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Hellenic Foundation for Research & Innovation

Description of the funded research project

1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment

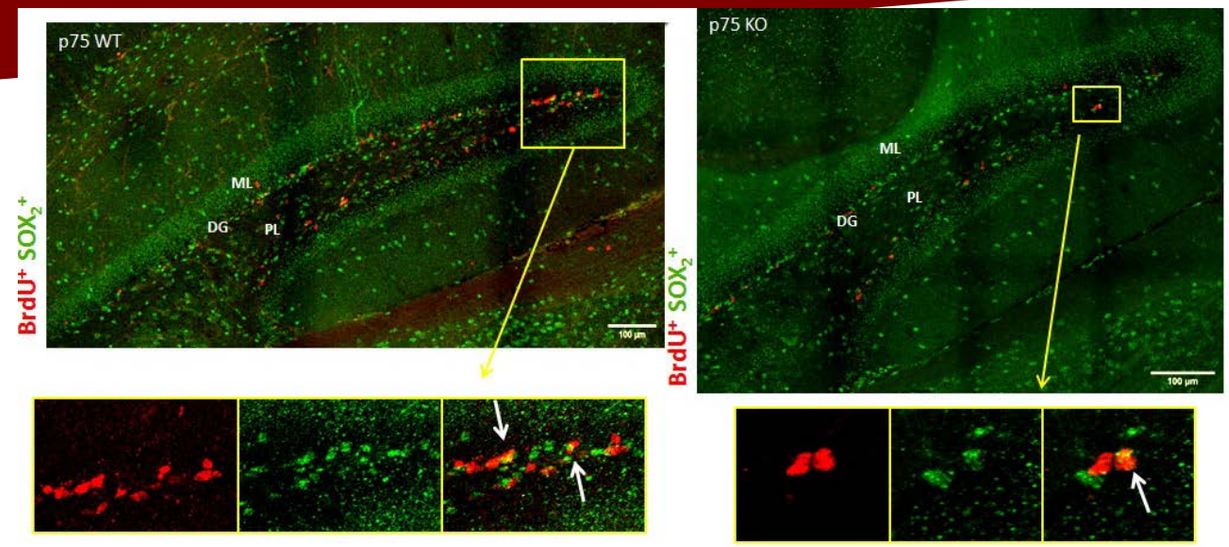

Figure Legend: Immunostainings with specific markers (BrdU and Sox2) for neural stem cells proliferation at the hippocampal dentate gyrus of wild type and p75NTR-Knock out mice.

Title of the research project: Deciphering the role of the p75 pan-neurotrophin receptor in adult hippocampal neurogenesis as a novel therapeutic approach to Alzheimer's Disease

Principal Investigator: Ioannis Charalampopoulos

Reader-friendly title: Revealing neurotrophin receptor-mediated effects on adult neurogenesis as a new tool against Alzheimer's Disease

Scientific Area: Life Sciences (Medical & Health Sciences)

Institution and Country: Medical School, University of Crete, Greece

Host Institution: University of Crete

Collaborating Institution(s):

- Professor Carlos F. Ibáñez (Karolinska Institutet, Sweden and National University of Singapore)
- Dr Ioannis Sotiropoulos (ICVS institute, University of Minho, Portugal)

Please insert a photo of the PI and/or the Research Team

Principal Investigator:
Ioannis Charalampopoulos
Associate Professor of Pharmacology

PhD student:
Papadopoulou Marianna, BSc, MSc

Budget: 180.000

Duration: 36 months

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Research Project Synopsis

Alzheimer's disease is associated with increased rates of apoptotic cell death, as well as decreased levels of adult neurogenesis that represent a critical stepA novel therapeutic approach consists of increasing the levels of neurogenesis and reducing cell death at the onset and progress of the disease., through the selective activation of the pan-neurotrophin receptor p75NTR. Our research project focuses on dissecting the cellular and molecular mechanisms of p75NTR in adult neurogenesis of the dentate gyrus of rodent hippocampus, under physiological and neurodegenerative conditions, such as Alzheimer Disease (AD). Additionally, we aim to detect receptor's activity and functions that are related to neuronal cell death. By revealing and controlling the specific signaling pathways that are necessary to mediate the actions of p75NTR on stem cell properties, we could enhance the endogenous neurogenic potential and the repairing ability against AD-induced neuronal loss. For this purpose, we will identify neurogenesis levels on newly-established mouse transgenic models using immunocytochemical methods as well as behavioral studies. In addition, neural stem cells from these mouse lines will be isolated and cultured *in vitro*, while different mutations on the receptor are going to be evaluated according to their signaling properties. Finally, we aim to perform experiments in human induced Pluripotent Stem cells (hiPSCs) that are derived from healthy donors and AD patients. hiPSCs-derived neurons and glial cells will be co-cultured in 3D platforms in order to create novel neuronal networks that emulate neurodegenerative conditions and thus to provide a tool for screening potential drugs against diseases like AD.

Project originality

The hippocampus, a brain area critical for learning and memory, is especially vulnerable to damage at early stages of Alzheimer's Disease (AD). Emerging evidence has indicated that altered neurogenesis in the adult hippocampus represents an early critical event in the course of AD, indicating that reduced neurogenesis is limiting neuronal repair and memory restoration. In order to bypass this disease-induced condition and enhance the endogenous neurogenesis, we propose to genetically characterize and decipher the multiple and extremely variable $p75^{NTR}$ signal transduction pathways in Neural Stem Cells (NSCs) of the adult brain. Our study will range from *in vivo* detection of adult neurogenesis in combined p75KO/knock-in and AD mouse models (both Aβ- and Tau-dependent) to *in vitro* 3D cultures of mouse and human NSCs and mature neuronal cells. Since we will reveal specific components of the p75-dependent signaling machinery that are important to NSCs fate upon different ligand stimulation (such as mature and pro-neurotrophins, Aβ amyloid), we will explore the neurogenic potential of synthetic analogs of neurotrophins with preferable pharmacological properties, that could act both neuroprotective and neurogenic. Moreover, we aim to establish a 3D platform that will host human neuronal cells, derived from healthy and AD patients, using the induced Pluripotent Stem Cells technology. This effort will provide an optimal platform for drug screening in human biological material that emulates neurodegenerative conditions and thus, it will augment new therapeutic applications against AD pathology.

Expected results & Research Project Impact

The recent discovery of adult neurogenesis in humans and the properties of the neural stem cells in the adult brain open new avenues and opportunities for treating neurological disorders, particularly through the exploitation of endogenous regenerative capacity. The therapeutic value of stem cell transplantation or reprogramming of endogenous glial cells towards neurons are currently assessed in animal models of neurodegeneration and the first results support a future application of stem cell therapy to the clinical setting.

The detailed mapping of properties and functions of the neurotrophin receptor $p75^{NTR}$ could provide an enormous advantage for controlling hippocampal neurogenesis and the related cognitive functions. Endogenous molecules like neurotrophins and its receptor, $p75^{NTR}$, are strongly involved in both neuroprotective and regenerative processes. However their therapeutic potential is limited due to non preferable pharmacological properties. Thus, our team has developed synthetic compounds that mimic the effects of neurotrophins and selectively activate specific pathways of the $p75^{NTR}$, offering precious pharmacological tools for holistic treatment of neurological disorders, such as Alzheimer's Disease.

Cutting edge research is geared toward discovering novel drugs that target specific receptor-mediated adult neurogenesis. The findings of the present study will provide the pharmacological basis for proposing a new therapeutic approach of neurodegenerative diseases via pharmacological activation of residual adult neural stem cell proliferation and migration towards the neuropenic, suffering brain areas of Alzheimeric brain. Moreover, our work will create the basis for the development of a 3D platform using AD-derived human stem cells that mimics specific neuronal networks under neurodegenerative conditions and could be used for drug screening.

Fianlly, the program is offering training opportunities to young investigators for innovative technologies, as well as opportunities to strengthen the interdisciplinary collaboration of the participating research groups.

The importance of this funding

The funding of our research project is the key and the driving force to perform our experimental studies on deciphering the role of neurotrophin receptors to adult neurogenesis and their impact on Alzheimer’s Disease pathology, resulting potentially on the development of new therapeutic tools. The H.F.R.I. funding and its overall support is of utmost importance, providing multiple benefits in the training and specialization of young scientists, as well as connecting the greek scientific community with important research institutes abroad, and finally, developing new therapeutic schemes and tools, improving the long-term treatment of neurological diseases such as Alzheimer's disease. The importance of this funding is also documented from the following beneficial results: firstly, on the recruitment and exploitation of scientific human resources in Greek Universities and Research Institutes, providing them the proper settings for conducting excellent research, and secondly, on the whole society through the improvement of health and financial opportunities.

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