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P13. INHIBITION OF S1P DEGRADATION IS BENEFICIAL IN THE TRANSGENIC R6/2 MOUSE MODEL OF HUNTINGTON DISEASE

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Background. Huntington's disease (HD) is the most common neurodegenerative disorder with no effective cure currently available. Over the past few years our research has shown that alterations in sphingolipid metabolism represent a critical determinant in the pathogenesis of the disease. In particular, we have provided the first evidence of aberrant metabolism of sphingosine-1-phosphate (S1P) in multiple disease settings including human post-mortem brains from HD patients. Importantly, we have also demonstrated that pharmacological interventions aimed at reducing S1P degradation, by inhibition S1P-Lyase (SGPL1), resulted beneficial in an HD cell model.

Aim. In this study, we aimed to investigate whether inhibition of SGPL1 may exert therapeutic action in-vivo in the R6/2 HD mouse model.

Results. Our results indicate that chronic administration of 0.1 mg/kg THI is safe and well tolerated in manifest R6/2 HD mice. The compound significantly slowed down the progressive mouse motor deficit associated with the worsening of the disease. Immunoblotting analysis reveals a significant increase in the levels of cortical post synaptic density protein PSD-95 in HD treated animals. Further analyses are in progress for establishing any other disease- modifying properties of the compound.

Conclusion. Our preliminary data indicate that the beneficial effect of THI treatment may be likely associated with an increased synaptic activity. These findings further support the idea that modulation of S1P metabolism may represent a promising therapeutic approach for the treatment of the disease.