Towards deciphering the role of N-terminal post-translational modifications in regulating the function of Huntingtin (Htt) in health and disease

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Switzerland

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Towards deciphering the role of N-terminal post-translational modifications in regulating the function of Huntingtin (Htt) in health and disease

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SNSF

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€ 315,560

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3

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Research Abstract
Several post-translational modifications (PTMs) within the N-terminal 17 residues of the Huntingtin protein plays major roles in regulating its function and its role in the pathogenesis of Huntington’s disease (HD). For elucidating the relationship between specific PTMs and HD

progression and pathology, a better understanding of how individual modifications and cross-talk between different modifications influence the biochemical, structural and cellular properties of this protein is essential.

The overall objective of this proposal is to apply chemical biology approaches to dissect the role of all known N-terminal modifications on modulating the structural, aggregation, and biochemical properties of exon1 of the Huntingtin protein, 1-90, Httex1). To achieve this goal, we plan to develop new methods that would allow for the first time site-specific introduction of single or multiple post-translational modifications into Httex1. Investigations of the biochemical, structural, aggregation and functional properties of the modified semi-synthetic proteins in vitro will provide novel and important insight into the mechanisms by which PTMs regulate the function of Httex1 under physiological and pathological conditions. The effect of different PTMs on the cellular and toxic properties of Httex1 will be assessed by introducing these proteins into primary neurons, cellular models of the disease. We will also seek to determine how these modifications influence the interaction of this protein with other proteins. These studies could result in the elucidation of novel disease mechanisms and the identification of therapeutic targets for the treatment and/or prevention of neurodegeneration in HD.
In addition, the availability of homogeneous and site-specifically modified forms Httex1 will help advance current mechanistic studies and efforts to develop diagnostic tools based on assessing changes in the levels of these modifications during disease progression.

Further information available at:

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Switzerland

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