利用超音波遺傳學非侵入式刺激神經並治療神經退化疾病

Sonogenetics: using ultrasound to non-invasively activate neurons and ameliorate neurodegenerative diseases

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In addition to diagnostic imaging, medical ultrasound has great potential for developing gene therapies in virtue of the non-invasive essence, penetrability into deep tissue, and good spatiotemporal resolution. In this project, we attempt to establish sonogenetic approaches for various therapeutic applications. By making use of the engineered auditory sensing proteins, mPrestin(N7T, N308S), we are able to render mammalian cells to sense focused ultrasound stimulation (FUS), which evoked a calcium influx from the extracellular space into their cytosol under a low-frequency and low-pressure FUS condition (**Figures 1 and 2**). Moreover, pulsed FUS can also non-invasively activate target neurons transfected with mPrestin(N7T, N308S) in deep regions of mouse brains (**Figure 2**) (Huang et al., 2021, 2020)(Patent: I720319). To our knowledge, this is the first study using sonogenetic tools to activate target cells in deep brain regions. Despite the non-invasive nature of the FUS-dependent sonogenetic modulation, how to deliver the genetic components to the target sites is the critical problem to be solved. To access the ultimate goal for non-invasive therapeutic approaches, we also developed the non-invasive transfection via mPrestinNTNS-loaded microbbubles (pPrestin-MB) (**Figure 4**). The disruption of the blood-brain barrier by FUS allowed the sonotransfection of the pPrestin-MB into neurons at the specific sites in the mouse brains without causing tissue damages. After 2 days, the transfected neuron cells were then selectively and transcranially stimulated by the low frequency FUS. (**Figure 4**) (Wu et al., 2020). Parkinson's disease is one of the most common neurodegenerative disorders. We tried to test the possibility of using our sonogenetic tools to treat Parkinon's disease mice. The persistent expression of mPrestinNTNS was observed in the substantia nigra of Parkinson's disease mice at the 56th days after a single shot of adeno-associated virus infection, which enabled the long term and repeated treatments through the transcranial FUS activation. (**Figure 5**) The FUS to the dopaminergic neurons of the parkinson's disease mice activates neuron cells expressing mPrestinNTNS, and alleviates the degeneration of the dopaminergic neurons and motor symptoms (**Figure 5**)(Fan et al., 2021). Our results not only uncover the underlying mechanisms of ultrasound sensing but also offer new strategies to non-invasively treat neurodegenerative diseases.

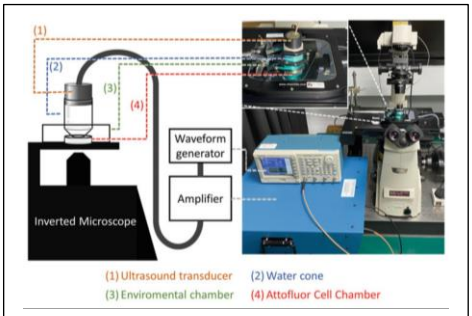

Figure 1.

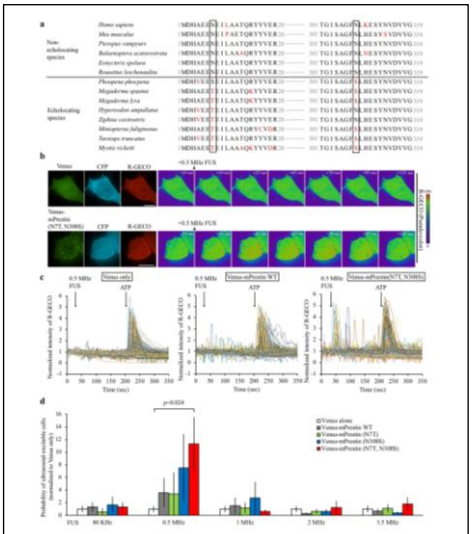

Figure 2.

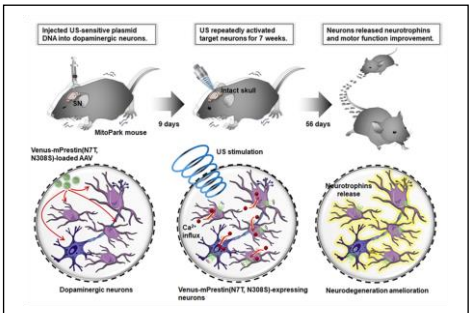

Figure 5.

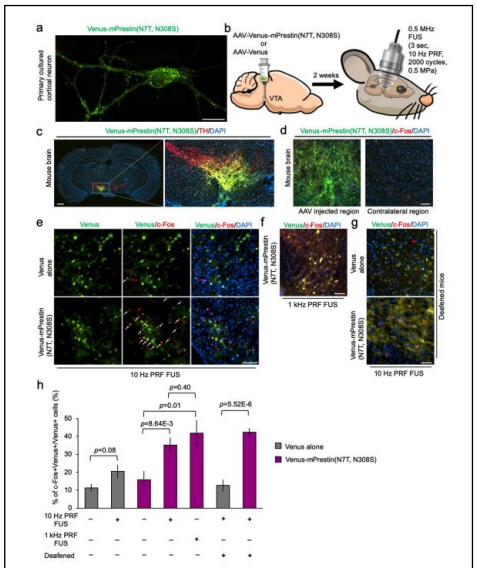

Figure 3.

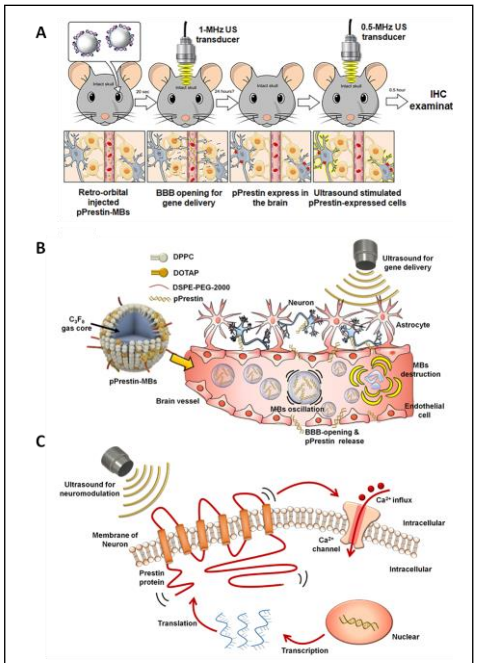

Figure 4.

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Patent:

中華民國專利 I720319　　超音波感應蛋白質以及利用超音波刺激細胞的方法