

RECRUITING AND TRAINING PHYSICIANS-SCIENTISTS TO EMPOWER TRANSLATIONAL RESEARCH
A MULTILEVEL TRANSDISCIPLINARY APPROACH FOCUSED ON METHODOLOGY, ETHICS AND INTEGRITY IN
BIOMEDICAL RESEARCH - 2018-2023



FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO



FONDAZIONE
MONDINO
Istituto Neurologico Nazionale
& Clinico Scientifico IRCCS

RESEARCH TRAINING PROGRAM

I. General Information

Title of the research project:

GBA1 mutation and Parkinson's disease: focus on macrophage role

Name and address of the department:

Fondazione Mondino – IRCCS, via Mondino 2, 27100 Pavia

Student's supervisor:

Dr. Silvia Cerri

II. Description of the project

Background

Heterozygous mutations in the GBA1 gene - encoding for lysosomal enzyme glucocerebrosidase (GCase) - are numerically the most important risk factor for Parkinson's disease (PD), increasing the risk by 20-30x. Macrophages are the major cellular target of GBA1 mutation-dependent GCase defects and, possibly, the primary disease effectors. Moreover, they can recapitulate hallmark features of this condition thus representing a valuable biomarker of pathological status. Mutant GBA macrophages accumulate undigested lysosomal material, including aggregated alpha-synuclein.

What is the aim of the project?

- To investigate how GBA1 mutations affect peripheral inflammation and to identify a peripheral inflammatory signature, by evaluating macrophages from PD patients with and w/o GBA1 mutations;
- To examine how GBA1 mutations influence lysosomal-dependent proteolysis and alpha-synuclein phagocytosis in macrophages;
- To evaluate the efficacy of small molecule chaperones intended to rescue GCase activity (e.g. ambroxol) on macrophage phenotype and function.

What techniques and methods are used?

Clinical assessment of PD patients, phenotypic analysis of macrophages by flow cytometry, evaluation of cytokine/chemokine gene expression and secretome profile, analysis of lysosomal function and live-imaging of macrophage uptake of alpha-synuclein.

When did the department start working on this project? 2019

Type of research project:

- Basic science Clinical research without lab work Clinical research with lab work

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III. Student's involvement

- The student will mainly observe YES NO
- The student will observe the experiments but will be involved in data analysis YES NO
- The student will take active part in experiments ("lab work") YES NO
- The student will take active part in clinical examination (clinical research) YES NO
- The student will be allowed to work with patients YES NO

What are the tasks expected to be accomplished by the student?

The student will learn laboratory techniques for the generation and phenotypic assessment of human macrophages, evaluation of lysosomal function and immunolabeling of cells. S/he will be directly involved in the experiments, data analysis and interpretation, and will collaborate in collecting and recording patients' clinical data.

What is expected from/what will be the general outcome of the student?

- To prepare a poster / presentation / scientific report / abstract
- The student's name will be mentioned in a future publication
- Opportunity to present together with the supervisor the results on a conference
- No specific outcome is expected

IV. Requirements

What skills are required from the student?

Ability to work in team, collaboration and communication skills, knowledge of Scientific English.

Is there any special knowledge or a certain level of studies needed?

- Subjects passed:
Neuroscience (required)

Previous experience with:

Certificate of:

None

Are there any legal limitations in the student's involvement in the project? YES NO

If yes, what are the limitations?

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For the use of students considering participating in the project, further information can be found from the following references:

Blandini F, Cilia R, Cerri S, Pezzoli G, Schapira AHV, Mullin S, Lanciego JL. **Glucocerebrosidase mutations and synucleinopathies: Toward a model of precision medicine.** *Mov Disord.* 2019 Jan;34(1):9-21

Cerri S, Ghezzi C, Sampieri M, Siani F, Avenali M, Dornini G, Zangaglia R, Minafra B, Blandini F. **The Exosomal/Total α -Synuclein Ratio in Plasma Is Associated With Glucocerebrosidase Activity and Correlates With Measures of Disease Severity in PD Patients.** *Front Cell Neurosci.* 2018 May 18;12:125.

Ambrosi G, Ghezzi C, Zangaglia R, Levandis G, Pacchetti C, Blandini F. **Ambroxol-induced rescue of defective glucocerebrosidase is associated with increased LIMP-2 and saposin C levels in GBA1 mutant Parkinson's disease cells.** *Neurobiol Dis.* 2015 Oct;82:235-242.

V. Schedule

Duration of the project:

1 month 2 months 3 months

There are approximately 5 hours of work per day.

Available months:

January February March April May June
 July August September October November December

How many students can you accept to the project at the same time? __ 1 __

Special remarks:

(e.g., students should bring a stethoscope and a white coat, any vaccinations required, etc.)

Students should bring a white coat.

NOTE: a scientific report is required at the end of the program