# AutoFus

## Facilitating focused ultrasound-mediated Tau clearance in Alzheimer's disease and other Tauopathies by understanding the underlying autophagic mechanisms

Ultrasound (US) is routinely used for a wide range of diagnostic imaging applications. However, given that US is a highly variable modality, the applicability of US extends far beyond the bio-imaging field. In fact, US is already being used as a surgical tool to treat essential tremor, or in stroke patients via sonothrombolysis to remove blood clots.

In recent years, US has further been explored in a range of animal species (and in human study participants) as neuromodulatory and blood-brain barrier (BBB)-opening tool, the latter facilitating the delivery of blood-borne factors (some having a therapeutic effect) or intravenously injected drugs (such as therapeutic antibodies). Different from systemic drug administration, therapeutic US at low frequency not only allows for global but also local brain treatment by e.g., directing a focused ultrasound (FUS) beam exclusively to certain brain areas such as the hippocampus. Different from radiation therapy, FUS exerts its effects only in the focal zone and not in tissue through which the sound waves travel, adding to its safety profile. When treating the human brain, lower frequencies are used than for imaging purposes aimed at peripheral soft tissue such as the womb, because high frequency US is attenuated by the human (and less so, mouse) skull.

The potential of low-frequency US for Alzheimer's disease (AD) has been explored by our groups and others over the recent years. We have been exploring two paradigms: US with intravenously injected microbubbles to transiently open the BBB, and US without microbubbles, achieving a wide range of bioeffects including Aß and Tau clearance, as well as improved memory and motor functions. Importantly, these improvements were obtained in the absence of a co-administered drug. We have shown that US clears Aß by activating microglia. We also found that US clears Tau, albeit not via microglial activation, but rather concomitantly with the induction of neuronal autophagy, suggesting that pathological Tau is removed by autophagy. Whether blood-borne factors taken up by the brain due to a transiently disrupted BBB contributed to some of the bio-effects remains to be established. Notably, a general role for autophagy in Tau clearance has been shown by several groups.

Here, we hypothesize that autophagy is a fundamental mechanism by which Tau is cleared in response to therapeutic US. This international consortium is aimed at attaining a basic understanding of how US induces autophagic removal of Tau in vitro and in vivo, and how US-induced autophagy can enhance the efficacy of an anti-Tau antibody. It brings together experts in autophagy, US applications to preclinical models of AD, and multimodal (optoacoustic, fluorescence, and magnetic resonance) imaging to establish optimal US conditions and monitor autophagic clearance in vitro and in vivo. We further hypothesize the existence of an optimal sonication parameter regime that maximizes the therapeutic outcome. In addition, we propose a causal link between local cerebral blood flow (CBF, via nutrition and oxygen supply) and local autophagy in the brain. The proposed collaborative work package constitutes an important step towards implementing US as a non-pharmacological treatment modality for AD, thus supporting and complementing ongoing clinical trials and facilitating the design of future trials.

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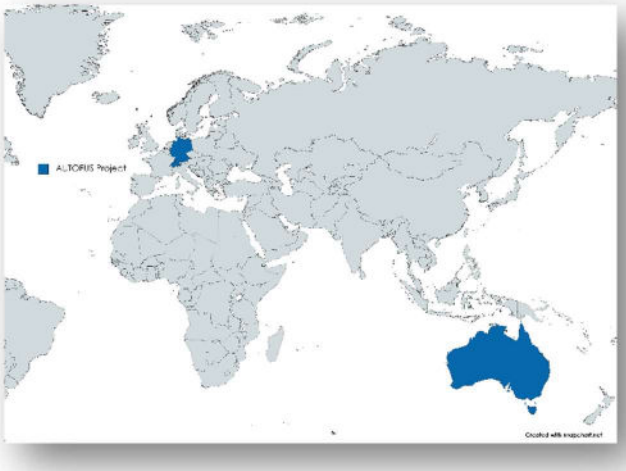


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