Abstract track: “Theme C: α-Synucleinopathies / C02.k. Therapeutic Targets, Mechanisms for Treatment: Gene therapy and gene editing”

Title: NON-INVASIVE AND TARGETED VIRAL VECTOR-MEDIATED NEUROTROPHIC FACTOR DELIVERY TO THE BRAIN WITH THERANOSTIC ULTRASOUND INDUCES NEURORESTORATIVE EFFECTS IN A PARKINSON’S DISEASE MOUSE MODEL

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Aims:

To induce restoration of degenerated dopaminergic neurons with non-invasive viral vector-mediated neurotrophic factor delivery achieved by targeted blood-brain barrier opening (BBBO) with theranostic ultrasound (ThUS) in vivo.

Methods:

BBBO with focused ultrasound in conjunction with systemically administered microbubbles is a safe and reversible technique for targeted drug delivery to the brain, providing a non-invasive alternative to direct intracranial injection. A novel configuration for transcranial BBBO developed by our group, called ThUS, was used to perform simultaneous bilateral delivery of AAV encoding human neurturin (NTRN) to the murine substantia nigra (Fig. 1A-B).

To induce neurodegeneration, 16-week-old male C57BL/6J mice (Charles River, Kingston, NY) underwent a sub-acute dosing scheme of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) consisting of daily intraperitoneal injections (30 mg/kg) for 5 days. After a 21-day period of neurodegeneration, mice were anesthetized with isoflurane anesthesia and underwent 2 minutes of ThUS-mediated BBBO immediately after intravenous co-injection of AAV9-hSynapsin-hNTRN (Vector Biolabs) and house-made polydisperse microbubbles (8e8 microbubbles/mL). 90 days post-BBBO, mice were sacrificed for histology with tyrosine hydroxylase (TH) staining (Fig. 1C).

Results:

Quantification of GFP fluorescence area revealed a significant ~96% increase in dendritic network density in the substantia nigra pars reticulata (SNr) in MPTP mice which received ThUS+AAV (Fig. 2A-C). No significant differences in SNr dendrite density were observed between groups receiving either ThUS or AAV alone compared to MPTP mice which did not receive treatment intervention (Fig. 2C). A 2-fold increase in cell body density within the pars compacta (SNc) was observed in MPTP mice treated with ThUS+AAV relative to MPTP mice alone (Fig. 2D).

Conclusions:

ThUS-mediated AAV-hNTRN delivery induced histological evidence of neurorestoration in Parkinsonian mice, demonstrating the potential for a more effective and non-invasive option for gene delivery in PD treatment.

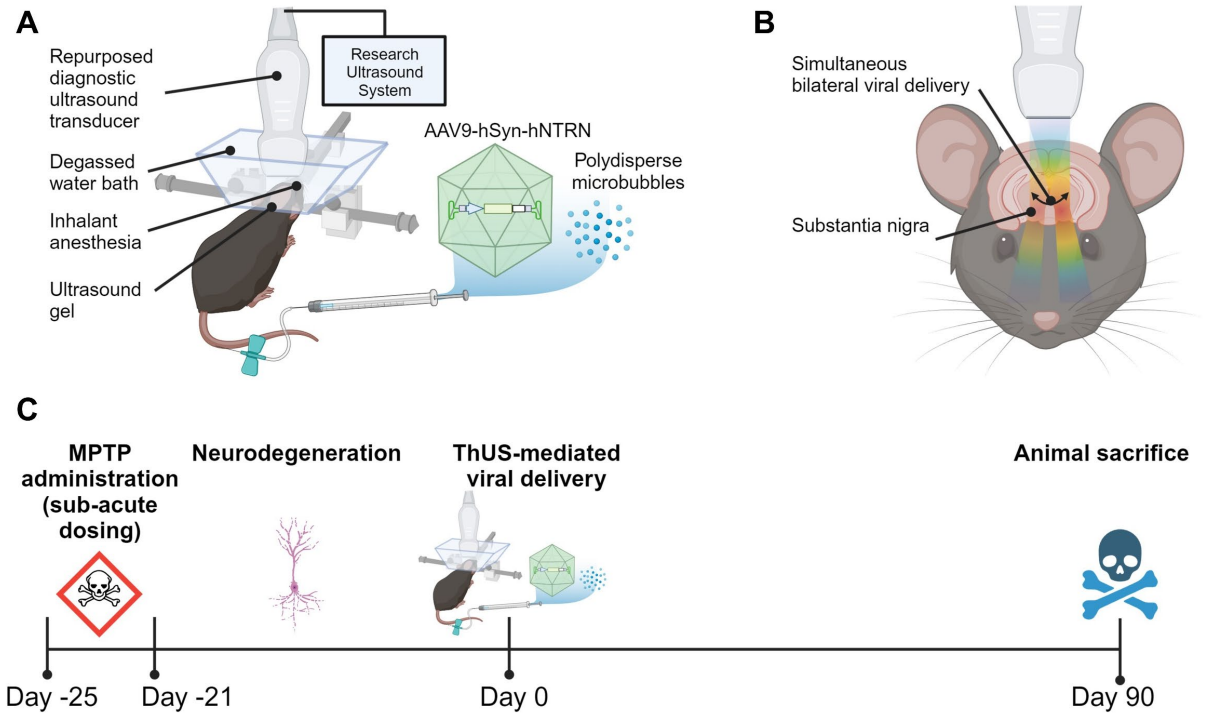

Figure 1: Experimental apparatus and study overview. A) Experimental setup for ThUS-mediated viral gene delivery. **B)** Schematic of ultrasound targeting. **C)** Study timeline.

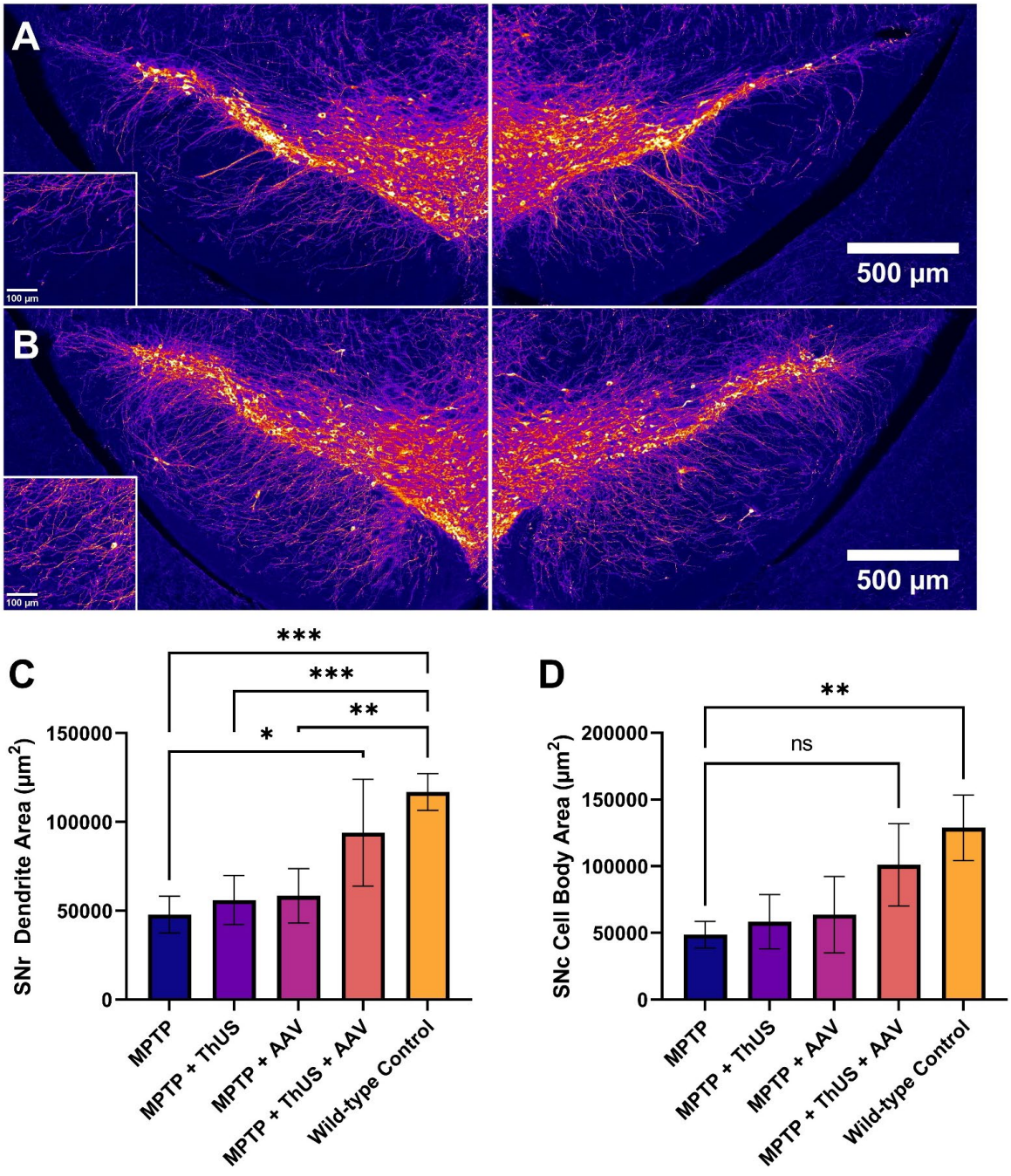

Figure 2: TH immunohistochemistry reveals neurorestorative effects after ThUS-mediated AAV-NTRN delivery. A) Representative images of left and right substantia nigra from MPTP mouse with no treatment intervention. **B)** Representative images of left and right substantia nigra from MPTP mouse after ThUS+AAV treatment. Insets in (A-B) show enlarged images of representative dendritic network density. **C)** Group-wise quantification of dendritic network in SNr. **D)** Group-wise quantification of cell body density in SNc. Statistical significance determined by one-way ANOVA with post-hoc Tukey's multiple comparisons test. *p<0.05, **p<0.01, ***p<0.001