FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

REPÚBLICA PORTUGUESA

**Código do Concurso I** Concurso de Projectos de I&D em todos os Domínios Científicos 2020

**Designação do projeto |** PTDC/MED-NEU/3890/2020 Estudo das propriedades sináticas do envelhecimento em neurónios humanos derivados por conversão direta

**Referência do projeto |** PTDC/MED-NEU/3890/2020

**Região de intervenção |**Lisboa

**Entidade Proponente|** Instituto de Medicina Molecular João Lobo Antunes / Fundação GIMM - Gulbenkian Institute for Molecular Medicine **Entidade Participante |** Centro de Neurociências e Biologia Celular

**Data de aprovação |** 2020-12-17

**Data de início |** 01/03/2021

**Data de conclusão |** 29/02/2024 **Data de prorrogação |** 31/12/2024

**Custo total elegível |** 248.050,00 euros

**Apoio financeiro Orçamento de Estado I** 248.050,00 euros

With progressive age some individuals maintain a stable cognitive function while others suffer from a rapid cognitive decline. Animal models of aging, namely rats and primates, also recapitulate this dissociation between age-impaired and unimpaired features but the exact mechanism remains unknown.
Pluripotent stem cell (iPSC)-based models have provided fascinating insights into disease-relevant mechanisms of patient-derived human neurons. While this approach appears highly useful, a main LIMITATION is that AGE-related physiological changes are disregarded, since iPSC reprogramming 'resets' the epigenetic state of the cell into an embryonic-like state. By contrast, direct transcription factor-based conversion of fibroblasts into induced neurons (iNs) represents an alternative for generating human neurons without erasing putative cellular aging markers. Indeed, fibroblast-derived iNs obtained from a cohort of near centenarian human donors retain transcriptomic and functional signatures of aging (Mertens et al. 2015) and can be traced back to THE AGE of the fibroblasts that they were derived from.
We were recently able to discriminate memory-impaired aged rodents by a particular synaptic plasticity shift (Temido-Ferreira, 2018). In contrast, another subset of age-unimpaired animals performed within the range of young rats. The alterations oberved in age-impaired animals are significantly correlated with spatial memory Y-maze preference index and are associated with an overactivation of NMDA/mGluR5 and calcium overload.
This suggests the possibility of correlating particular SYNAPTIC SIGNATURES with memory performance, in human patients. Whilst sufficient resolution to assess early synaptic dysfunction in patients is not possible using current imaging techniques, we propose to overcome this resorting to the novel iN-based technology. Taking advantage of this novel age-equivalent strategy to obtain human-derived induced-neurons (iNs), we are now in a position to translate the knowledge obtained in animal models to the human setting and expand our knowledge on the mechanisms involved.
We propose to directly assess whether direct neuronal conversion (iN) will RETAIN the SYNAPTIC EQUIVALENCE of their human donor. We will characterize the synaptic properties of iNS derived from young and aged PATIENTS through patch-clamp coupled to calcium imaging and correlate with cognitive status; subsequently, we will generate a transcriptomic signature of human aged and AD synapses from iNs derived from patients, compared to age- matched healthy neurons, and screen its potential as SYNAPTIC diagnosis tool.
In the case we prove significant, consistent and reliable correlations of synaptic function to the cognitive status of each patient, this could be applied to healthy patients as a way to detect early synaptic dysfunction or even to evaluate efficacy of potential personalized therapies in a model much closer to the human setting.