CIBM Center for Biomedical Imaging

CIBM Annual Symposium 2024

Forum Rolex Learning Center, EPFL, Lausanne Switzerland | 7th November 2024

20th Anniversary

P21

INVESTIGATING ULTRASOUND-MEDIATED BLOOD-BRAIN BARRIER OPENING AS A STRATEGY TO IMPROVE DRUG DELIVERY IN ALZHEIMER'S DISEASE

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BACKGROUND

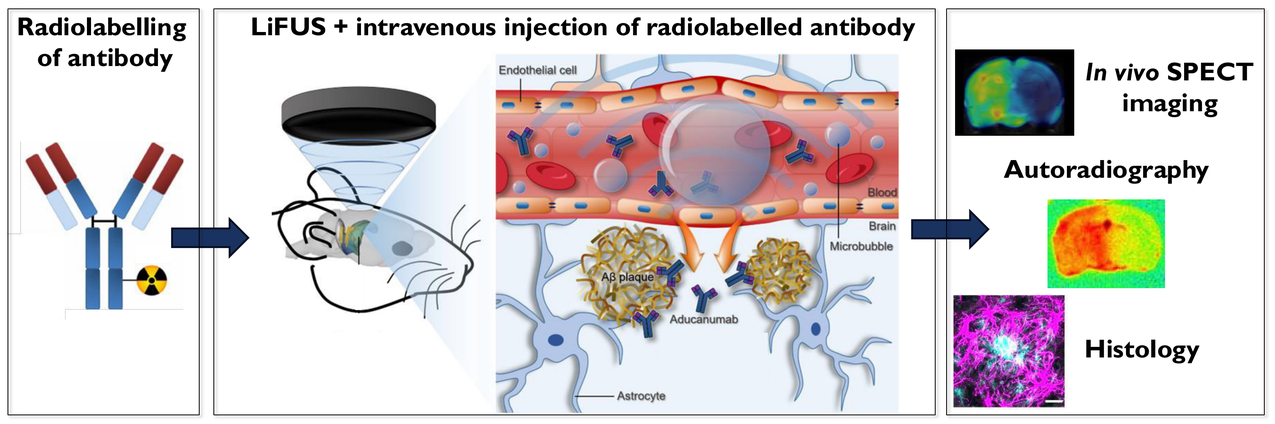
Alzheimer's disease (AD) is the most common form of dementia and represents one of the main clinical challenges of the century as the number of patients is predicted to triple by 2050. Recent advances, particularly immunotherapy with the approval of 3 anti-amyloid antibodies in US, are promising for drug development. However, a critical concern in AD treatment and neurological disorders in general, revolves around the **ability of drugs to effectively cross the blood-brain barrier** (BBB). A **synergy between a technology increasing brain delivery and pharmacology** appears therefore crucial to achieve therapeutic effects while reducing the risk of side effects associated with systemic administration of high doses.
To address this challenge, the use of **low-intensity focused ultrasound to mediate BBB opening** (LiFUS-BBBO) appears as an innovative and **non-invasive strategy** for facilitating the safe and efficient entry of therapeutic agents into the brain. Moreover, the absence of adverse effects of repeated LiFUS treatment has been studied in numerous preclinical and clinical trials, including in patients with AD. Despite growing interest in LiFUS-BBBO strategy, significant gaps in our knowledge persist, particularly regarding its combined therapeutic application with immunotherapy. This includes understanding the pharmacokinetics (PK) of therapeutic agents following LiFUS, the impact of repeated LiFUS exposure on BBB dynamics and elucidating the cellular mechanisms underlying LiFUS-immunotherapy synergistic effect.

AIMS

To unravel the potential of low-intensity focused ultrasound to facilitate the brain entry and potentiate the efficacy of therapeutic agents, the first steps of our research project were to:

- **Optimize the LiFUS protocol** to confirm safe, transient and efficient BBB opening in our specific rodent models.
- **Evaluate different radiolabelling strategies** of antibodies.
- **Validate increased antibody delivery** into the brain in different animal models of Alzheimer's disease.

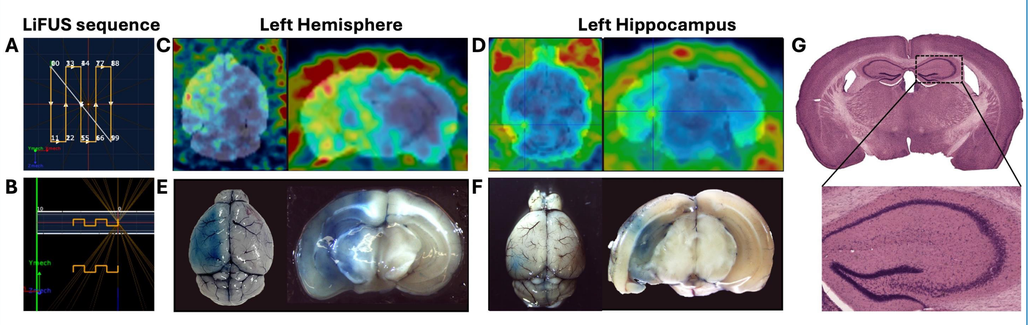
METHODS



RESULTS

Optimization of LiFUS protocol

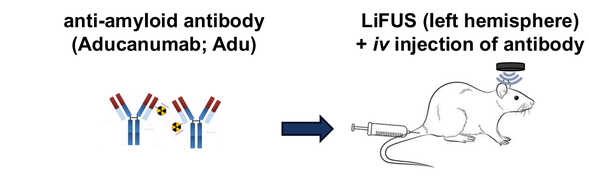
➢ **Efficient spatial control and safe BBB opening**



A. 2D representation of the LiFUS sequence used to target the left hemisphere, showing the scanning trajectory of the transducer. **B.** 3D representation of LiFUS sequence showing both trajectory of the natural point (-20 mm; up) and stirring point (-25 mm; bottom) allowing an in-depth BBBO. LiFUS-BBBO showed by *in vivo* SPECT images of the radiotracer [^{99m}Tc]DTPA (**C, D**) and Evans blue staining (**E, F**), two molecules normally blocked by BBB. **G.** Coronal slices of mouse brain stained with Hematoxylin/Eosin. No tissue damage (edema, bleeding) was observed after LiFUS. *Unpublished data.*

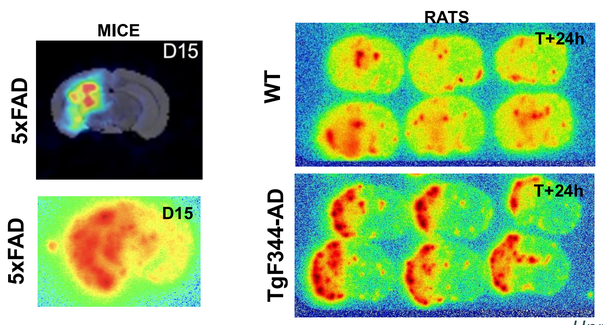
Radiolabelling optimization of anti-amyloid antibodies

➢ **Direct radiolabelling with Iodine 125**

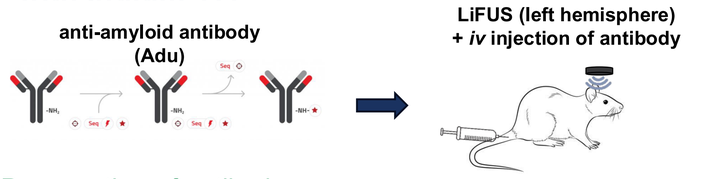


- High yield of the labelling
- Iodine 125 = long half-life
➔long-term follow-up

- Random fixation of the radioisotope
➔ could reduce affinity

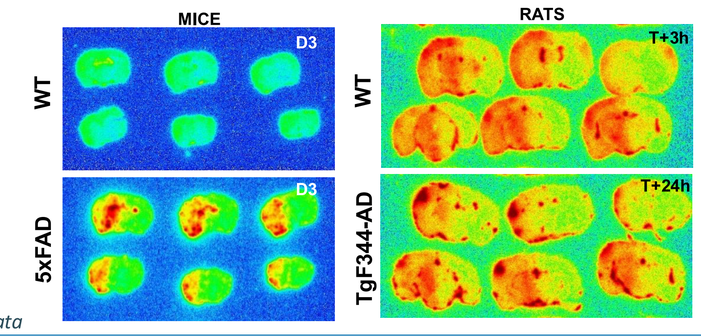


➢ **Debiopharm AbYlink™ conjugation technology with Indium 111**



- Preservation of antibody affinity

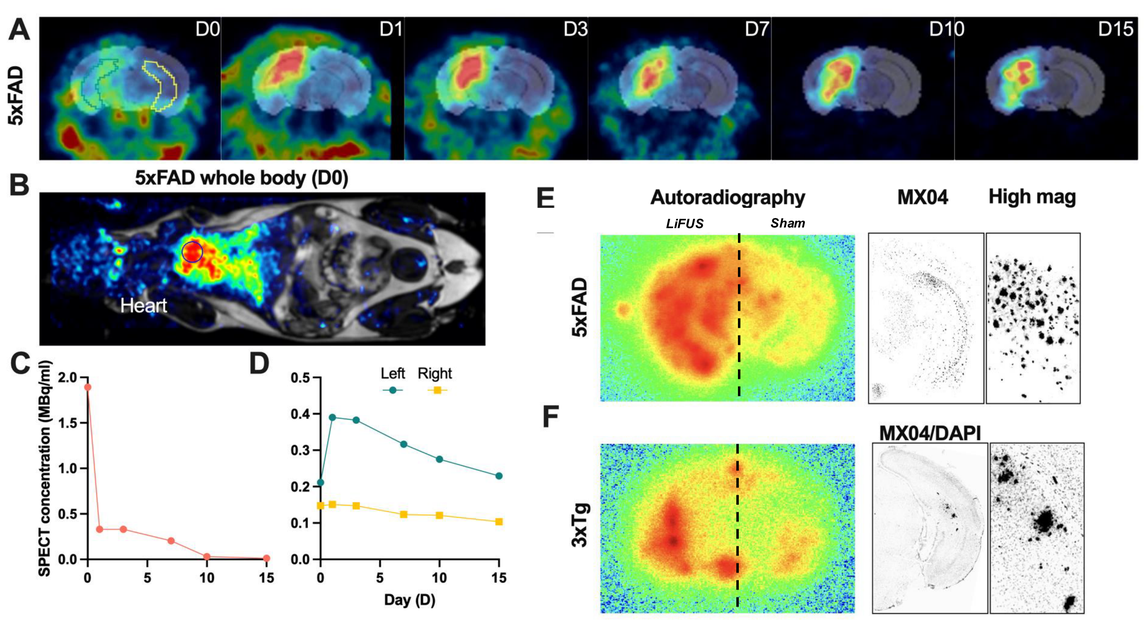
- Indium 111 = shorter half-life
➔ short follow-up



Unpublished data

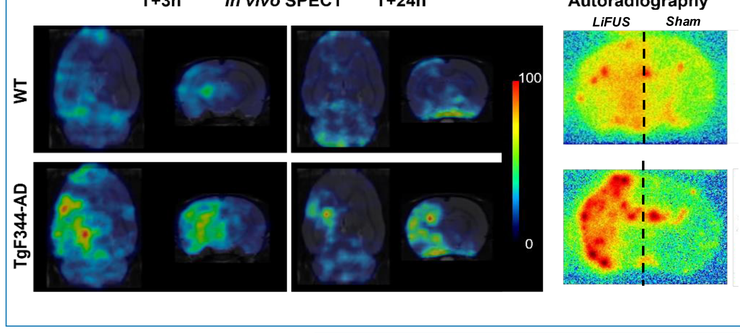
Improving Aducanumab brain penetration with LiFUS in different animal models

➢ **ImmunoSPECT in the brain of 5xFAD mice validating the increased delivery of Aducanumab in LiFUS-treated hemisphere.**



A. [^{125}I]Adu-SPECT imaging after LiFUS treatment of the left hemisphere with an MRI brain template (Pmod 4.5), showing an improvement in the signal-to-noise ratio from D1 to D15. **B.** [^{125}I]Adu-SPECT imaging in the whole body. **C.** Image-derived input function in the left ventricle of the 5xFAD heart (blue circle in B). **D.** Time-activity curves obtained in the left and right hippocampi of 5xFAD mouse, with the signal clearly elevated by LiFUS (+170% at D1). Autoradiography and Aβ plaques staining (MX04, black points) on the same slice in 5xFAD at D15 (**E**) and 3xTg mice at D10 (**F**). *Unpublished data.*

➢ **LiFUS treatment improves Aducanumab brain delivery in TgF344-AD rats.**



A. [^{125}I]Adu-SPECT imaging 3h and 24h after LiFUS treatment of the left hemisphere of WT and TgAD rats. The accumulation of [^{125}I]Adu in the targeted hemisphere demonstrated the ability of LiFUS-BBBO to improve Adu delivery in rat brain. The very low signal observed in the WT brain validated the specific binding, as confirmed by ex vivo autoradiography (**B**).

Abjean L, …, Ceyzériat. K bioRxiv 2024.09.25.614692

CONCLUSION & PERSPECTIVES

We have validated the efficient and safe BBB opening with our LiFUS protocol. Both direct and AbYlink™ conjugation technologies seems efficient with anti-amyloid antibodies tested. The brain penetration of the anti-amyloid antibody Aducanumab was clearly increased by LiFUS pretreatment in both mice and rats. Our data show the significant interest and potential of this translational technique in the treatment of brain diseases such as AD.

The next main objectives of our project are to :
- Develop a precise PK model for antibodies within the brain following LiFUS pre-treatment, aiming to **optimize the therapeutic dosage and treatment schedule**.
- Evaluate the **therapeutic impact of combining LiFUS with Aducanumab** on AD pathological outcomes and on amyloid-related imaging abnormalities side effects.
- **Investigate the cellular mechanisms** underlying the effects of the combined treatment.

Our overarching goal is to establish a versatile and personalized approach that enhances the delivery of various brain therapeutic agents, offering potential innovative strategy to improve the management of neurological disorders as a whole.