

**Investigations into the cellular function of ataxin-2 by the use of ssRNA aptamers**  
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**Scientific abstract**

The focus of this project is to explore the molecular function of ataxin-2 (ATX2) and the pathways contributing to the pathogenesis of spinocerebellar ataxia 2 (SCA2). We aim to generate a human protein network for ATX2, analyse its protein-protein interactions and how elevated ATX2 levels and/or an expansion of the polyglutamine stretch influence these interactions. To resolve the role of ATX2, we will apply a novel screening technique to obtain blocking ssRNA aptamers, which can be used to validate particular protein-protein interactions and therefore, elucidate their role in the disease. The ssRNA aptamers will be generated by a combined *in vitro* / *in vivo* method using SELEX (Systematic Evolution of Ligands by EXponential enrichment) and the reverse yeast-2-hybrid system, and they allow the validation of single biological processes without affecting any additional function of the gene product. The resulting ssRNA aptamers will be validated in mammalian systems by phenotypic analyses.

The envisaged outcome of the proposed studies will give a better understanding of the cellular networking ataxin-2 is involved and the pathways affected in the disease. The knowledge of occurring interactions - which can potentially be targeted - will open novel avenues in SCA2 research finally allowing the development of therapeutic strategies in the future.

**Lay summary**

Spinocerebellar ataxia type 2 is a late-onset neurological disorder that is characterised by progressive gait and limb ataxia, slow saccadic eye movements, speech difficulties, and intellectual impairment. The disease is caused by an extended polyglutamine stretch in the ataxin-2 protein. By now, we know that ataxin-2 is interacting with several other proteins in the cell and some of these interactions are altered in the disease. However, its function on the cellular level and how it is involved in disease onset and progression is yet unclear. In this project we aim to increase the knowledge of ataxin-2's role in the cell function by blocking individual interactions of ataxin-2-interacting proteins and investigating the response of the cell to the loss of a specific function. The blocking molecules are nucleic acid-based aptamers and will be generated in a novel screening method recently developed in our laboratory. In addition to gaining functional data, the nucleic acid-based aptamers have also good potential to be developed into therapeutic drugs in the future.

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