REBALANCE

Mechanisms of focused ultRasound mEdiated BrAin cLeAniNg Coupled with enhanced mEchanosen-sation

Focused ultrasound (FUS) is a non-invasive, ground-breaking technique suggested for the treatment of Alzheimer's disease (AD). The partners of the REBALANCE consortia have demonstrated therapeutic efficacy for FUS alone and FUS stimulation combined with microbubbles. At the cellular level, FUS promotes transient opening of the blood brain barrier (BBB) and enhances microglial-mediated clearance of beta-amyloid (Aß). However, there is a clear lack of studies deciphering molecular mechanisms underlying these beneficial effects of FUS, a fact that clearly limits its full translation into the therapeutic arena.

We hypothesise, that FUS, through activation of mechanosensitive Piezo1 channels, enhances microglial-mediated phagocytosis of Aß and facilitates the removal of waste from the brain into the blood stream. This occurs through improvement of glymphatic flow together with transient increase in the BBB permeability. Moreover, FUS-induced increase in BBB permeability enables drug delivery into the brain further boosting the Piezo1-mediated clearance of Aß. Together, this concerted reinforced effect of FUS represents a novel approach to improve the impaired brain function in AD patients. Further, we propose to establish a synergetic approach based on combination of FUS with an added advantage pharmacological activation of mechanosensitive Piezo1 to prevent or slow down the progression in AD. We analyse the plasma and cerebral spinal fluid (CSF) samples of the treated mice in order to discover blood or CSF-secreted proteins indicative of the treatment response and correlate the obtained data with AD patient samples undergone FUS therapy and to large AD patient cohorts.

REBALANCE aims to discover the key cellular targets and molecular mechanisms underlying FUS-induced brain cleaning and therapeutic efficacy in AD. In addition, we further aim to combine FUS together with pharmacological activation of Piezo1 (combined FUS, cFUS). We will mechanistically link the cellular players and intracellular pathways responsible for the increase in BBB permeability, microglia-mediated Aß clearance and enhancement in glymphatic flow and evaluate the underlying molecular, cellular, neuronal and neuro-glia networks involved in the protection. The combination of human-based models and state-of-the-art animal models bridges the preclinical mechanistic findings to clinical data and provide biomarkers indicative of therapeutic benefit. Continuous analysis of ethical issues will allow us to identify ethical challenges in the R&D process from the point of view of different stakeholders, to minimize ethical risks and to involve patient organizations in the dialog. Combined these efforts will lead to efficient clinical translation of the preclinical findings and towards more efficient treatment of patients with AD.

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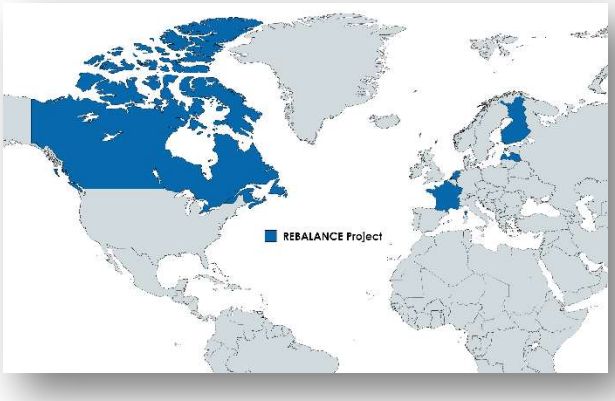

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