

### Research Fellowship (m/f)

**Project title:** “Ageing: cells losing their mitotic fitness and chromosome balance”

(financiado pelo OE, no âmbito do PIDDAC - e através da Fundação para a Ciência e a Tecnologia), nas seguintes condições:

**Reference:** PTDC/BEX-BCM/2090/2014

**Internal Reference:** PR661901

#### **Candidate profile:**

We are looking for candidates with a Master's degree in Biology, Biochemistry and related fields with a final score of 17 or higher. The candidate must have experience and full autonomy in cell and molecular biology and, in particular, be familiarized with state-of-the-art methodologies such as ATAC-seq and 4C-seq. Knowledge of English language, both spoken and written, and good interpersonal qualities in the context of a multidisciplinary research team are also essential attributes.

#### **Background and work plan:**

Aneuploidy, an abnormal chromosome number, has been linked to aging and age-associated diseases, but the underlying molecular mechanisms remain unknown. Our group has recently shown, through direct live-cell imaging of young, middle-aged, and old-aged primary human dermal fibroblasts, that aneuploidy increases with aging due to general dysfunction of the mitotic machinery. Increased chromosome mis-segregation in elderly mitotic cells correlates with an early senescence-associated secretory phenotype (SASP) and repression of Forkhead box M1 (FoxM1), the transcription factor that drives G2/M gene expression. FoxM1 induction in elderly and Hutchinson–Gilford progeria syndrome fibroblasts prevents aneuploidy and, importantly, ameliorates cellular aging phenotypes. Moreover, we have shown that senescent fibroblasts isolated from elderly donors' cultures are often aneuploid, and that aneuploidy is a key trigger into full senescence phenotypes.

We aim now to understand how is *FOXM1* repressed during aging, focusing on its transcriptional *cis* regulation. Considering our previous finding that repression of *Forkhead box M1* (*FOXM1*) in aged fibroblasts accounts for >50% age-associated changes in gene expression, the genomic regions interacting with the *FOXM1* promoter have been specifically ascertained through 4C-seq. Several promoters and other CREs were found to interact with the *FOXM1* promoter. Those CREs will now be tested for enhancer activity *in*

*in vitro*, in both young and elderly human dermal fibroblasts (HDFs). In order to identify the age-dependent alterations in cis regulatory elements (CREs) activity and to determine how they contribute to the gene expression profiles observed during aging, we will additionally profile by ATAC-seq, chromatin accessibility in HDFs retrieved from young and elderly healthy donors. We expect our work will disclose an association between *FOXM1* expression, activity signatures of CREs and cellular senescence.

The work will be developed at the *Ageing and Aneuploidy* group of i3S under the supervision of Elsa Logarinho.

### Application procedure:

Applications should include a detailed CV and the degree's certificate, and should be submitted between 18 January 2019 and 31st January 2019 on the IBMC webpage:

<http://www.ibmc.up.pt/gestaocandidaturas/index.php?codigo=PR661901>

**Legislation and applicable laws:** Employment at the IBMC is regulated by current laws relating to the Statute of Science Research Fellows of Fundação para a Ciência e Tecnologia, I.P. - 2015, namely Law 40/2004 of August 18, amended and republished by Decree-Law No. 202/2012 of 27 August and the Regulation of Scientific Research Studentships of the IBMC approved by Fundação para a Ciência e Tecnologia ([www.ibmc.up.pt/fellowships.php](http://www.ibmc.up.pt/fellowships.php)).

### Evaluation of applications:

The candidates will be evaluated based on the CV. The top 2 most qualified candidates will be selected for a personal interview. If interviewed, the final score of the top 2 candidates will be based on CV (50%) and interview (50%).

### Jury:

President: Elsa Logarinho (PhD);

Ordinary members: Joana Macedo (PhD), Sofia Pereira (PhD)

### Grant conditions:

The fellowship is due to start in March 1st 2019. The grant will be awarded for 8 months and is not renewable. The monthly amount of the fellowship is € 980 (<http://alfa.fct.mctes.pt/apoios/bolsas/valores>) paid by bank transfer.