NVG-291 Promotes Multiple Repair Mechanisms Following Nervous System Damage

Nana Collett1,2, Rajalakshmi Santhanakrishnan1,2, Marc A DePaul1,2,*

1NervGen Pharma Corp, Vancouver, British Columbia, Canada
2NervGen US Inc, Cincinnati, Ohio, USA

*Contact: mdepaular@nervgen.com

Introduction and Background

Nervous system damage triggers the formation of a glial scar rich in chondroitin sulfate proteoglycans (CSPGs) that inhibit neural plasticity and nervous system repair. CSPGs are also expressed in the perineural net where they restrict axonal plasticity.

Protein tyrosine phosphatase sigma (PTPσ), a receptor for CSPGs, is a key mediator of this inhibition. NVG-291-R is a peptide mimetic of the rodent PTPα intracellular wedge domain and has been shown to alleviate CSPG-driven inhibition of repair in several neural cell types. Reported effects include:

- Enhanced axonal regeneration around areas of CNS damage
- Enhanced axonal sprouting (plasticity) in areas away from CNS damage
- Enhanced oligodendrocyte precursor cell (OPC) survival, migration, maturation, and oligodendrocyte myelination
- Reduction of pro-inflammatory markers and increase in anti-inflammatory markers, and
- Enhanced neural precursor cell survival, proliferation, and differentiation into neurons and OPCs.

NVG-291 has led to improved functional recovery in several animal models of CNS damage including traumatic spinal cord injury, ischemic and hemorrhagic stroke, multiple sclerosis and models of CNS demyelination, and peripheral nerve injury. Functions that have shown improvement include motor, sensory, autonomic function, visual acuity, and cognition. Improvement in recovery of these functions would have high impact on the injured warfighter’s health and quality of life.

NVG-291 is currently in a Phase 1 trial in healthy volunteers to investigate safety, tolerability, and pharmacokinetics.

Citations:


Magnetic Resonance Imaging

(A) Schematic representation of the biotin dextran amine (BDA) injection. NVG-291-R (ISP) treatment began one day following unilateral proximal middle cerebral artery occlusion (MCAO) stroke for 4 weeks in mice. BDA axonal label was injected in the contralateral sensorimotor cortex (red) to visualize sprouting of the non-injured cortex. Blue dotted lines indicate degenerated cortical-spinal tract (CST) axons. (B-G) Representative images of the cortical-cortical sprouting from BDA labeled axons (black). (H) Quantification of the cortical-cortical sprouting (J-K) Representative images of BDA labeled corticospinal tract axons (black) to visualize axonal sprouting across the midline to denervated regions of the spinal cord (white arrow heads). (L) Quantification of length of axons crossing midline in the spinal cord as seen in J-K. Graphs show mean ± SEM. *p < 0.01; **p < 0.001 Student’s t-test.

Magnetic Resonance Imaging

(A) Representative luxol fast blue stained sections and (B) quantification of lysolecithin (LPC) lesions from the spinal cords of vehicle or NVG-291-R treated mice. ***P < 0.0001

Spinal Cord Injury

NVG-291-R Enhances 5-HT Regeneration and Sprouting Far Distal from the Lesion

(A) NVG-291-R Promotes Spreading and Plasticity of the Contralateral Sensorimotor Cortex

Ischemic Stroke

Enhanced oligodendrocyte precursor cell (OPC) survival, migration, maturation, and oligodendrocyte myelination.

Enhanced neural precursor cell survival, proliferation, and differentiation into neurons and OPCs.

Enhanced axonal regeneration around areas of CNS damage.

Enhanced axonal sprouting (plasticity) in areas away from CNS damage.

Enhanced oligodendrocyte precursor cell survival, migration, maturation, and oligodendrocyte myelination.

Reduction of pro-inflammatory markers and increase in anti-inflammatory markers, and

Enhanced neural precursor cell survival, proliferation, and differentiation into neurons and OPCs.

CNS damage

Animal models of CNS damage include traumatic spinal cord injury, ischemic and hemorrhagic stroke, multiple sclerosis and models of CNS demyelination, and peripheral nerve injury. Functions that have shown improvement include motor, sensory, autonomic function, visual acuity, and cognition. Improvement in recovery of these functions would have high impact on the injured warfighter’s health and quality of life.

NVG-291 is currently in a Phase 1 trial in healthy volunteers to investigate safety, tolerability, and pharmacokinetics.

Ischemic Stroke

Enhanced oligodendrocyte precursor cell (OPC) survival, migration, maturation, and oligodendrocyte myelination.

Enhanced neural precursor cell survival, proliferation, and differentiation into neurons and OPCs.

Enhanced axonal regeneration around areas of CNS damage.

Enhanced axonal sprouting (plasticity) in areas away from CNS damage.

Enhanced oligodendrocyte precursor cell survival, migration, maturation, and oligodendrocyte myelination.

Reduction of pro-inflammatory markers and increase in anti-inflammatory markers, and

Enhanced neural precursor cell survival, proliferation, and differentiation into neurons and OPCs.

CNS damage

Animal models of CNS damage include traumatic spinal cord injury, ischemic and hemorrhagic stroke, multiple sclerosis and models of CNS demyelination, and peripheral nerve injury. Functions that have shown improvement include motor, sensory, autonomic function, visual acuity, and cognition. Improvement in recovery of these functions would have high impact on the injured warfighter’s health and quality of life.

NVG-291 is currently in a Phase 1 trial in healthy volunteers to investigate safety, tolerability, and pharmacokinetics.

CNS damage

Animal models of CNS damage include traumatic spinal cord injury, ischemic and hemorrhagic stroke, multiple sclerosis and models of CNS demyelination, and peripheral nerve injury. Functions that have shown improvement include motor, sensory, autonomic function, visual acuity, and cognition. Improvement in recovery of these functions would have high impact on the injured warfighter’s health and quality of life.

NVG-291 is currently in a Phase 1 trial in healthy volunteers to investigate safety, tolerability, and pharmacokinetics.