POST-DOC in cell biology

ANGERS UNIVERSITY
MINT UNIT

Junior Contract Researcher
Post-doctoral contract in public law

Category : A

Presentation of the University of Angers

In the heart of a region recognized for its quality of life, the University of Angers, the 3rd largest employer in the region, offers an environment conducive to the development of its staff and students. The UA is a multidisciplinary university, welcoming more than 26000 students spread over 3 campuses and 2 relocated campuses (in Cholet and Saumur). It has 8 components (5 UFR, 1 IUT, 1 internal engineering school and 1 internal business and management school), and 31 federative research units and structures. Thanks to the many innovative projects it carries out and its openness to the world, the AU allows everyone to evolve in a stimulating environment. Its annual budget is €156 million (including €123 million in payroll). The UA has 1167 teachers and teacher-researchers, 917 administrative and technical staff and nearly 2000 individual contractors and is looking for involved and daring actors. You recognize yourself in this job offer ? Join us !

Contract features:

Starting date : 01/11/2025
Contract duration : 12 months French law work contract
Work quota : 100%
Monthly wage : 2700€
Location : Angers University, MINT Laboratory

Name of research project : Synergy of Inhibitors for IntraNasal Therapy of Glioblastoma (SITING)

Description of the research project in which the research activities entrusted to the officer take place:

Glioblastoma is the most aggressive primary tumor of the central nervous system (Miller et al. 2021). Existing treatments are invasive and of limited efficacy as the mean survival is about 15 months after diagnosis. Blood-brain barrier (BBB) prevents most drugs from brain entry, limiting their intracerebral concentration and activity (Arvanitis, Ferraro, and Jain 2020). In tumoral situation, BBB permeability can be increased, but efflux transporters, mainly P-glycoproteins (P-gp) can be overexpressed which reduce cerebral access to therapeutic molecules (Arvanitis, Ferraro, and Jain 2020). Even when first line therapy is effective, relapses are constant and associated with glioblastoma stem cells (GSC) presence inside the tumor. GSC resist to conventional therapies and regenerate the tumor (Biserova et al. 2021). It appears essential to develop therapies efficient on GSC as well as new administration strategies to avoid BBB.

In our lab, *in vitro* dedifferentiated 3D GSC models were developed and characterized to validate their use in pharmacological studies (Doualle et al. 2023). Models' characterization underlined potential therapeutic targets in MIF pathway. High MIF expression was observed as well as a dedifferentiation-

induced increase in its receptors (CXCR4, CD74, CD44). Dedifferentiated GSC were resistant to various conventional cytotoxic therapies, but complete viability loss was achieved with MIF inhibition by 4-IPP (article ongoing). The effect of drugs combinations was evaluated to reduce treatment doses while being the most efficient and specific. Synergy score was calculated using ZIP (Zero Interaction Potential) method on Synergy Finder 3. Cyclosporine A (CsA), a calcineurin and P-gp inhibitor, decreased GSC viability in a synergistic way with MIF inhibitor, achieving high ZIP synergy scores (>30) (article ongoing). In addition to synergism, the inhibition of P-gp efflux by CsA would help maintaining intracerebral concentration of 4-IPP or other drugs. As CsA is already clinically approved for other applications, such drug repositioning would facilitate treatment development. Moreover, CsA has also been studied for neuroprotective ability after stroke (Mazzeo et al. 2008). However, given CsA affinity for P-gp, its BBB permeability is low and 4-IPP BBB passage has not been studied yet.
The intranasal route is an efficient and non-invasive method to reach the brain while bypassing the BBB (Koo, Lim, and Oh 2024). To protect drugs and facilitate nasal epithelium crossing, nanomedicine strategies are considered for CsA and 4-IPP. Preliminary work encapsulated CsA into lipid nanocapsules (CsA-LNC). LNC with a size of about 100nm with narrow-size distribution were obtained by solvent-free phase-inversion temperature process (Heurtault et al. 2002). Formulations were stable (>2 months) and achieved >98% encapsulation efficiency. To improve the mucoadhesive properties of LNC after administration, chitosan was added at the surface. Preliminary *in vitro* studies on adherent glioblastoma cells showed internalization in less than 24h and conserved CsA toxicity after encapsulation into LNC. However, to achieve toxicity also on GSC, CsA drug loading must be increased. Solubility in formulation oil has been determined to be >300mg/g. LNC formulation is currently under optimization to enable high CsA encapsulation at such doses.

Provisional project schedule: XX

The postdoctoral candidate will continue the development of CsA -LNC and initiate 4-IPP encapsulation. The candidate will benefit from the help of MINT engineers for analytical method (UPLC-UV and LC-MS) and formulation development. CsA-LNC will be optimized concerning CsA loading, which is ongoing. 4-IPP encapsulation strategy is planned to be chitosan-functionalized LNC, as for CsA, but may be adapted beneficiating from ADDRes expertise. Formulation efficacy will be first evaluated on glioblastoma cell lines as well as 3D dedifferentiated GSC and then confirmed on patient derived stem cell lines (BTIC). Viability will be measured by resazurin assay and cell death pathway activation will be checked by western blot (cell death pathways induced by free CsA and 4-IPP are being characterized and will be published in early 2025). Nanoparticles internalization will be evaluated in 2D GBM cells as well as in 3D GSC model by microscopy using a fluorescent molecule (DiD). 4-IPP and CsA LNC will also be tested in combination, to confirm synergism observed on free molecules. In Parma, the ability to cross the nasal mucosal barrier will be evaluated using *in vitro* transwell model with RPMI 2650 cell line and mucus. Results will be confirmed using human nasal healthy cells. A co-culture of intranasal barrier model and glioblastoma cells (including 3D GSC) will be developed. Formulation efficiency on GBM cells after intranasal barrier passage will be evaluated using resazurin viability assay.

Overall, this project will pave the way for *in vivo* preclinical study of vectorized CsA/4-IPP combination therapy for intranasal administration.

Expected results : XX

The main goal of this project is to obtain *in vitro* proof of concept that LNC can improve CsA and 4-IPP delivery via intranasal epithelium and efficiently eliminate glioblastoma cells (including GSC).

Definition of research activities and tasks to be accomplished:

Conducting experiments and writing an article

Expected skills :

Knowledge :

Cell culture
Cell and molecular biology
Toxicology

Know-how:

- Cell culture
- Cell and molecular biology
- Toxicology

Soft skills:

- Relationships
- English
- Writing papers

Qualifications

PHD degree of less than 3 years
Specialty : cell biology - cancerology

Recruitment procedures and contact :

You must submit your CV, cover letter and doctoral degree by mail at :
Franck.letournel@univ-angers.fr copy to : recrutement@univ-angers.fr

Deadline for applications: **03/10/2025**
This job description is available until the closing date for applications.
On that date, it will no longer be available on the website.

If needed, your contact for any further information:
at 02 41354735 or franck.letournel@univ-angers.fr