PROJECT ABSTRACTS – PHD CALL: OCTOBER 2025

a. Laboratory of Signal Transduction, Department of Biochemistry and Molecular Pharmacology

Area of Research: Single-Cell Transcriptomic Analysis of Breast Cancer.

Cancer is composed of heterogeneous tumor cells that coexist with immune cells within the tumor microenvironment. Breast carcinoma, in particular, exhibits a poor response to immunotherapy. To better understand the interaction between tumor cells and their microenvironment, and to enhance the effectiveness of immunotherapy, we aim to conduct single-cell transcriptomic analyses in tumor-bearing mouse models with specific genetic alterations in immune system cells (for example, ERO1-alpha knockout, a protein whose role in cancer we have been studying for many years). This approach will allow us to precisely identify the pathways that modulate the immune component within the tumor microenvironment.

Preferred academic and scientific backgrounds: the ideal candidate for the PhD program should possess strong computational skills, particularly in the analysis of RNA and DNA sequences.

b. Laboratory of Clinical Epidemiology, Department of Medical Epidemiology

Area of Research: Assessing the impact of Emergency Department Crowding on the Hospital Admission Decision and its Appropriateness (part-time position).

Emergency Department (ED) overcrowding is a major and persistent challenge, linked to adverse outcomes for patients and healthcare professionals. Yet, its measurement remains problematic. Existing indicators fail to reflect the complexity of clinical practice and align with healthcare workers' perceptions. Furthermore, overcrowding influences critical clinical decisions such as hospitalization. Evidence on the relationship between crowding and hospital admission rates is limited and inconclusive, particularly regarding the distinction between appropriate and inappropriate admissions.

This project will be performed in collaboration with the Italian Fenice network, coordinated by the Mario Negri Institute, and aims to (i) develop and validate an objective ED crowding indicator through comparisons with staff perceptions; (ii) evaluate the appropriateness of hospital admissions; (iii) investigate the influence of crowding on appropriate admission decisions.

Preferred academic and scientific backgrounds: for this part-time project, they include a medical degree with specialization, ideally with ED experience, proven research involvement, and competence in data analysis with the R software.

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c. Laboratory of Stroke and Vascular Dysfunctions, Department of Acute Brain and Cardiovascular Injury

Area of Research

Coronary artery disease is characterized by the progressive atherosclerotic plaque accumulation in the epicardial arteries. When the plaque becomes vulnerable, it represents a risk factor for acute cardiovascular events. Inflammation plays a role at every developmental stage of the disease, with the complement system being a key contributor, as underscored by previous research of ours.

The successful PhD candidate will employ new 3D in vitro models of plaque cellular populations - i.e. smooth muscle cells, endothelium and macrophages - to identify emerging molecular mechanisms and new biomarkers linked to plaque morphological evolution. Then, she/he will contribute to markers' exploration in an in vivo atherosclerotic mouse model with acute cardiovascular event (ApoE-KO mice fed with high-fat diet undergoing coronary artery ligation). The candidate will be part of the FUN AT PLAQUE project funded by FRRB, Regione Lombardia.

Main objective of the project: this study will shed light on the molecular mechanisms of complement system's effectors in the plaque's morphological evolution, providing key information to develop new diagnostic and therapeutic tools.

Preferred academic and scientific backgrounds for prospective candidates: proficiency with in vitro applications using organ-on-chip tools.

d. Lab. of Traumatic Brain Injury and Neuroprotection, Department of Acute Brain and Cardiovascular Injury

Area of Research

TBI, resulting from mechanical or physical forces to the head, ranges in severity from mild to severe cases, and can cause cognitive, memory, emotional, and physical disturbances, which often persist or even worsen many years after the initial event. As such, TBI represents a leading risk factor for neurodegenerative disease, with unique potential to contribute mechanisms leading to development of ADRD.

To understand the transition from TBI to ADRD, there's an urgent need for animal models that mimic post-TBI ADRD, mirroring human conditions. These models not only provide insights into disease mechanisms but also serve as vital tools for testing new therapies. Additionally, they aid in developing biomarkers, supporting drug development and clinical trial design. Current TBI-ADRD studies often rely on transgenic mice expressing dominant AD genes (e.g., presenilin mutants, APP mutants, tau overexpression). However, these models have limitations. They spontaneously develop neurodegenerative features over time, confounding the study of TBI-induced ADRD progression. Many existing models only capture some ADRD neuropathological, neurochemical, and neurocognitive features, and the progression of these characteristics remains poorly. In response to this RFA, we have brought together an expert and highly experienced collaborative team of researchers to address the following critical gaps in TBI-ADRD modeling:

(I) Exploiting genetic diversity,

(II) Integrating neuroinflammatory factors,

(III) Integrating transmission of polyproteinopathy in TBI-ADRD.

Main objective of the project: by leveraging a team science approach, we will efficiently and systematically execute a two phase TBI-ADRD model development strategy: (i) In Phase 1: We will systematically screen for mouse strain determinants affecting TBI ADRD formation (4

strains, 2 TBI models) to provide a better probability of identifying 1 promising paradigm (mouse strain-injury type) to advance in phase 2. (ii) In Phase 2: Using the selected mouse strain injury type model, we will introduce and rigorously evaluate two TBI ADRD model enrichment factors (LPS challenge to mimic systemic inflammation and human brain proteinopathy transmission). As the final output we will deliver an optimized and validated murine TBI-ADRD model that will mimic key neuropathological, neurochemical signatures/biomarker, and cognitive deficit observed in human TBI-ADRD.

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