

## BOLSA DE INVESTIGAÇÃO (M/F)

**Referência:** PTDC/SAU-FCF/100749/2008

**Título do Projecto:** Implication of sirtuin proteins in the regulation of antigen presenting cells apoptosis during leishmaniasis: a therapeutic approach.

**Código interno:** PR293003

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 1 ano, eventualmente renovável, com início previsto em 15 de Julho de 2010.

O valor mensal da bolsa será de € 980,00, pago por transferência bancária (preferencialmente).

**Local de trabalho:** IBMC - Instituto de Biologia Molecular e Celular (Grupo “Parasite Disease”)

**Programa de trabalho:** ver anexo.

### **Perfil pretendido:**

Os candidatos devem ter o grau de mestre em Bioquímica, Ciências Biológicas, Farmacêuticas ou afins, sendo dada preferência a quem tiver média de licenciatura igual ou superior a 15 valores e manifesta experiência pós-graduada em Imunologia, Parasitologia, Biologia molecular e celular.

O prazo para recepção de candidaturas decorre de 28 de Junho a 12 de Julho de 2010.

As propostas deverão incluir carta de motivação, CV e ser enviadas por correio electrónico para [candidaturas@ibmc.up.pt](mailto:candidaturas@ibmc.up.pt) com indicação do código interno (PR293003).

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)).

## “Implication of sirtuin proteins in the regulation of antigen presenting cells apoptosis during leishmaniasis: a therapeutic approach.”

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### Project summary:

In order to survive inside a hostile environment, a large number of pathogens manipulate host cell apoptotic pathways to their own advantage, either by preventing apoptosis of their target host cells and/or promoting apoptosis in effector immune cells. Indeed, the biased manipulation of host cell apoptosis by certain pathogens provide a fascinating starting point to understand how these organisms evade host immune responses and sustain an infection. However, the current knowledge of the involved signaling events is unclear. The Silent Information Regulator 2 (SIR2 or sirtuin) comprise a family of highly conserved proteins defined as a nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent deacetylase and/or ADP-ribosyltransferase enzymes. The varied localization (nuclear and mitochondrial) and NAD<sup>+</sup>-dependence activity of the sirtuin family of proteins places them at the center of many cellular pathways and provides a link between cellular metabolic status (expressed by the NAD<sup>+</sup>/NADH ratio) and adaptive transcriptional and post-translational responses. Hence, all the members of the mammalian sirtuin family have been implicated in the regulation of longevity, cell survival and apoptosis. As a consequence, sirtuin are considered as one of the primary therapeutic targets to combat metabolic, neurodegenerative and proliferative disorders. However, the role of sirtuin proteins in the modulation of host cell survival in response to an infectious process has never been addressed. We and others reported the modulation of host cell apoptosis as an immunological mechanism by which *Leishmania* spp., an obligate intracellular parasite of mononuclear phagocytes, interfere with the effector responses. The inability of the host to mount an efficient immune response against *Leishmania* antigens is well correlated with the development of sub-optimal activation of antigen presenting cells (APC), namely dendritic cells and macrophages. Therefore, the modulation of macrophages and dendritic cells life span and effector functions plays a pivotal role in the intracellular parasite survival, replication and persistence. Although it is clear that sirtuin proteins play a critical role in regulating cell survival and death, the underlying mechanisms by which sirtuin functions can be modulated by pathogens remain unresolved. Our research project consists in characterizing, at the molecular level, the mechanisms involved in sirtuin regulation of macrophages and dendritic cells survival using leishmaniasis as an infectious model.

Specific objectives are:

- 1) Screening through quantitative techniques the sirtuin member(s) that appear deregulated after *in vitro* *Leishmania* infection using both dendritic cells and macrophage cell lines and primary cells as targets.
- 2) Evaluation of the intracellular localization and post-translational modifications of the selected sirtuin(s) in response to the infection.
- 3) Transient and stable inactivation or overexpression of the selected sirtuin(s). Analysis will focus on the apoptotic and/or autophagic cell death pathways and the further consequences over the parasite multiplication and persistence.
- 4) Identification of the intracellular pathways downstream of the sirtuins that are modulated by the intracellular infection using DNA microarray and proteomic strategy.
- 5) Efficacy evaluation of commercial or newly chemically selective sirtuin activators or inhibitors during a *Leishmania* infection.