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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

Title of the research project:
From blood to brain: Platelets as novel regulators of brain stem cells in their niches, in neurodegeneration and in remyelinaton.

Principal Investigator:
Ilias Kazanis

Reader-friendly title:
Platelets and neural stem cells

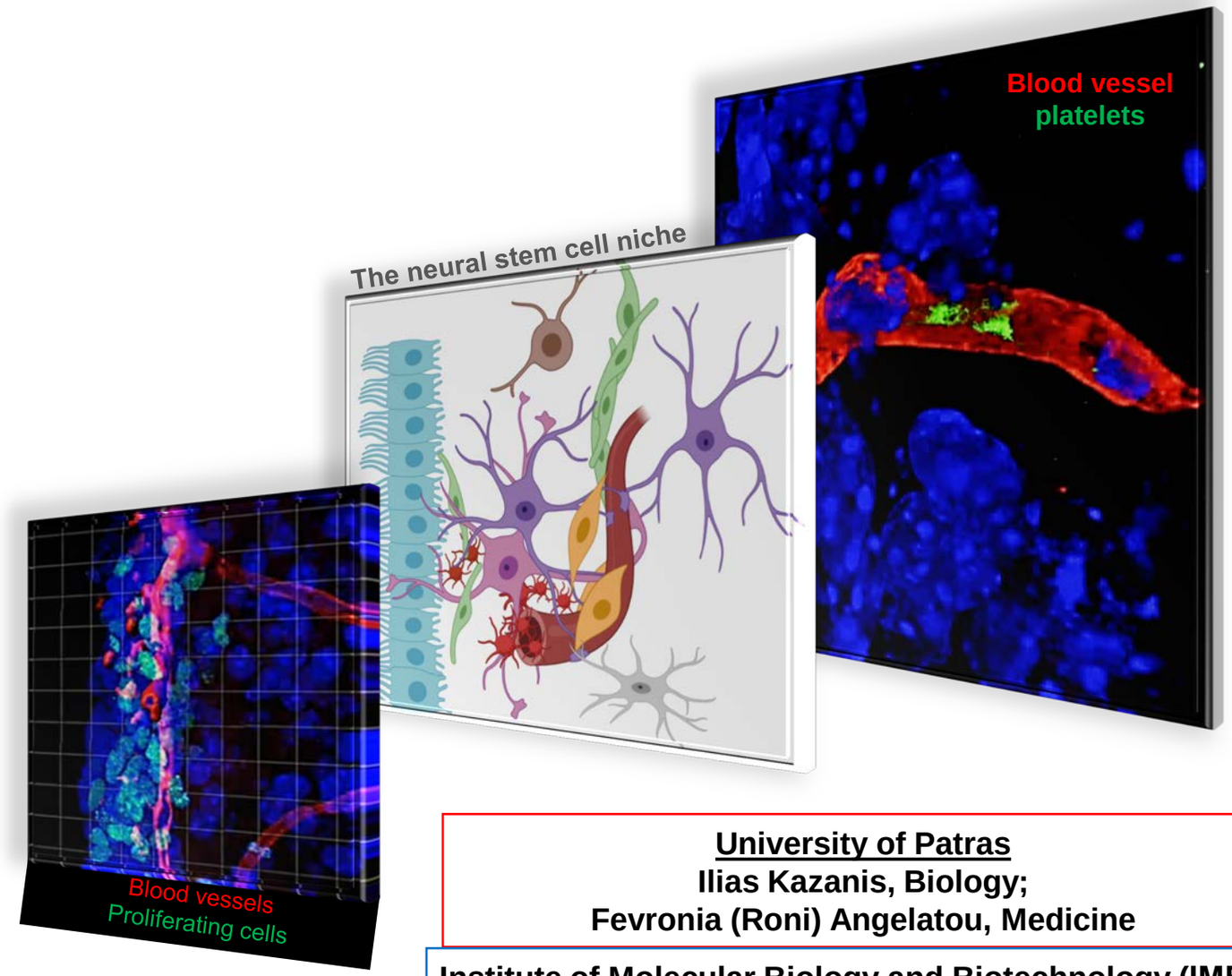
Scientific Area:
Life sciences (Medical & Health Sciences)

Institution and Country:
University of Patras, Greece

Host Institution:
Departments of Biology and Medicine

Collaborating Institution(s):
Institute of Molecular Biology and Biotechnology, Crete

Project webpage:
https://www.researchgate.net/project/From-blood-to-brain-Platelets-as-novel-regulators-of-brain-stem-cells-in-their-niches-in-neurodegeneration-and-in-remyelinaton



University of Patras
Ilias Kazanis, Biology;
Fevronia (Roni) Angelatou, Medicine

Institute of Molecular Biology and Biotechnology (IMBB)
Domna Karagogeos

Budget: € 180000

Duration: 36 months

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Images contributed by Christina Dimitriou

Research Project Synopsis

Different types of neural stem and progenitor cells survive within the postnatal rodent and primate (including the human) brain, such as *bona fide* neural stem cells (NSCs), neuroblasts and oligodendrocyte progenitor cells (OPCs).

In response to injury, newborn cells are generated in stem cell niches or locally in the parenchyma and are recruited to sites of lesion, a process that has been observed even in the aged human brain. However, our and others' experimental work has revealed that **the contribution of NSCs to regeneration is sub-optimal** because of spatiotemporal restrictions in their response within the niche and due to high failure of survival and maturation of new cells in their target areas. **Therefore, the identification of endogenous brain factors that control the activation and survival of NSCs and of their daughter cells is an important goal in the effort to design novel cell-based therapies, irrespective of the source of stem cells (endogenous tissue-specific, embryonic or induced pluripotent stem cells)**.

Our working hypothesis is that platelets constitute a newly-discovered endogenous player in the control of the cytogenic capacity of NSCs and OPCs and we propose to investigate this using a range of transgenic and disease-modeling animal experiments and *in vitro* assays. We will also investigate the molecular signature of the brain's endothelium within the neural stem cell niche in order to identify the molecular pathways that underlie this crosstalk.

We aim at **providing experimental proof that platelets are an important regulator of the response of postnatal brain NSCs to a range of neurodegenerative conditions and we will identify potential molecular mechanisms that govern this activity.**

Project originality

Platelets (PLTs) contain three storage compartments (α & δ-granules and lysosomes) that carry a variety of molecules such as chemokines, cytokines, growth factors, RNAs and microparticles; thus, they can exert multiple functions other than haemostasis. Activated platelets participate in the recruitment and infiltration of leukocytes, but also to the inflammatory response of endothelial cells and of microglia, the innate immune system of the brain. Furthermore, injection of PLTs, or PLT-derived factors, in the brain's lateral ventricles, has been shown to promote neurogenesis and angiogenesis in experimental models of stroke.

In this project we will investigate for the first time **the endogenous regenerative properties of platelets in respect to postnatal brain Neural Stem Cells (NSCs)**.

We will achieve that **by integrating three key experimental approaches**: a) the use of animal models of neurodegeneration (mimicking aspects of Parkinson's disease) and of demyelination (mimicking aspects of multiple sclerosis). b) The use of transgenic mouse lines (kindly provided by Dr. Cedric Ghevaert, University of Cambridge, UK) exhibiting thrombocytopenia (low numbers of PLTs). c) The investigation of the molecular signature of the platelet/endothelium/NSC interaction using transcriptomic analysis.

Expected results & Research Project Impact

Neurodegenerative disorders or injuries affect all age groups, from infancy (e.g. cerebral palsy and leukodystrophies) to young and middle life (e.g. MS, traumatic brain injury) and up to old age (e.g. Alzheimer's, cerebral stroke). The social and financial burden to patients, their carers and governments is immense, and even small breakthroughs in the direction of therapy, clinical management and alleviation of symptoms will have high impact. **This project will provide a clear answer on whether platelets constitute a valid therapeutic target in regenerative medicine** and will lead to the identification of key mechanisms by which the platelet-pbNSC interaction is governed and can be manipulated. **Platelets constitute an abundant type of cell that can be easily collected** from the blood circulation. Moreover, their physiology is not known to be affected in neurodegenerative conditions and their generation remains robust in the elderly. **Therefore, they can be an ideal component of autologous cell-based therapies** in a wide range of neuropathologies, which can be developed in a short time-frame and with limited cost.

The significance of this work, in terms of biomedical research, also lies in two potential future directions:

a) Platelets could be used as a novel route of delivery of molecules targeting pbNSCs; a prospect facilitated by the current progress in generating artificial platelets (biopharma sector).
b) Information on the regulatory role of platelets on pbNSCs might be extrapolated in other adult stem cell systems.

The importance of this funding

RESEARCH- COLLABORATION- EMPLOYMENT & TRAINING

Funding basic or pre-clinical research in Greece is sparse; while securing international funding is extremely competitive and hard if a project proposal is not mature enough.
HFRI funding allows research to expand towards avenues that are promising, but demand resources, and increases the chances for obtaining further funding.

This project will also reinforce and nurture the collaboration between three different academic groups and two major institutes of Greece and will strengthen research at a cutting-edge field of biomedicine.

Importantly, it will support 2 PhD students and will provide opportunity for employment and further training to 2 post-doctoral researchers.

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