***DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO***

**Cycle XXXIX**

**Project proposal for a PhD scholarship (with no financial support from Sapienza)**

**Title of the research: Study of neural stem cell reactivation in mouse models of aging and with defective neurogenesis**

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**Summary**

The research project concerns the study of neurogenesis processes in the brain of adult and aged subjects, through the use of specific mouse models. Particular attention is paid to the role of stem cells involved in these processes and to the possibility of their use as therapeutic targets. In addition, the cellular and molecular mechanisms involved are investigated.

In particular, the project is based on the following **Objective**:

Study of neurogenesis (production of new neurons from stem cells in the neurogenic niches of the dentate gyrus, DG, and sub-ventricular zone, SVZ) and of the effect of different neurogenic stimuli (e.g. voluntary running, administration of natural substances) in mouse models with defective adult neurogenesis (aged mice and p16Ink4a-ko).

This Objective includes the following tasks:

**Task A)** Molecular studies by RNA-sequencing of the neurogenic niches of mouse models in which neurogenesis is impaired in the aged animal (p16Ink4a-ko). We thus intend to identify genes whose activation is related to the reactivation of defective stem cells of neurogenic niches by physical exercise (running). We then aim to study in vitro and in vivo the function of the genes identified by RNAseq;

**Task B)** Cellular and behavioral studies in aged p16Ink4a-ko mice subjected to voluntary running. In 12-month-old mice belonging to this mouse model, voluntary running stimulates stem cells to come out of quiescence;

**Task C)** Molecular, biochemical, cellular and behavioral studies in mice treated with hydroxytyrosol (HTyr), a natural component present in EVOO (extra virgin olive oil). HTyr stimulates the production of new neurons in adult and aged mice (D'Andrea et al., 2020). With these studies we will be able to verify the level of plasticity of the dentate gyrus stem cells and the possibility of reactivating it in defective cells or in aged animals, thus deducing indications on the self-renewal model even in old age.

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* *Kempermann G, Song H, Gage FH. Neurogenesis in the Adult Hippocampus. Cold Spring Harb Perspect Biol. 2015 Sep 1;7(9):a018812.*
* *de Pablos RM, Espinosa-Oliva AM, Hornedo-Ortega R, Cano M, Arguelles S. Hydroxytyrosol protects from aging process via AMPK and autophagy; a review of its effects on cancer, metabolic syndrome, osteoporosis, immune-mediated and neurodegenerative diseases. Pharmacol Res. 2019 May;143:58-72.*

**Pertinent publications of the proponent (last 5 years)**

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* Micheli L, Creanza TM, Ceccarelli M, D'Andrea G, Giacovazzo G, Ancona N, Coccurello R, Scardigli R, Tirone F. Transcriptome Analysis in a Mouse Model of Premature Aging of Dentate Gyrus: Rescue of Alpha-Synuclein Deficit by Virus-Driven Expression or by Running Restores the Defective Neurogenesis. Front Cell Dev Biol. 2021 Aug 17;9:696684.

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