Identification of oculomotor-restricted genes with motor neuron protective properties for the development of ALS therapeutics

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Amyotrophic Lateral Sclerosis (ALS) is a disease characterized by the selective degeneration (death) of motor neurons that innervate voluntary muscles in arms, legs, trunk and face, with resulting muscle wasting. However, while many motor neurons degenerate in ALS, there are populations of motor neurons that for unknown reasons appear resistant to degeneration and in fact persist throughout the disease progression. Our research focuses on one such population, the oculomotor motor neurons, which innervate the muscles around the eyes and enables us to look up and down and to the sides. We want to understand why the oculomotor motor neurons can resist degeneration in ALS. We believe that identifying mechanisms that render these motor neurons resistant to disease could lead to future therapies to prevent the progressive loss of vulnerable motor neuron in ALS.

Towards our goal we have identified a group of genes that are only active in oculomotor motor neurons and that appear able to protect also sensitive spinal motor neurons when introduced to these (Hedlund et al, 2010). We now propose to modify vulnerable motor neurons with **gene therapy**, conferring onto them properties of resistant oculomotor motor neurons. We will test the possible protective properties of oculomotor specific molecules on rodent motor neurons in culture and *in vivo* in a mouse model of ALS. Our aim is to identify genes that in the future can be modulated in the individual to prevent continued degeneration of motor neurons after diagnosis of ALS. The research project is a joint collaboration between the University of Milan in Italy (Stefania Corti) and the Karolinska Institutet in Sweden (Eva Hedlund).

What is gene therapy?

Gene therapy is the insertion of new genes into an individual's cells and tissues to modify the expression of the gene. Its major goal is to treat a disease. It can be a hereditary disease in which an altered gene is replaced with a functional one. It can also be to insert a gene that encodes a therapeutic protein. Although the technology is still in its infancy, it has been used with some success. Scientific breakthroughs continue to move gene therapy toward mainstream medicine.

StefaniaCorti is an Assistant Professor of Neurology, at the Department of Neurological Sciences at the University of Milan. With a degree in Medicine and Surgery in Milan, she specialized in Neurology and she has a PhD in Molecular Medicine. In 2005 she worked as a visiting researcher at the Stem Cell Institute, located at the University of Minnesota, USA. Since 2006 she is the PI of the Neural Stem Cell lab at the Department of Neurological Sciences University of Milan.

Dr Corti's five publications most relevant to this research are:

Riboldi G, Nizzardo M, Simone C, Falcone M, Bresolin N, Comi GP, **Corti S**. ALS genetic modifiers that increase survival of SOD1 mice and are suitable for therapeutic development. **ProgNeurobiol.** 2011;95(2):133-48.

Corti S, et al., Systemic transplantation of c-kit+ cells exerts a therapeutic effect in a model of amyotrophic lateral sclerosis. **HumMolGenet.** 2010 Oct 1;19(19):3782-96.

Corti S, Nizzardo M, Nardini M, et al. Embryonic stem cell-derived neural stem cells improve spinal muscular atrophy phenotype in mice. **Brain.** 2010 Feb;133(Pt 2):465-81.

Corti S, et al. Motoneuron transplantation rescues the phenotype of SMARD1 (spinal muscular atrophy with respiratory distress type 1). **J Neurosci.** 2009 Sep 23;29(38):11761-71.

Corti S, Nizzardo M, Nardini M, et al. Neural stem cell transplantation can ameliorate the phenotype of a mouse model of spinal muscular atrophy. **J Clin Invest.** 2008 Oct;118(10):3316-30.

Eva Hedlund is an Associate Professor of Neurobiology, at the Department of Neuroscience at the Karolinska Institutet, Sweden. She has a PhD in Molecular Endocrinology from the Karolinska Institutet. In 2001-2002 she was a postdoctoral fellow at the Department of Psychiatry, UCLA School of Medicine, CA, USA. 2002-2007 she worked as a Postdoctoral fellow at the Center for Neuroregeneration Research at Harvard Medical School, MA, USA and in 2007 she was promoted to Instructor. Since 2011 she is the PI of a Motor Neuron Disease focused lab at the Department of Neuroscience, Karolinska Institutet

Pr Hedlund's five publications most relevant to this research are:

Deng Q, Andersson E*, **Hedlund E*,** Alekseenko Z, Coppola E, et al (2011) Specific and integrated roles of Lmx1a, Lmx1b and Phox2a in ventral midbrain development. *Development* **138**:3399-3408. * Equal contribution

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Hedlund E*, Karlsson M, Osborn T, Ludwig W and Isacson O* (**2010**) Global gene expression profiling of somatic motor neuron populations with different vulnerability identify degenerative and protective molecules. *Brain* **133:**2313-2330.* corresponding authors.

Hedlund E*, Pruszak J, Lardaro T, Ludwig W et.al. (**2008**) Embryonic stem (ES) cell-derived Pitx3-eGFP midbrain dopamine neurons survive enrichment by FACS and function in an animal model of Parkinson's disease. *Stem Cells* **26**:1526-1536. *corresponding. authors

[#]Wernig M, Zhao J-P, Pruszak J, **Hedlund E**, Fu D, Soldner F, Broccoli V, Constantine-Paton M, Isacson O and Jaenisch R (**2008**) Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. *PNAS* **105**:5856-5861.[#]*Received the* ***Cozzarelli Prize*** *as an exceptional paper.*