

BOLSA DE INVESTIGAÇÃO (M/F)

Referência: PIC/IC/82824/2007

Título do Projecto: “Therapies in familial amyloidotic polyneuropathy ”

Código interno: PR 531906

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 .

A bolsa, em regime de exclusividade, terá a duração de 12 meses, com início previsto a 1 de Julho de 2009.

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

Local de trabalho: Unidade de Investigação de Neurobiologia Molecular do Instituto de Biologia Molecular e Celular (IBMC), Porto

Programa de trabalho: ver anexo.

Perfil pretendido:

Os/as candidatos/as devem possuir Licenciatura em áreas afins a Biologia e Bioquímica, média final igual ou superior a 14 valores. É condição preferencial possuir experiência na área de experimentação animal, e análise de tecidos.

O prazo para recepção de candidaturas decorre de 1 a 19 de Junho de 2009.

As propostas deverão incluir uma carta de motivação, CV, e ser enviadas por correio ou e-mail para:

Prof.^a Maria João Saraiva
Instituto Biologia Molecular e Celular - IBMC
Grupo de Neurobiologia Molecular
Rua Campo Alegre 823
4150-180 Porto
mjsaraiv@ibmc.up.pt
tel: +351-22-6074900
fax: +351-22-6099157

A contratação será regida pelo estipulado na legislação em vigor relativamente ao Estatuto de Bolseiro 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).

“Therapies in familial amyloidotic polyneuropathy”

Supervisor:

Maria João Saraiva

Project Summary:

Transthyretin (TTR) amyloidoses are a group of lethal, autosomal dominant inherited diseases characterised by the deposition of amyloid fibrils in several organs. The majority of these amyloidoses are associated with single aminoacid substitutions in TTR, due to point mutations in the TTR gene. More than 100 mutations are now described, the most common of which is a substitution of Met for Val at position 30 (TTR V30M) which is associated with Familial Amyloidotic Polyneuropathy (FAP). FAP is characterised by the deposition of amyloid fibrils predominantly in the peripheral nervous system. No treatment specifically causes the resolution of TTR deposits, to improve survival and preserve organ function. In this regard, the only therapy for FAP has been liver transplantation, since the liver is the main organ of TTR synthesis. The strategies put forward so far as potentially therapeutic for FAP follow for most aspects directions generally taken for other amyloidoses, such as inhibiting aggregation and/or disrupting TTR amyloid by selective molecules. As far as disruption of TTR amyloid by selective drugs is concerned, we reported that tetracyclines are capable to disrupt TTR amyloid fibrils in vitro producing noncytotoxic species (FASEB J. 2003). The experimental in vitro data indicating the anti-amyloid activity of a well tolerated, widely used drug, such as doxycycline, warranted a first pilot study at the Pavia Amyloid Center in Italy, to verify its activity in TTR amyloidosis. Doxycycline was given at the dosage 200 mg/day, since this was the most commonly used dosage of the drug in clinical practice. The first pilot study demonstrated a good drug tolerability. 5 out of 10 patients presented a stabilization of the neurological and cardiac disease over a 6 months treatment period. We further demonstrated that in an animal model of ATTR (mice) doxycycline has a clear-cut effect on reabsorption of TTR deposits (FASEB Journal 2006) at dosages 10 times higher compared to the dose used in the first pilot study, which warrants further studies on doxycycline doses and protocols both in the animal model and in clinical trials. We propose to pursue with these studies in the present application. A robust set of novel biomarkers of disease will be investigated for the follow up of this and other therapeutic approaches for FAP. As far as inhibition of aggregation is concerned, several candidate small drugs have been proposed, based in *in vitro* studies; however, demonstration of their activities in vivo is lacking precluding their clinical applicability. We have developed a unique animal model for FAP (Neurobiology of Aging, 2008) with TTR deposition in the peripheral nervous system, which will be used to evaluate the anti-amyloidogenic effect of a set of candidate drugs in the animal model, before testing in clinical trials.