

BOLSA DE TÉCNICO DE INVESTIGAÇÃO (M/F)

Referência: PTDC/SAU-GMG/099704/2008

Título do Projecto: “Functional dissection of mitotic spindle assembly pathways by comparative genomics”

Código interno: PR093304

Está aberto concurso para recrutamento de um(a) bolseiro(a) de Investigação para colaborar no projecto acima referido, financiado pelo programa COMPETE - Programa Operacional Factores de Competitividade na sua componente FEDER e pelo orçamento da Fundação para a Ciência e a Tecnologia na sua componente OE.

A bolsa, em regime de exclusividade, terá a duração de 6 meses, eventualmente renováveis, com início previsto em 1 de Maio de 2010.

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

Local de trabalho: IBMC - Instituto de Biologia Molecular e Celular (Grupo de Dinâmica e Instabilidade Cromossómica), Porto, Portugal

Programa de trabalho: ver anexo.

Perfil pretendido:

Os candidatos devem possuir pelo menos o grau de licenciatura nas áreas de Bioquímica, Biologia ou área afim, experiência comprovada de laboratório e domínio de técnicas de biologia molecular e cultura de células.

O prazo para recepção de candidaturas decorre de 9 a 23 de Abril.

As propostas deverão incluir carta de motivação, CV, e duas cartas de recomendação e ser enviadas por correio electrónico para candidaturas@ibmc.up.pt com indicação do código interno (PR093304).

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).

“Functional dissection of mitotic spindle assembly pathways by comparative genomics”

Supervisor:

Helder Maiato

Project Summary:

Mitosis is an essential process for life and mitotic abnormalities have been related with aneuploidy and chromosomal instability observed in many human cancers. Aneuploidy is also the basis of many birth defects and spontaneous abortions in humans. In order to maintain their inherited genetic background, cells developed a specialized microtubule-based structure called the mitotic spindle that mediates the segregation of chromosomes during cell division. Many cancer therapies currently in clinical practice employ the use of drugs that target microtubules (e.g. taxanes and vinca alkaloids) with the aim of preventing cell division by blocking (and killing) cells in mitosis. However, current therapies with microtubule drugs have undesirable side effects (e.g. neurotoxicity) in cells that are not undergoing mitosis but whose function relies on microtubules. Impaired axonal transport in neurons can cause nerve cell loss with subsequent dementia, parkinsonism or affect motor skills and lead to muscle atrophy in cancer patients subjected to chemotherapy. It is therefore of utmost importance to unveil potential non-microtubule targets that are required for mitotic spindle assembly and will not interfere with normal microtubule functions in non-dividing cells. Given its essential role, mitotic spindle assembly in animal cells is a highly conserved and redundant process that involves multiple parallel pathways. The best characterized pathway is the one involving the centrosome, which nucleates dynamically unstable microtubules that “search-and-capture” chromosomes after nuclear envelope breakdown. Another mechanism, known as the chromatin pathway, was originally identified in acentrosomal *Xenopus* meiotic oocytes and shown to involve the formation of a RanGTP gradient around chromosomes that promotes the nucleation of microtubules, which are subsequently organized into a bipolar structure by motor proteins. Curiously, animal somatic cells that normally have centrosomes were shown to form a functional spindle after genetic or physical removal of centrosomes, indicating that a centrosome-independent pathway for spindle assembly exists in animal cells. On this regard, we have found that kinetochores, a trilaminar proteinaceous structure present at the centromeres can act as microtubule organizing centers (MTOCs) and participate in mitotic spindle morphogenesis in living animal cells, even in the presence of centrosomes. Yet, the underlying molecular and structural requirements behind acentrosomal spindle formation in animal somatic cells remain largely unknown. In order to address these we have recently performed a semi-automated high-throughput genome-wide RNAi screen for genes required for spindle assembly in the absence of functional centrosomes in *Drosophila* S2 cells. Among previously known genes involved in mitosis, we have found 46 new genes potentially involved in acentrosomal spindle assembly, including 22 genes whose function is totally unknown. Here we propose to characterize the function of these genes at high spatio-temporal resolution using state-of-the-art live-cell microscopy combined with RNAi. An additional advantage from our screen is that for the first time it will be possible to establish a functional comparison at the genome level with a previous screen carried out by our collaborators in the same cells, performed in the presence of functional centrosomes. This unique opportunity will allow us to identify the molecular players that are specifically involved in the centrosomal and acentrosomal spindle pathways in animal somatic cells. Subsequent molecular and functional characterization of available mutant alleles in the fly and the respective human orthologues using *in vitro* systems will allow us to shed light on the cellular and physiological relevance of the confirmed genetic hits and how they could be used as potential chemotherapy targets.