

Post-doctoral position in ALS research

Topic: RNA metabolism in motoneuron degeneration

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Description:

We have recently been involved in a clinical study that has identified mutations in a gene encoding for the RNase angiogenin in ALS patients [1]. In initial work, we demonstrated that angiogenin is expressed and enriched in motoneurons [1], and protects cultured motoneurons against ALS-associated, stress-induced cell death [2, 3]. In further work, we demonstrated that systemic angiogenin protein delivery significantly increased life-span and improved motor function in SOD1G93A mice [2]. These results suggest that angiogenin protein delivery may be beneficial in treating patients with newly diagnosed ALS.

Despite this significant genetic and biological data, the mechanism of action of Angiogenin remains unclear. The project funded by the Thierry Latran Fondation will test the hypothesis that motoneurons utilise angiogenin as an intercellular stress-response signal, which modulates RNA cleavage and the translational output of neurons and astroglia in order to enhance motoneuron survival.

In this project, you will characterise the stress-induced angiogenin production and release from motoneurons, and determine the effects of secreted angiogenin on astrocytes and endothelial cells. Angiogenin is known to suppress cap-dependent translation by cleaving tRNA, however we have recently identified a group of alternative RNA targets which may also regulate translation. You will identify and characterize these novel angiogenin RNA cleavage products, and their ability to protect motoneurons.

Given the preliminary work we have undertaken as a basis for this project and the technical experience incumbent in our laboratory, we anticipate this project to be suitable for a well qualified neurobiologist / molecular biologist. A background in RNA biology and/or ALS research would be of advantage.

References:

1. Greenway, M.J., et al., ANG mutations segregate with familial and 'sporadic' amyotrophic lateral sclerosis. *Nat Genet*, 2006. 38: 411-3.
2. Kieran, D., et al., Control of motoneuron survival by angiogenin. *J Neurosci*, 2008. 28: 14056-61.
3. Sebastià J, et al., Angiogenin protects motoneurons against hypoxic injury. *Cell Death Differ*. 2009. 16:1238-47.