Advanced models of polyglutamine disorders (HD, SCA3, SCA7) – *ModelPolyQ*

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Polyglutamine (PolyQ) diseases are a group of 9 neurodegenerative diseases caused by over-repetition of the CAG codon, which translates into polyglutamine tracts within specific proteins for each disorder. Despite important progresses in the knowledge of the pathological mechanisms involved we still miss effective therapies. Advances in this field depend on innovative, predictive, models of disease for which there is an urgent need for both mechanistic and preclinical studies. In this project we focused on 3 polyglutamine (polyQ) disorders: Huntington's disease, and spinocerebellar ataxias type 3 and 7. We proposed to a) generate novel, improved disease models, b) to thoroughly characterize and compare both these and previously generated models and, c) to standardize, reproducible methodologies to investigate pathomechanisms that present commonalities between polyQ diseases. We concentrated on the leading models, namely the genetically-modified rodent models and the induced pluripotent stem cells (iPSC). ModelPolyQ project was organized in six work packages and was successfully initiated in July 2016 and the project activities developed as planned.

PolyQ diseases are widely seen as model neurodegenerative diseases as they have features in common with other neurodegenerative diseases such as Alzheimer's and Parkinson's and therefore therapeutics developed for polyQ disease are likely to have potential to be rapidly retooled for other neurodegenerative diseases. The novel and thoroughly characterized iPS-based models and rodent models of HD, SCA3 and SCA7 which were developed in this project are a unique tool set and are expected to have important impact in research in the field. These strategies will form the basis for biomarker identification, pathogenesis studies and the discovery of disease modifying drugs. Overall, the ModelPolyQ project allowed generation and characterization of models and methodologies to enable significant advances in a) the knowledge of the mechanisms of these diseases and b) pre-clinical identification and validation of new effective therapies for polyglutamine disorders.

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