



Neural regeneration in the cerebellum: Development of cell replacement strategies for the management of spinocerebellar ataxias

Principal researcher: Dr Gian Giacomo Consalez, Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy

Names of co-applicant: Professor Ferdinando Rossi, Department of Neuroscience, University of Turin, Italy

Scientific summary

Overall objectives

The project will use the postnatal and adult mouse cerebellum as a model system to set up stem cell-based replacement protocols to treat spinocerebellar ataxias.

Specific aims

1. Perfect *in vitro* techniques to produce Purkinje Cells (PCs) from Neural Stem (NS) cells obtained from various sources (ES cells, IPS cells, postnatal and adult cerebellum)
2. Determine the ability of PC progenitors generated *in vitro* from NS cells or isolated from the embryonic cerebellum to proliferate in the host tissue and integrate into the wildtype and mutant cerebellar cortex
3. Analyze the spatio-temporal distribution of cues guiding PCs in their migration into the developing and adult cerebellar cortex
4. Manipulate the system to restore developmentally regulated cues guiding PC progenitor homing and connectivity

Description of the project

We plan to analyze the ontogenetic mechanisms that direct the integration of PCs into the cerebellar cortex and determine whether they are still available (or they can be re-activated) in the adult to promote repair. Our strategy for cerebellar regeneration will be driven by this analysis, in the attempt of exploit existing cues and enhancing those that are lost in time, eventually favoring the integration of exogenous precursors in the mature cerebellum.

Lay summary

Spino-cerebellar ataxias (SCAs) are a collection of genetic diseases characterized by motor incoordination due to neuronal degeneration in the cerebellum. Among the different types of SCAs that have been classified, SCA2 is due to the selective loss of a particular category of cerebellar neurones, the Purkinje cells. Because of this



selective neuronal degeneration, SCA2 may be successfully treated by transplanting embryonic Purkinje cells to replace the lost ones. However, to rewire the disrupted neural circuits of the SCA2 cerebellum, newly-added neurones must be precisely inserted in the texture of the recipient tissue. Crucial to achieve this goal is a profound knowledge of the mechanisms that guide immature donor neurones into the adult host environment and allow their correct placement and maturation. This project is specifically aimed at addressing these questions in the perspective of developing a cell-replacement therapy for SCA2 and other spinocerebellar ataxias. Part of our project will be devoted to investigate the cerebellar environment of SCA2 mutant or normal mice to discover factors and conditions that influence the behaviour and fate of transplanted neurones. Starting from the results of these experiments, we will design procedures aimed at modifying the cerebellar environment so to make it more receptive for the transplanted neurones. At the same time, we will set up a protocol to induce neural stem cells to generate Purkinje cells. In this way, we will obtain a population of donor cells specifically suitable for transplantation to SCA2 cerebella. Finally, we will transplant these cells to the cerebella of normal or SCA2 mice, treated to enhance their receptivity to donor neurones. By combining the use of donor cells endowed with specific developmental properties and targeted manipulations that render the host environment more receptive, we expect to obtain the engraftment of significant numbers of Purkinje cells transplanted to the SCA2 cerebellum.

For more support or information please contact: Ataxia UK, Lincoln House, Kennington Park, 1 – 3 Brixton Road. London SW9 6DE

Website: www.ataxia.org.uk.

Helpline: 0845 644 0606 **Tel:** +44 (0)20 7582 1444 **Fax:** +44 (0)20 7582 9444

Email: helpline@ataxia.org.uk.