



## **DNA Single-Strand Break Repair and Ataxia Oculomotor Apraxia**

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### **Scientific summary**

Oxidative stress is an etiological factor in several spinocerebellar ataxias and is a major source of DNA single-strand breaks (SSBs), which are the commonest type of DNA damage arising in cells (tens of thousands per cell/per day). Recently, defects in the repair of SSBs have been implicated in *ataxia oculomotor apraxia-1* (AOA1), the commonest recessive hereditary spinocerebellar ataxia in Europe after Friedreich's ataxia. The goal of this proposal is to; (1), Elucidate the impact of unrepaired SSBs on AOA1 neural cell fate. (2), Evaluate the neuroprotective effect of SSBR in vivo, by correlating the level of specific SSB lesions in whole brain/cerebellum with defined physiological end points in mouse model systems for AOA1. It is expected that this project will identify why and how SSBs lead to neuronal dysfunction in AOA1 and define the impact of SSBR defects on neurodegeneration. It is anticipated that this work will provide the appropriate training for a PhD student in molecular biology and neural cell culture and, in the longer term, will serve as a platform for improving diagnosis and for the development of small molecules for novel therapeutic intervention.

### **Lay summary**

DNA repair defects have been implicated in immunodeficiency, cancer, and neurodegenerative disorders. By understanding DNA repair mechanisms, not only can we employ more effective treatments against disease but also improve the assessment of the risk factors that might lead to disease. Here, we will address the importance of the rapid repair of DNA single-strand breaks (SSBs), which are the commonest DNA lesions arising spontaneously in cells. Recent work has led to the hypothesis that repair of SSBs is particularly important for neurons. This is based on the existence of two hereditary neurodegenerative diseases, spinocerebellar ataxia with axonal neuropathy-1 (SCAN1) and ataxia oculomotor apraxia-1 (AOA1), in which proteins involved in single-strand break repair are deficient. The proposed research will focus on AOA1, the commonest recessive hereditary spinocerebellar ataxia in Europe after Friedreich's ataxia. We will employ a combination of molecular, cellular, and whole animal approaches to understand the cellular mechanisms of SSBR in neural cells and to determine the impact of the loss of these mechanisms on specific aspects of neurological function. Addressing these questions will not only determine the importance of SSBR for preventing neurodegenerative disease but will



underpin the development of novel diagnostic and therapeutic approaches for these diseases.

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