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Combination of focused ultrasound and long-circulating nanoparticles for nucleic acid delivery to the brain

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Gene therapy and editing have emerged as a potent means to treat otherwise incurable neurological disorders, spanning brain tumors to neurodegenerative diseases. However, the task has been challenging primarily due to the inability to overcome a serious of biological barriers that hamper efficient delivery of therapeutic nucleic acids to the disease areas and cells within the brain. Systemically administered nucleic acid delivery nanoparticles must avoid liver accumulation to stably circulate, traverse the blood-brain barrier, distribute throughout the disease area within the brain, and finally introduce nucleic acid payloads into target cells. To this end, we introduce a two-pronged delivery strategy that address these challenges. The first component is biodegradable nanoparticles capable of stably circulating in the bloodstream and efficiently penetrating brain tissue, and the second component is focused ultrasound that opens the BBB in a transient, reversible, and targeted manner. We demonstrate that this combined delivery strategy enables efficient delivery of various nucleic acid payloads, including plasmid DNA and mRNA, to the brain and nucleic acid-based genome editing in the brain, both in a targeted manner.