[POSTDOCTORAL POSITION] -Blood-brain barrier (BBB) passage of functionalized molecules for antitumor therapeutic purposes

DESCRIPTION

A postdoctoral position aimed to study the blood-brain barrier (BBB) passage of functionalized molecules for antitumor therapeutic purposes is available at the Lorraine University, France.

This project is part of the Lorraine University of Excellence (LUE) program, and specifically the "BIOMOLECULES" IMPACT project, aimed at identifying new anti-inflammatory, anti-proliferative and antioxidant compounds, with a focus among other on their functionalization or their encapsulation/vectorization and the validation of their biological activity for their integration in agro-chemistry, biocontrol, agro-alimentary, cosmetic, pharmaceutical and medical products.

This project hires a consortium comprising six academic laboratories, which are CALBINOTOX (EA 7488), CITHEFOR (EA 3452), CRAN (UMR 7039), LRGP (UMR 7274) and LCPM (UMR 7375) from the University of Lorraine, and MEDyc (UMR 7369) from the University of Reims.

Research area

The BBB located in the cerebral capillaries, is the physical and metabolic interface between blood and brain tissue, which prevents the intrusion of physiological or exogenous substances into the brain *via* the BBB's tight junctions of endothelial cells and efflux pumps activity. Thus, the administration of diagnostic or therapeutic compounds for brain tumor targeting may be limited by the presence of this barrier. Moreover, the strategy to target brain tumors needs to fit with the type of tumor: avascular or vascular foci. One exploited strategy for increasing brain penetration of biotherapeutics is to target receptor-mediated transcytosis system by conjugating the therapeutic and its carrier molecule to a ligand molecule (peptides) that has the capability of binding to the receptor overexpressed in tumor cells (vascular or avascular). LCPM, LRGP and CRAN laboratories are experienced in working together on the development of vascular targeting strategies via a Neuropilin-1 (NRP-1) targeting peptides, and avascular targeting strategies allowing in extra the transport of antitumor drugs from the blood to the brain tumors via a Low density lipoprotein receptor-related protein 1 (LRP-1) targeting peptide. The final step will be the validation of the passage of these drugs with an in vitro BBB model as tool. This *in vitro* model of BBB is based on primary endothelial cells co-cultured remotely with primary astrocytic cells isolated from rat cerebral cortex in a Transwell system.

The objective of this project is to validate 1) the establishment of the *in vitro* BBB model, and 2) the passage through the BBB of the therapeutics conjugated to NRP-1 or LRP-1 targeting peptides which are developed by the LCPM/LRGP/CRAN/MEDyC consortium and having a high therapeutic potential in targeted therapy of brain tumors.

1) The postdoc will primarily work for validate the *in vitro* BBB model with the:

- specific expression and localization of tight junctions and transporters such as occludin, claudin-5, Zonula Occludens 1 (ZO-1), P-GlycoProtein (P-gp) and LRP-1,
- presence of physical barrier (measurement of Transepithelial/transendothelial electrical resistance (TEER), permeability assay of Lucifer Yellow),
- presence of metabolic barrier (transport assay of referent molecules such as transferrin, rhodamine 123 or tissue plasminogen activator).

2) Secondly, the postdoc will evaluate the passage of functionalized drugs through the *in vitro* BBB model.

Depending on the BBB passage efficiency, peptides stability and maintenance of the BBB integrity, an optimization of the peptides could be envisaged by a feedback mechanism. The transport of these optimized molecules (*i.e.* therapeutics conjugated to NRP-1 or LRP-1 targeting peptides) will be tested again and the passive and/or active mechanism of their BBB passage will be studied.

Thus, the postdoc candidate will have on charge the validation of the *in vitro* BBB model, the investigation of functionalized drugs transport, the communication and interpersonal relationships between the different teams, the co-supervision of research students (B.Sc., M.Sc. students), the preparation of scientific publications and will contribute to establish industrial contacts.

Experimental approaches will include *in vitro* model. Techniques and methods will include biochemical and molecular analyses, functional assays,.

Ideal candidate will have been awarded its PhD in cell biology or in related disciplines with a background in BBB research and transport biology. The candidate requires hands-on experience in one or more of the following areas: animal experimentation, *in vitro* model, primary endothelial cells and/or primary astrocyte culture cells, biochemistry and molecular biology methods, confocal and/or fluorescence cell imaging.

Scientific contacts: MAGUIN-GATE Katy, MCU, CALBINOTOX, katy.maguin-gate@univ-lorraine.fr

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DEVY Jérôme, MCU-HDR, MEDyC, jerome.devy@univ-reims.fr

TERMS AND TENURE

This position will be based at **CALBINOTOX** and **CITHEFOR** Labs, Vandœuvre-lès-Nancy, France. The duration cannot exceed 18 months.

The target start date for the position is ***January/February 2019,*** with some flexibility on the exact start date.

HOW TO APPLY

Applications are only accepted through email. All document must be sent to **katy.maguin-gate@univ-lorraine.fr**, **francois.dupuis@univ-lorraine.fr**, **celine.frochot@univ-lorraine.fr**, **samir.acherar@univ-lorraine.fr**, **noemie.thomas@univ-lorraine.fr**, jerome.devy@univ-reims.fr and aya.khanji@univ-lorraine.fr

Deadline for application is ***end of December 2018***.

JOB LOCATION

Nancy, Lorraine, France

REQUIREMENTS

Applicants are requested to submit the following materials:

- A cover letter applying for the position
- Full CV, including academic records and list of publications
- Statement of Research
- Two recommendation Letters