Inserm UMR 1253 Imagerie et Cerveau - Université de Tours

Intracerebral delivery of therapeutic molecules using the Sonococktail approach: Application to amyotrophic lateral sclerosis

Context **-** Nowadays, neuropathologies (*e.g.,* tumors, neurodegenerative and neuropsychiatric diseases, etc.) affect one in three people in the world, which represents a major public health issue. Although the integrity of the blood-brain barrier (BBB) is compromised during the evolution of most of these pathologies, the crossing of this barrier by therapeutic molecules remains a major challenge to overcome for the pharmacological treatment of these diseases. In this context, the concept of active delivery takes on all its interest because it implies both effective formulation and better targeting.

Issue **-** In recent years, promising new methods for the local delivery of anticancer drugs or nucleic acids based on the use of gas microbubble (MBs) have been proposed. This possibility, in combination with ultrasound (i.e., sonoporation), provides unprecedented alternatives for obtaining an effective and non-invasive therapeutic action. The term sonoporation denotes a process by which the activation of MBs by ultrasound (US) near the BBB transiently increases their permeability and thus allows the extravasation and penetration of therapeutic molecules into brain tissue. Thanks to this increased extravasation, the bioavailability of these molecules in the cerebral parenchyma is, in turn, increased, thus improving the therapeutic index.

The use of MBs has 2 major limitations: 1) their rapid clearance and 2) their polydispersity in size. Moreover, after permeabilization of the BBB by US, only a small amount of the therapeutic molecule administered intravenously in its free form will effectively cross the permeabilized BBB, reducing the therapeutic efficacy of the drug and increasing its systemic side effects.

Objectives – In this context, we propose to replace MBs by monodisperse and sonosensitive nanodroplets which can circulate for more than 2 hours after their intravenous injection. They can be exploited to permeabilize the BBB and convey therapeutic molecules. To demonstrate the effectiveness of our strategy, we will use a mouse model of amyotrophic lateral sclerosis in which we will deliver two therapeutic molecules, riluzole and anacardic acid (Coll. Prof. Vourc'h, iBrain, Inserm /University of Tours).

Methodology – To achieve these objectives, we will optimize the delivery protocol of therapeutic molecules by our Sonococktail approach (*i.e.,* ultrasound parameters, doses of NG1 and NG2, *etc.*) on a mouse model of ALS. The effectiveness of the intracerebral delivery of therapeutic molecules will be determined by mass spectrometry (Coll. Prof. Emond, iBrain, Inserm/University of Tours - PST ASB). Finally, the therapeutic efficacy of our protocol will be determined by a behavioral analysis of the treated animals.

References

- Huang, S.-L. *et al.,* Acta Neuropathol. Commun. 8, 3 (2020);
- Lu, H. *et al.,* Curr. Neuropharmacol. 14(4), 314–321 (2016);
- Presset A. *et al.,* Front. Mol. Neurosci. 15 :888318 (2022).

Profile of the candidate sought:

- Mandatory skills:
  - Scientific and technical skills in neurobiology or animal physiology.
  - Ability to work on animals;
  - Skills in statistics (R, Prism).

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- Ability to synthesize and write.
- Fluency in English (spoken and written).
- Participation in loco-regional conferences/congresses (Tours-Angers Biomedical Days, Functional Neuroimaging SFR Scientific Days), national (RITS) and international (ENCALS, IEEE IUS, ISTU);
- Participation in the collective life of the team and the laboratory (Seminars, Les Méridiennes), and in events for the public (Science festival, Brain awareness week).

- Optional skills:
  - Knowledge in acoustics.
  - Training: Animal experimentation – Designer level.

Place **-** The thesis will take place within the Imaging, Biomarkers, Therapy and Neurogenomics and Neuronal Pathophysiology teams of the iBrain laboratory (UMR1253, University of Tours, Inserm, Tours, France).

Funding – A thesis grant from the Centre-Val de Loire Region will finance this thesis from October 1, 2023 to October 1, 2026. This thesis is part of the ANR Sonococktail project.

Supervision – This thesis will be supervised by Jean-Michel Escoffre (Inserm Research Officer, Tel: 02 47 36 61 91, jean-michel.escoffre@univ-tours.fr) and co-supervised by Patrick Vourc'h (PU-PH, 02 34 37 89 10, patrick.vourch@univ-tours.fr).

Application file (deadline: 15/03/2023):

- Curriculum Vitae;
- Transcript of marks of B.Sc. and M.Sc. degrees;
- Motivation letter with 2 reference letters.

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