mecp2 null mouse brain along development. Then, we will elucidate the functional role of the protein in neurons and synapse development by using shRNA approach. Obtained results will be exploited in the attempt to rescue defective Haus7-dependent neuronal features which are altered in RTT. Further, by genome editing we will insert RTT mutations in human stem cells. By differentiating these iPSCs into neurons, we will validate whether human RTT neurons reproduce the observed downregulation of Haus7 and assess whether its normalization can modify typical RTT phenotypes in human neurons as well.

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