

## BOLSA DE INVESTIGAÇÃO (M/F)

**Referência:** PTDC/SAU-NEU/66740/2006

**Título do Projecto:**

“Animal model of Fabry disease: can the neuropathophysiology events be correlated with lipidomics?”

**Código interno: PR**

Está aberto concurso para recrutamento de um(a) bolseiro(a) de Investigação para colaborar no projecto acima referido, co-financiado pela Fundação para Ciência e a Tecnologia e pelo FEDER através do programa PTDC.

A bolsa, em regime de exclusividade, terá a duração de 6 meses, eventualmente renovável, com início previsto a 1 de Novembro de 2009.

O valor mensal da bolsa será de € 745,00, pago por transferência bancária (preferencialmente).

**Local de trabalho:** Unidade do Lisossoma e do Peroxisoma, IBMC.

**Programa de trabalho:** ver anexo.

**Perfil pretendido:**

Os candidatos devem possuir Licenciatura na área das Ciências da Saúde. Dá-se preferência a candidatos com experiência na área da histopatologia (imunohistoquímica e microscopia electrónica).

O prazo para recepção de candidaturas decorre de 16 a 30 de Outubro de 2009.

As propostas deverão incluir uma carta de motivação, CV, e duas cartas de referência e ser enviadas para:

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A contratação será regida pelo estipulado na legislação em vigor relativamente ao Estatuto de Bolsheiro de Investigação Científica, nomeadamente a Lei 40/2004, de 18 Agosto, e o Regulamento de Bolsas de Investigação Científica do IBMC([www.ibmc.up.pt/fellowships.php](http://www.ibmc.up.pt/fellowships.php)).



**“Animal model of Fabry disease: can the neuropathophysiology events be correlated with lipidomics?”**

**Supervisor:**

Doutora M. Clara Sá Miranda

**Project summary:**

Fabry disease (FD) is an X-linked inherited disorder of glycolipid metabolism resulting from deficient activity of the lysosomal enzyme, alpha-galactosidase A (alpha-Gal A; EC 3.2.1.22). Neutral glycosphingolipids with terminal alpha-linked galactosyl moieties, predominantly globotriaosylceramide (Gb3, also known as ceramide trihexoside) and to a lesser extent, two ceramides dihexosides (galabiosylceramide and lactosylceramide) accumulate in the liver, heart, spleen, kidney, vascular endothelial cells, brain, lung and in plasma of hemizygous FD patients and at a less extension in heterozygous females. FD is a multi-system disorder, with a wide spectrum of physical signs and symptoms predominantly affecting the nervous system, skin, heart, kidneys and the eyes. In the first two decades, acute and chronic neuropathic pain (NP), hypohidrosis, angiokeratoma and gastrointestinal symptoms significantly reduce the quality of life. Lifespan is shortened by late complications in adulthood that include heart failure, renal failure and cerebrovascular accidents. The enzymatic activity in hemizygous patients is variable ranging from undetectable values, in patients with the classic phenotype, to low residual activity in patients with the variants phenotypes (cardiac variant, and renal variant). FD affects also heterozygous females in these cases the clinical manifestations are in general milder than in males and the degree of severity is dependent on the random X-chromosomal inactivation. Human alpha-Gal A cDNA was cloned and sequenced, a wide genetic heterogeneity is observed in FD patients, more than 250 mutations were identified, and the great majority of these mutations are “private” being present in only a pedigree. The establishment of a genotype/phenotype correlation has been difficult as illustrated by the existence of clinical heterogeneity among FD patient males with the same pedigree (J Inherit Metab Dis, 2004. 27: 385, J Pediatr, 2004. 144: S20.). These observations suggest that modifier genes or other factors can influence the severity of the symptoms (J Inherit Metab Dis, 2004. 27: 385, J Pediatr, 2004. 144: S20.). An enzyme replacement therapy is available since 2001, however its



efficacy in correcting the symptoms, mainly the neuropathic ones is still controversial. Substrate reduction therapy (SRT) is other therapeutic approach approved for sphingolipidoses, it is based on the inhibition of glycosphingolipids biosynthesis, using ceramide-specific glucosyltransferase inhibitors (Adv Exp Med Biol, 2005. 564: 117.). SRT is not being used to treat FD patients though some in vitro and in vivo studies carried out in the FD knockout mice showed the reduction in Gb3 accumulation. As far as we know to date the Fabry knockout mouse model was not used to study the anxiety and/or depression provoked by pain as well as the possible mechanisms of pain involved in FD. Moreover although pain is one of the most distressing and less understood symptoms in FD, there are not, to our knowledge, any studies addressing the question if the iminosugar (NB-DGJ) Miglustat, which crosses the brain blood barrier, can be useful to treat NP in FD. The mouse model for FD was produced in 1997 by disruption of the mouse alpha-Gal A gene (PNAS, 1997. 94: 2540.), the biochemical phenotype of the knockout mice is similar to the one of FD patients, displaying extensive deficiency in alpha-Gal A and lipid accumulation of Gb3 in plasma, skin, kidney, lung, spleen, liver, heart and brain.

In this project we propose to investigate how the metabolic alterations in general and the glycolipids storage in particular occurring in different tissues progress and how it correlates with the development of anxiety and depression related with NP. Studies will be performed from birth until adult ages at different time points in order to correlate the course of the metabolic alterations events with the development of anxiety, depression and pain as shown by behavioural tests. Evaluation will be performed by comparing always wild type and knockout mice. The principal studies are: (1) establishment of lipids profile of different tissues using HPLC-MS/MS and its histopathology by immunohistochemistry and/or electronmicroscopy; (2) behavioural tests to assess anxiety and/or depression and NP; (3) characterisation of peripheral nervous system as well as motor nerve conduction and (4) study the effect of SRT, using NB-DNJ, in the correction of lipids storage and its consequences in the neuropathology.

