

Preclinical Development of ST-503: an Investigational Adeno-associated Viral Vector-Delivered Zinc Finger Repressor Novel Epigenetic Therapy for Idiopathic Small Fiber Neuropathy

Sangamo

THERAPEUTICS

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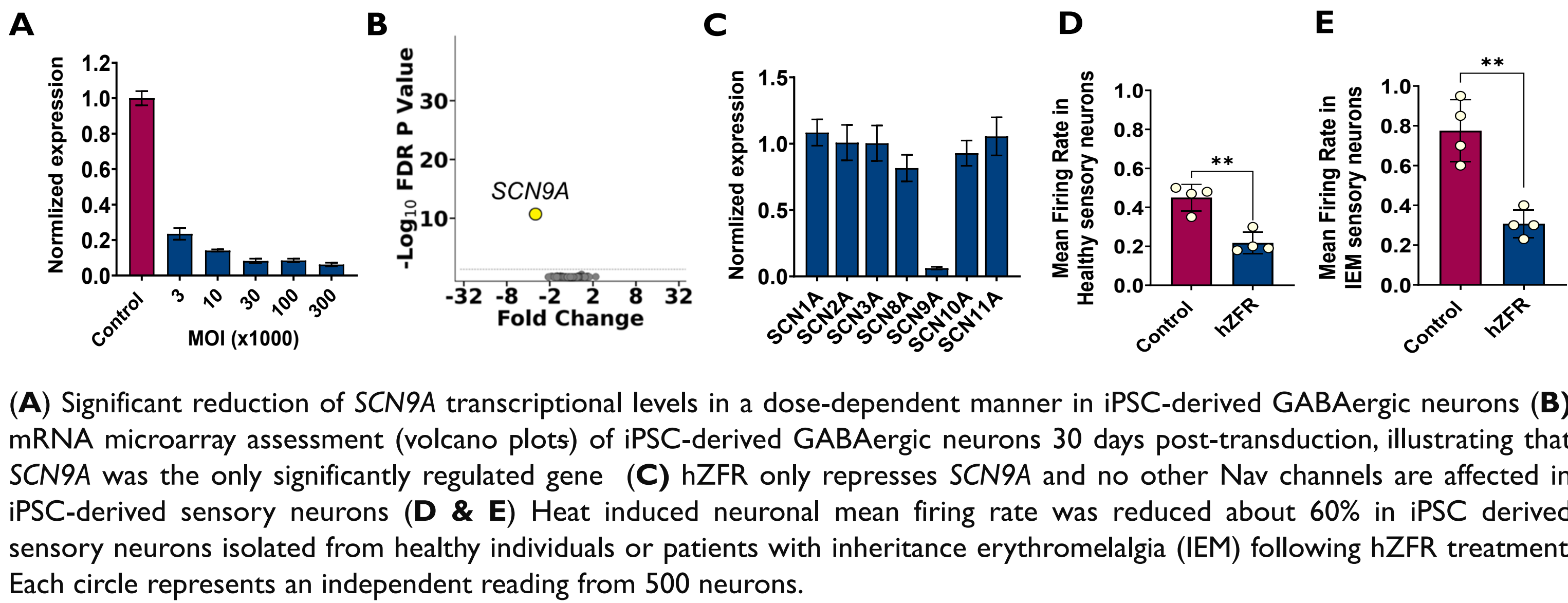
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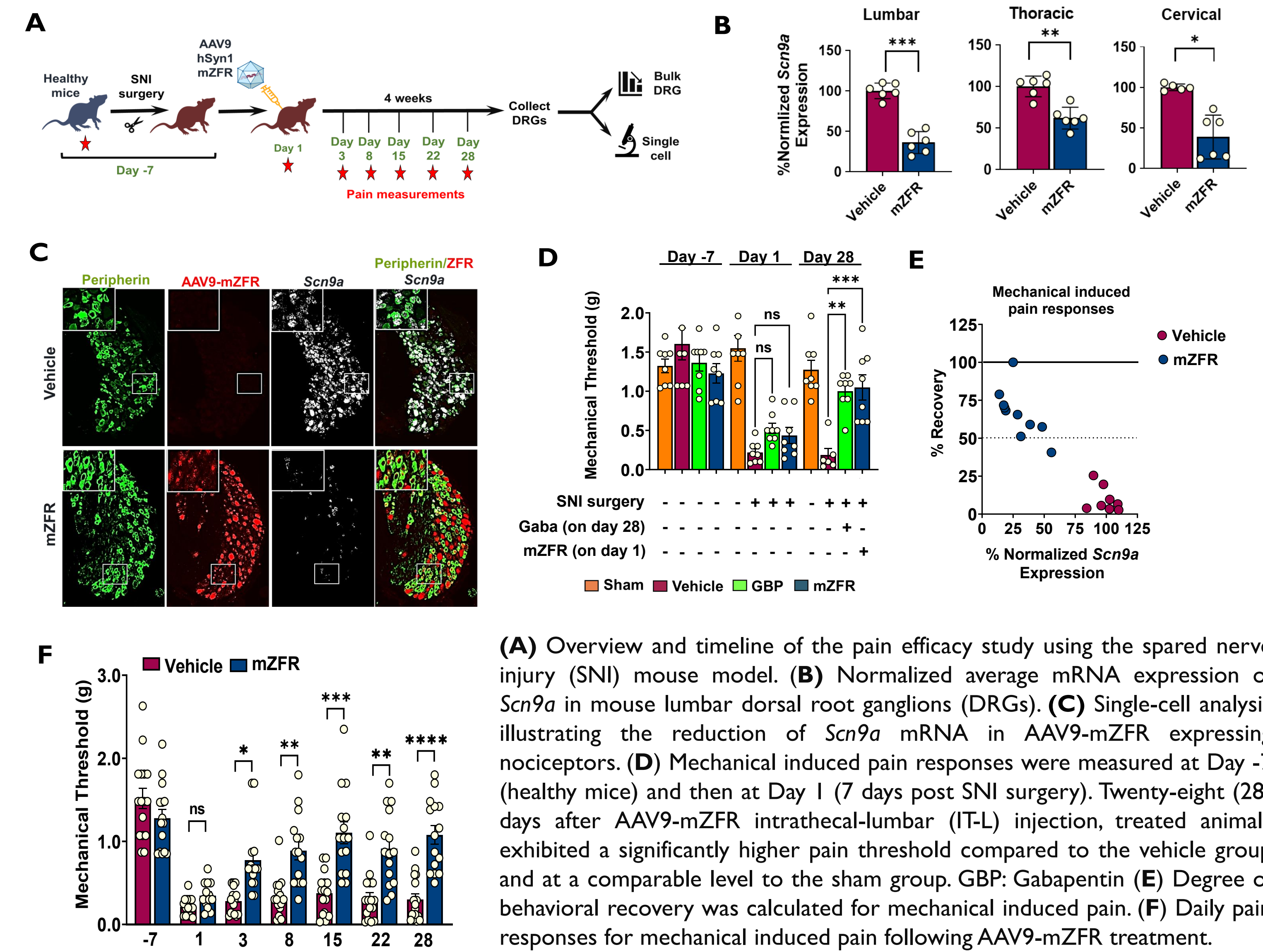
Introduction

- Peripheral neuropathies are estimated to affect several million patients worldwide with no long-lasting therapy currently available.
- In humans, the Nav1.7 sodium channel, encoded by the *SCN9A* gene, is involved in a spectrum of inherited neuropathies, and has emerged as a promising target for analgesic drug development.
- The development of a selective Nav1.7 inhibitor has historically been challenging, in part due to structural similarities among other Nav channels.
- Here we present preclinical studies for the first genomic medicine approach using an engineered zinc finger repressors (ZFRs) specifically targeting the human/nonhuman primate (NHP) *SCN9A* gene.
- Zinc finger (ZFs) are naturally occurring transcription factor proteins that have primarily evolved to regulate eukaryotic gene expression epigenetically and represent the most abundant and diverse class of DNA binding proteins in the human genome.
- The zinc finger array mediates site-specific binding to the *SCN9A* gene, and the KRAB domain represses the endogenous expression of *SCN9A* transcript, leading to a reduction in Nav1.7 protein.

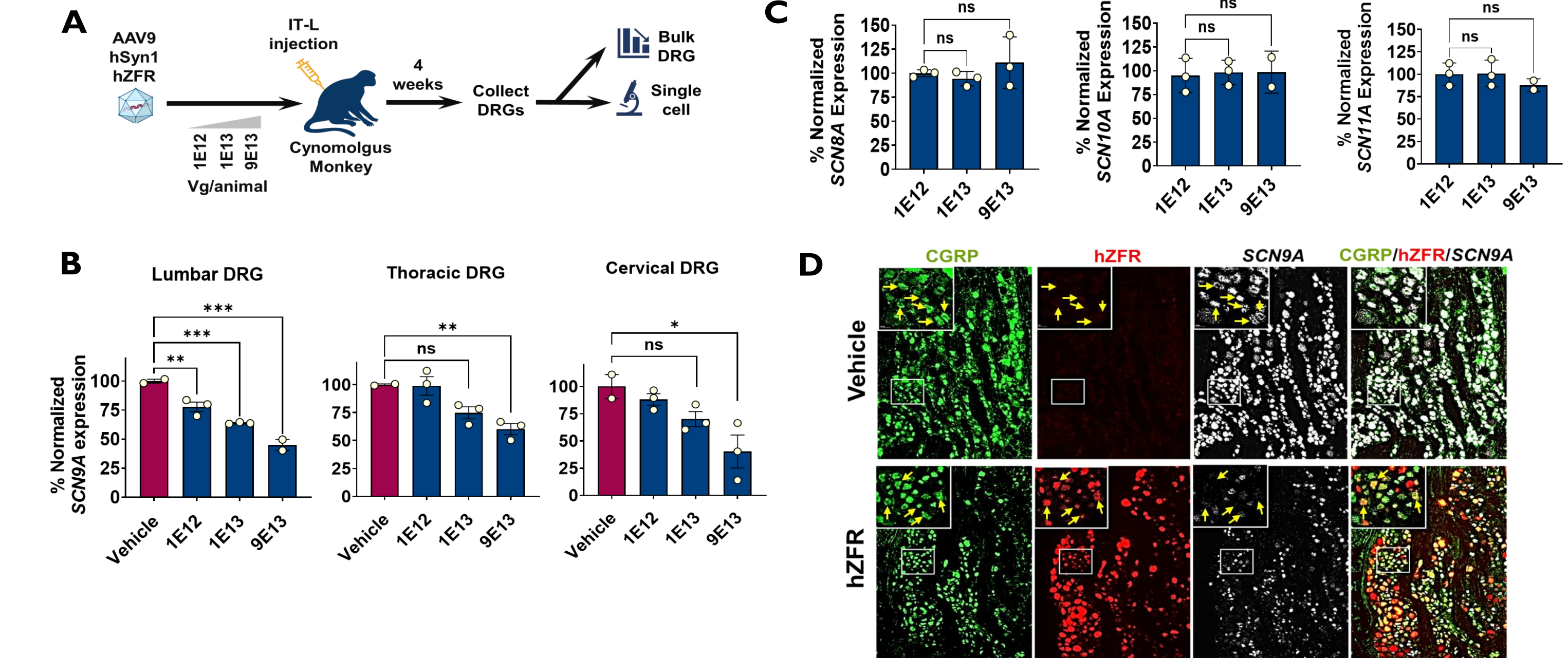
SCN9A-targeting hZFR specifically reduces human SCN9A mRNA levels and Nav1.7 function in iPSC derived neurons without repressing the expression of other Nav channels in vitro



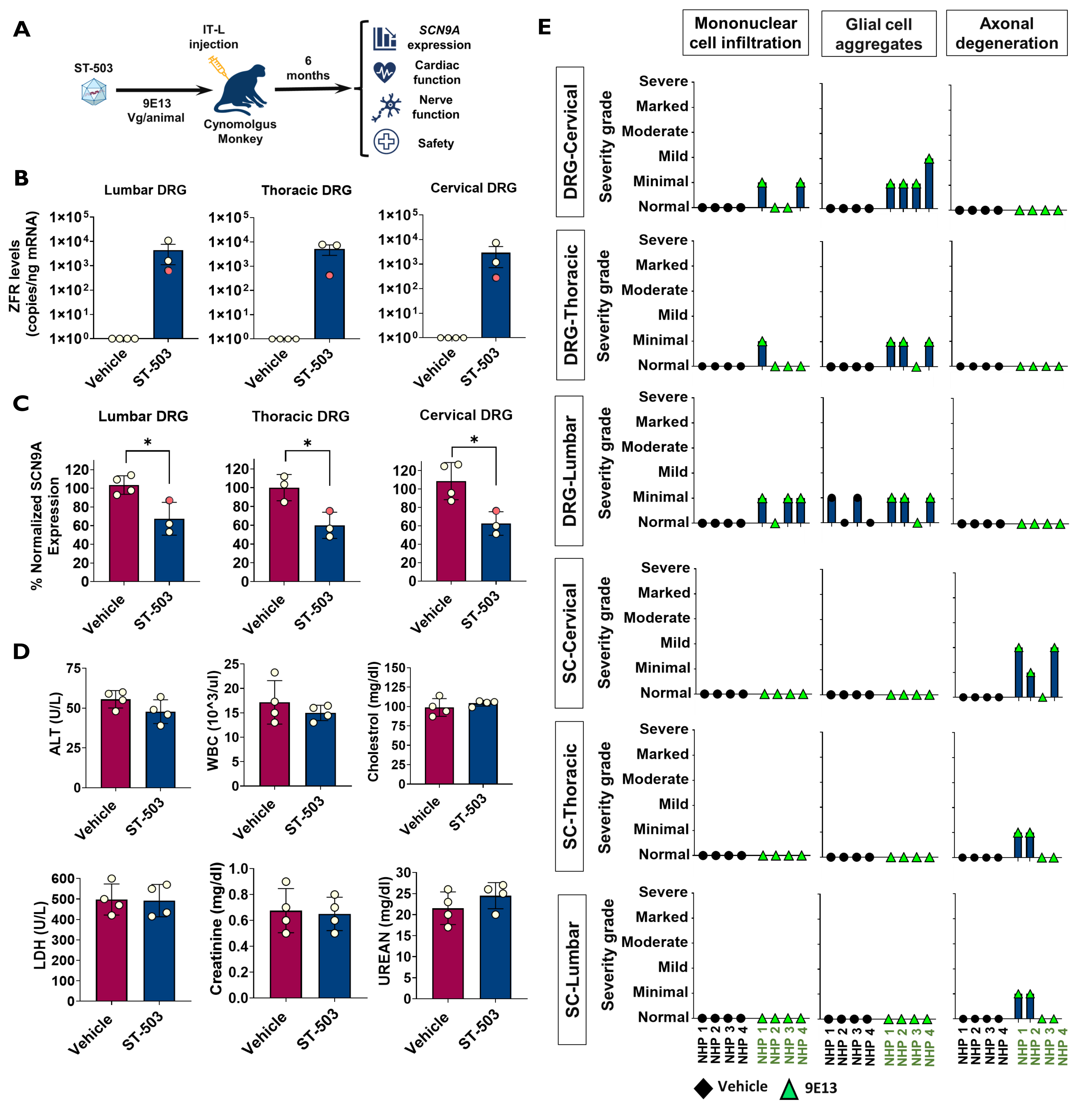
In vivo repression of mouse Scn9A reverses pain hypersensitivity in a mouse model of neuropathic pain without altering mice overall activity



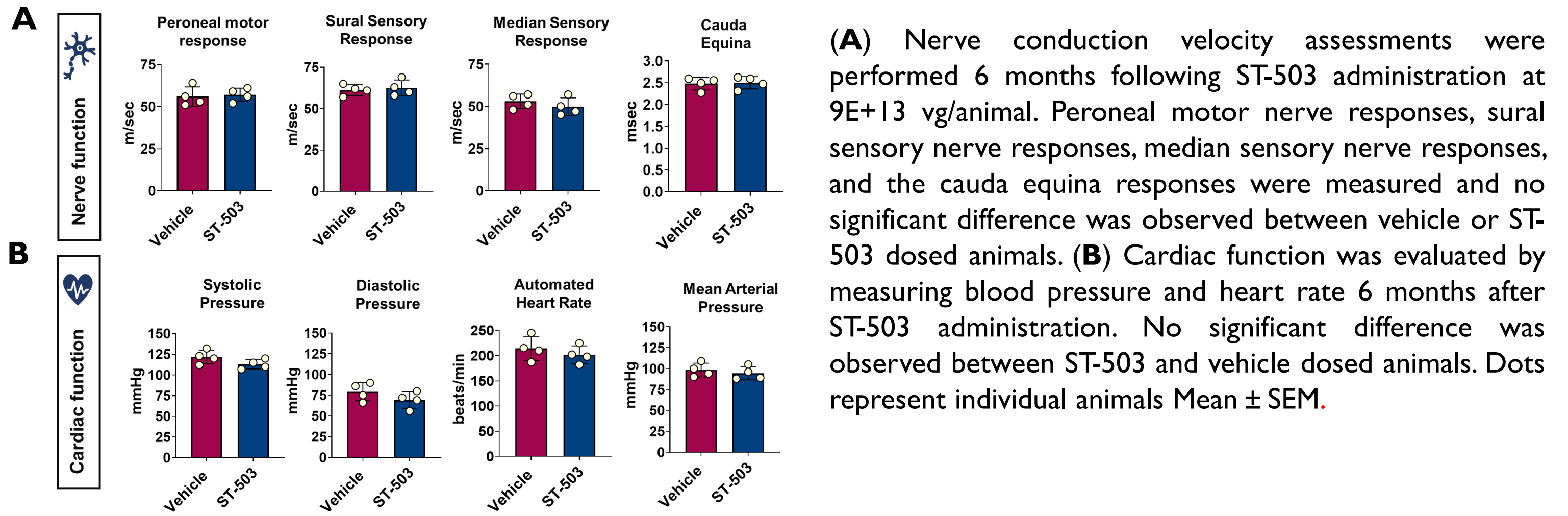
Dose-dependent repression of SCN9A in multiple DRG levels one month after IT-L administration in NHPs



ST-503 IT-L administration shows persistent and significant repression of SCN9A in DRGs 6 months following treatment, with no related clinical chemistry/hematology changes, and AAV-class related microscopic findings in DRGs and spinal cord



ST-503 does not lead to changes in nerve conduction velocity, heart rate or blood pressure at 6 months after IT-L injection in NHPs



Conclusions

The potency and selectivity of ST-503 in preclinical studies supported its development as a one-time treatment for intractable and chronic neuropathic pain

Repression of *SCN9A* gene leads to reduction in Nav1.7 protein

ZF Repressor

AAV

One-time Intrathecal injection

Dorsal root ganglia neuron

ST-503 is being evaluated in the Phase I /2 STAND study.

The first clinical site has been initiated.

Anticipating first patient dosing in the fall of 2025.

- hZFR potently and selectively repressed *SCN9A* and Nav1.7 function in human iPSC-derived neurons.
- AAV9 mediated delivery of an *Scn9a*-targeted ZFR rescued the pain hypersensitivity in mouse neuropathic pain model.
- AAV9 mediated delivery of hZFR in NHPs provided a-potent, selective, and durable repression of *SCN9A* up to 6 months in NHP DRGs.
- ST-503 investigational product was well tolerated with no dose-limiting effects.
- ST-503 did not induce changes in nerve conduction velocity, heart rate or blood pressure at 6 months after IT-L administration to NHPs.

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