Title of the PhD project: Using ABCG2 as Achilles Heel of cancer stem cells

Disciplines: Biochemistry and Cellular Biology
Laboratory: Molecular Microbiology & Structural Biochemistry (Head: Jean-Michel JAULT), Drug Resistance & Membrane Proteins group (Head: Pierre FALSON)

Doctoral school: Interdisciplinary Doctoral program in health-sciences (EDISS) - ED 205

Description

Scientific background and rationale: Solid cancers such as Lung cancer or Melanoma evade as circulating cancer stem cells (CCSC) that lead to metastases. Stem cells are characterized by typical proteins expressed at their plasma membrane such as CD44, CD133 or ABCG2. These proteins are used as biomarkers. In case of lung cancer, CCSC displaying a high tumorigenicity have been identified with an ABCG2 positive phenotype excluding the Hoechst 33342 DNA dye. The human ABCG2 is a transporter belonging to the large ATP-binding Cassette family, involved in the transport of compounds across membranes. ABCG2, also known as the breast cancer resistance protein is responsible for the anticancer drugs resistance, eg. mitoxantrone, topotecan or irinotecan in acute leukemias. ABCG2 has also a physiological role such as in stem cells, in which it is particularly abundant and where it mediates the efflux of porphyrins, compounds that are highly toxic when in excess.


Aim: To develop a strategy that will take advantage of the natural abundance of ABCG2 in stem cells as their Achilles Heel, by which, blocking its efflux activity will lead to porphyrin accumulation and trigger an oxidative stress and cell death.

Description of the project methodology:

1/ Isolation and characterization by flow cytometry of model stem cells, such as the lung cancer A549, in respect of anticancer drug and porphyrin efflux; expression pattern of ABCG2 and other biomarkers.

2/ Structure ABCG2 -based inhibitors design in collaboration with Pr. A. Boumendjel (Department of molecular pharmacology, University of Grenoble-Alpes) and their tests in cellulo for efficacy, selectivity and cytotoxicity. Characterization of their enzymatic inhibition action type.

3/ In vivo test on mouse xenografts or in ovo and finally on CCSC in collaboration with Pr. Léa Payen (Claude Bernard University, Lyon I).

Expected results:

1/ Proof of concept about the capacity of weakening stem cells through ABCG2 inhibition
2/ Set up potent, selective, and non-toxic ABCG2 inhibitors active on CSCC.

Perspectives:

New type of anticancer therapy preventing metastases formation

Skills required:

Master 2 in Biochemistry with cellular biology knowledge

Bibliography: (see above)

Key-words: ABCG2, Stem cells, Solid cancer, circulating tumoral cells

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Application should include: CV, application letter, Names and addresses of two references.

The application file should be sent before May 14, 2017 to: (helene.cortay@ibcp.fr).

The open competitive recruitment process is in two steps: 1. Internal laboratory procedure. 2. Interdisciplinary jury of EDISS.