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Title	Improving the safety profile of focused ultrasound in blood-brain barrier opening by using a combinatorial strategy that involves a claudin-5-specific binder
Abstract (max 300w)	Treatment strategies for neurological disorders such as Alzheimer's disease are hampered by the fact that the blood-brain barrier (BBB) establishes an efficient barrier for therapeutic. An emerging technology to overcome this limitation is focused ultrasound (FUS). When FUS interacts with intravenously injected microbubbles (MB), FUS+MB, the BBB opens, transiently allowing the access of therapeutic agents into the brain. However, the ultrasound parameters need to be tightly tuned: when the acoustic pressure is too low there is no opening, and when it is too high, tissue damage can occur. We therefore asked whether barrier permeability can be increased by combining FUS+MB with a second modality such that in a clinical setting lower acoustic pressures could be used. We generated a stable MDCK II cell line that expresses fluorescently tagged human claudin-5. Two claudin-5 binders, mC5C2 (a peptide) and cCPEm (a truncated form of an enterotoxin) were synthesized and assessed for their abilities to enhance the permeability of cellular monolayers. We then performed a comparative analysis of single and combination treatments. The novel cell line formed functional monolayers as validated by an increased TEER reading and a low (< 0.2%) permeability to sodium fluorescein (376 Da). The two binders exerted a time- and concentration-dependent effect on BBB opening when incubated over an extended period, whereas FUS+MB caused a rapid barrier opening followed by recovery after 12 hours within the tested pressure range. Importantly, preincubation with cCPEm prior to FUS+MB treatment resulted in greater barrier opening compared to either FUS+MB or cCPEm alone. The data suggest (in vivo data pending) that preincubation with clinically suitable binders to BBB tight junction proteins may be a general strategy to facilitate safer and more effective focused ultrasound-mediated BBB opening in cellular and animal systems and potentially also for the treatment of human diseases of the brain.

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