NervGen Pharma

Enabling the Nervous System to Repair Itself

NVG-291 - Stroke Indication

July 28, 2022

Financial Disclosure Statement

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NervGen Introduction

NervGen (OTCQX: NGENF, TSX-V: NGEN) is developing a **revolutionary new class of "neuroreparative" drugs** that **enable the nervous system to repair itself**

NervGen's lead drug candidate, **NVG-291,** is currently in a **Phase 1 clinical trial** in healthy volunteers

Pipeline addresses **significant unmet medical needs** with initial clinical trial program to target **spinal cord injury, Alzheimer's disease and multiple sclerosis**

Improvement demonstrated across 6 different animal models in fine and gross motor control, sensory function, autonomic functions, visual acuity, memory & learning, in many cases **unprecedented**

The mechanism of action of our drug, NVG-291, targets the scar that forms due to damage to the nervous system and **enhances natural repair mechanisms** resulting in **functional improvements**

Since there are currently no approved drugs promoting nervous system repair, NVG-291 has the potential to **redefine treatment paradigms** for conditions associated with nervous system damage

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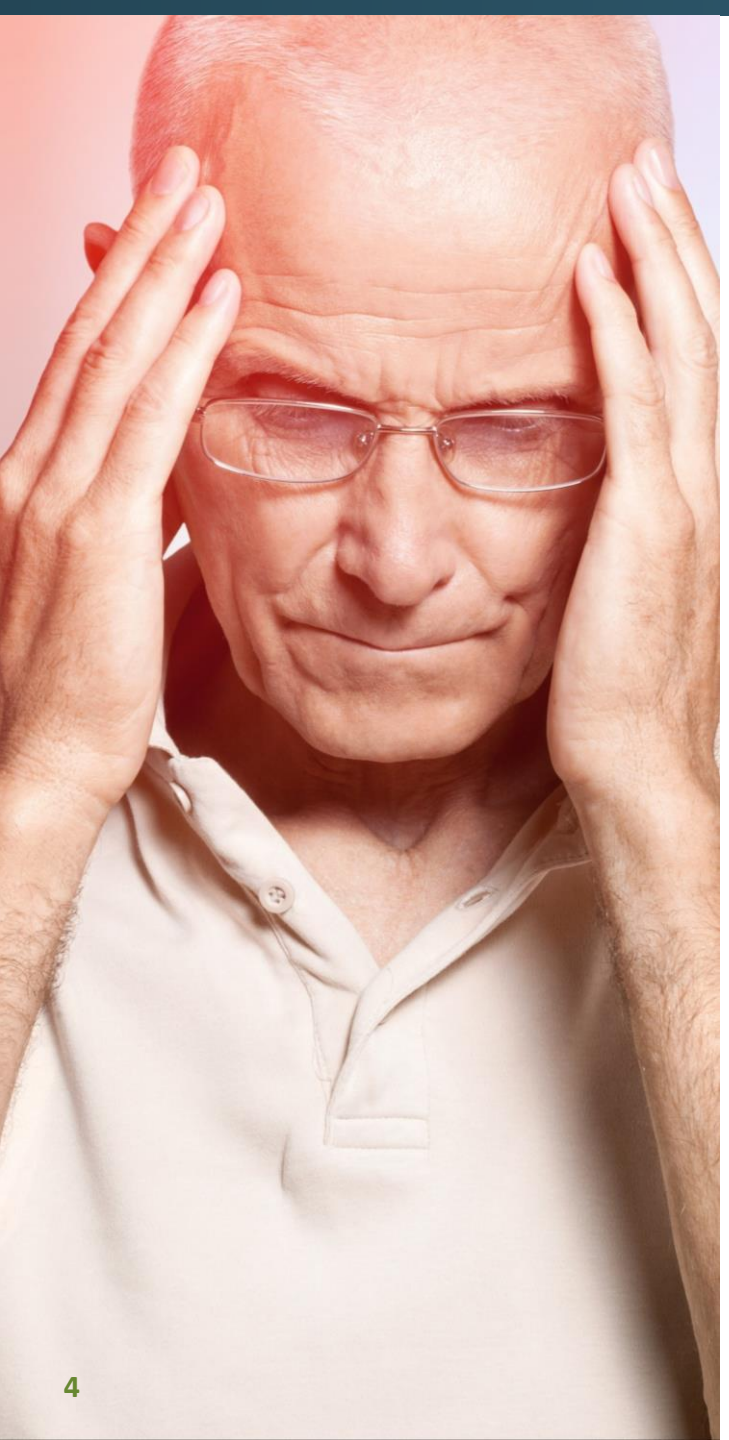

Stroke Overview

There is **No FDA-Approved Drug** that Repairs Damage Caused by Stroke

- Stroke is a disease that affects the blood vessels leading to and within the brain
- There are two types of stroke:
  - Ischemic (~87% of strokes) – caused by a clot in a blood vessel supplying the brain
  - Hemorrhagic (~13% of strokes) – caused by a rupture of a blood vessel in the brain
- Currently there is only 1 FDA-approved drug for ischemic stroke – tPA (tissue plasminogen activator)
  - tPA does not repair damage, instead it can reduce damage by breaking down clots and restoring blood flow
  - only ~5% of stroke patients are given tPA as:
    - tPA must be administered within 4.5 hours of a stroke to be effective
    - tPA can only be administered for ischemic strokes, and
    - a brain image to exclude the possibility of a hemorrhagic stroke is required
- There are no pharmaceutical treatments for hemorrhagic stroke

NervGen's goal is to **repair damage** following stroke

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Stroke Facts and Figures

Incidence and Prevalence of Stroke

In 2018, **1 in every 6 deaths** from cardiovascular disease was due to stroke[1]

Every year, more than **795,000 people in the US have a stroke**. About 610,000 of these are first or new strokes[2]

Worldwide the **annual incidence** is estimated to be **16.9 million**[3]

The Cost of Stroke

Although 80% of patients suffering from stroke return home within a month, **patients often need nursing care**, presenting a burden for both them and their family

Stroke-related costs in the US came to nearly **$46 billion** between 2014 and 2015[2]

The total costs of stroke in 2045 (in 2015 dollars) is **projected to be $81.1 billion**[1]

1. Centers for Disease Control and Prevention. Underlying Cause of Death, 1999–2018. CDC WONDER Online Database. Atlanta, GA: Centers for Disease Control and Prevention; 2018. Accessed March 12, 2020. 2. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. 2020;141(9):e139–e596. 3. Virani et al., Circulation 2020.

Cell Reports Publication on NVG-291-R and Stroke – Study Purpose & Design

Study Purpose

- This peer reviewed publication is composed of several *in vitro* and *in vivo* studies performed to **evaluate the pharmacodynamic, histological and functional effects** of administering NVG-291-R to rodents that experienced an ischemic stroke

Study Design

- Mice were given an ischemic stroke on one side of the motor-sensory cortex of the brain which resulted in motor, sensory and cognitive deficits
  - cognitive deficits assessed by the Barnes Maze Test which measures an animal's spatial learning & memory
- Animals were subcutaneously treated daily **starting either at 24 hours or 7 days after the stroke**, with either a placebo or 1 mg/kg of NVG-291-R
  - animals treated starting 24 hours after the stroke were treated for 4 weeks
  - animals treated starting 7 days after the stroke were treated for 3 weeks
- Assessments for the animal study included the following:
  - quantification of brain atrophy
  - measurement of axonal spouting
  - histology to track neuronal stem cell migration, proliferation and neurogenesis
  - neurobehavioral analysis, including locomotor function, sensory function, spatial learning and memory

Stroke Study Highlights

Treatment with NVG-291-R resulted in **significant improvement in cognitive function** when treated 24 hours - and **even 7 days** - after an ischemic stroke

Treatment with NVG-291-R resulted in a **significant increase in plasticity** - the creation of new connections between neurons

Treatment with NVG-291-R **significantly improved motor and sensory recovery**

Treatment with NVG-291-R **enhanced migration of newly created neurons derived from neuronal stem cells to the site of damage**

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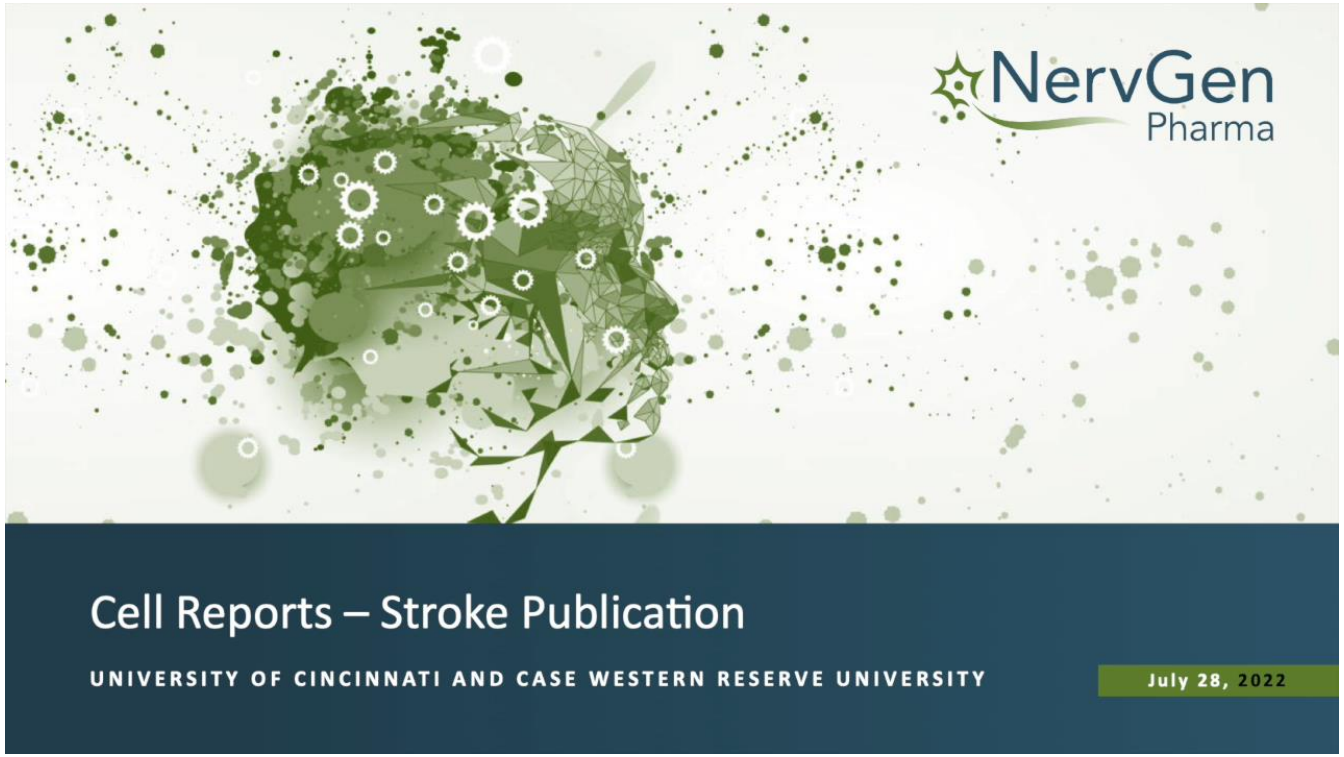
Dramatic and Unprecedented Recovery From a Stroke

STROKE MODEL

Play video



YouTube CA

Significant improvement in cognitive function
when treated 24 hours - and even *7 days* - after a stroke

Luo et al., Cell Reports Volume 40, Issue 4, 111137, July 26, 2022 (https://doi.org/10.1016/j.celrep.2022.111137)

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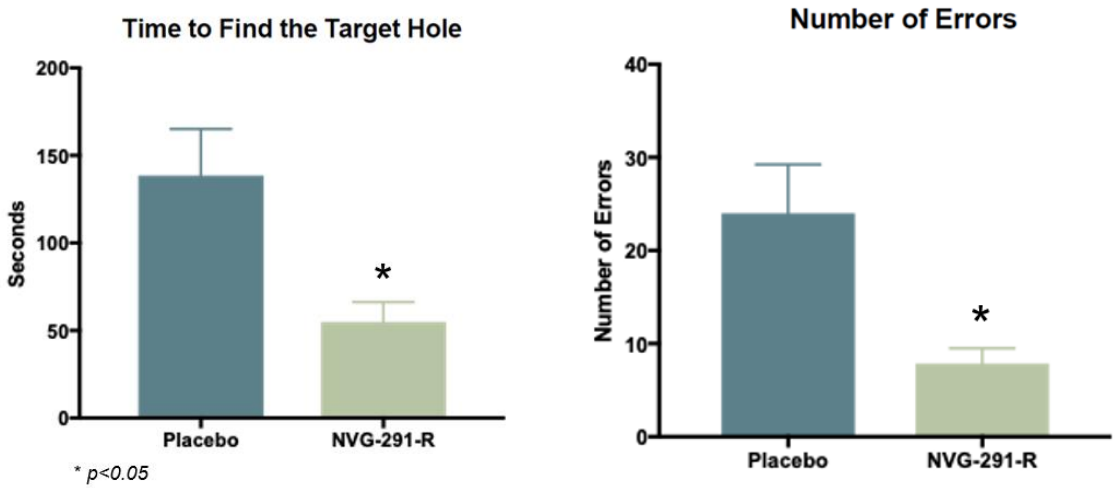
Improved Spatial Learning and Memory

Barnes Maze Test
Treatment beginning 7 days post stroke



Treatment with NVG-291-R resulted in a **faster time** to identify the target holes compared to placebo treated animals

Animals treated with NVG-291-R made **fewer errors** to identify the target holes compared to placebo treated animals

Significant improvements observed when NVG-291-R was administered 24 hours or 7 days after an ischemic stroke

Luo et al., Cell Reports Volume 40, Issue 4, 111137, July 26, 2022 (https://doi.org/10.1016/j.celrep.2022.111137)

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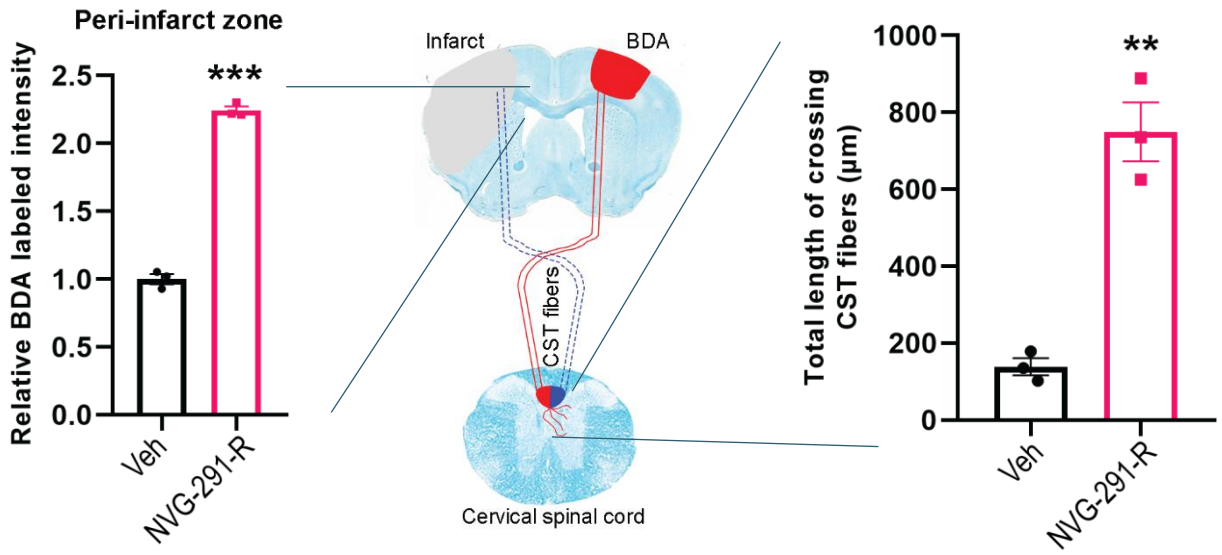
Enhances Plasticity



Once daily subcutaneous injection of either placebo or 1 mg/kg of NVG-291, starting 24 hours after the stroke for 4 weeks

Treatment with NVG-291-R resulted in a significant **increase in** plasticity**,** the creation of new connections between neurons

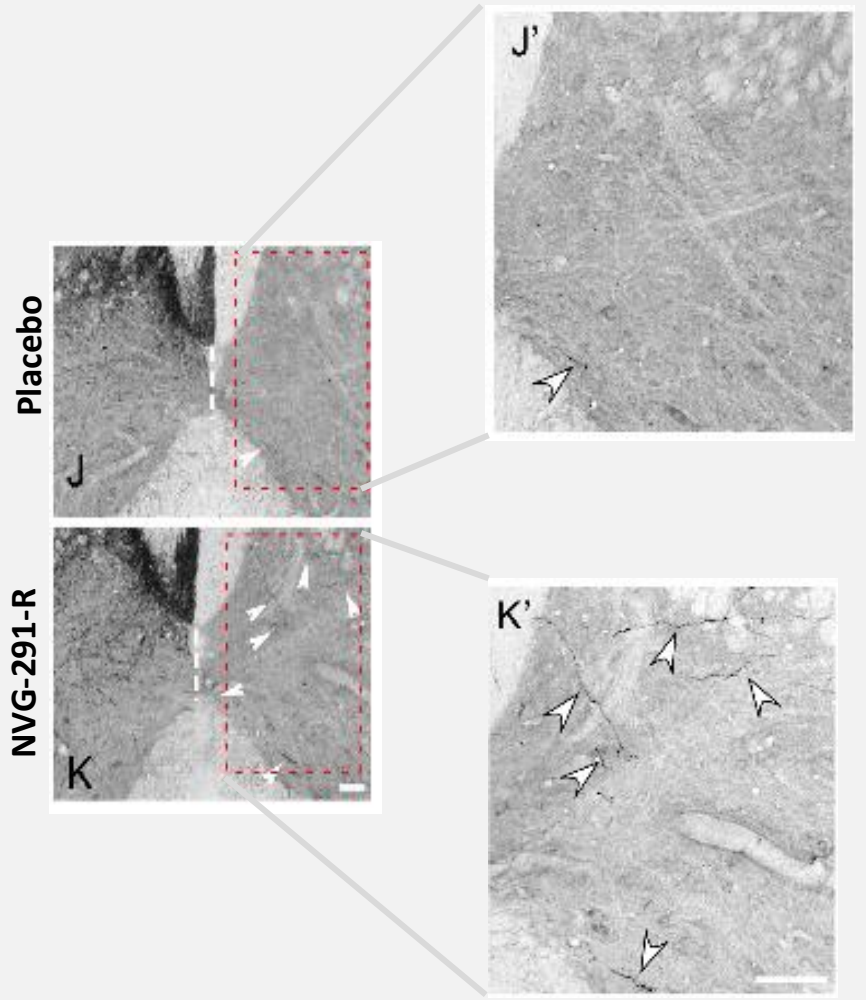
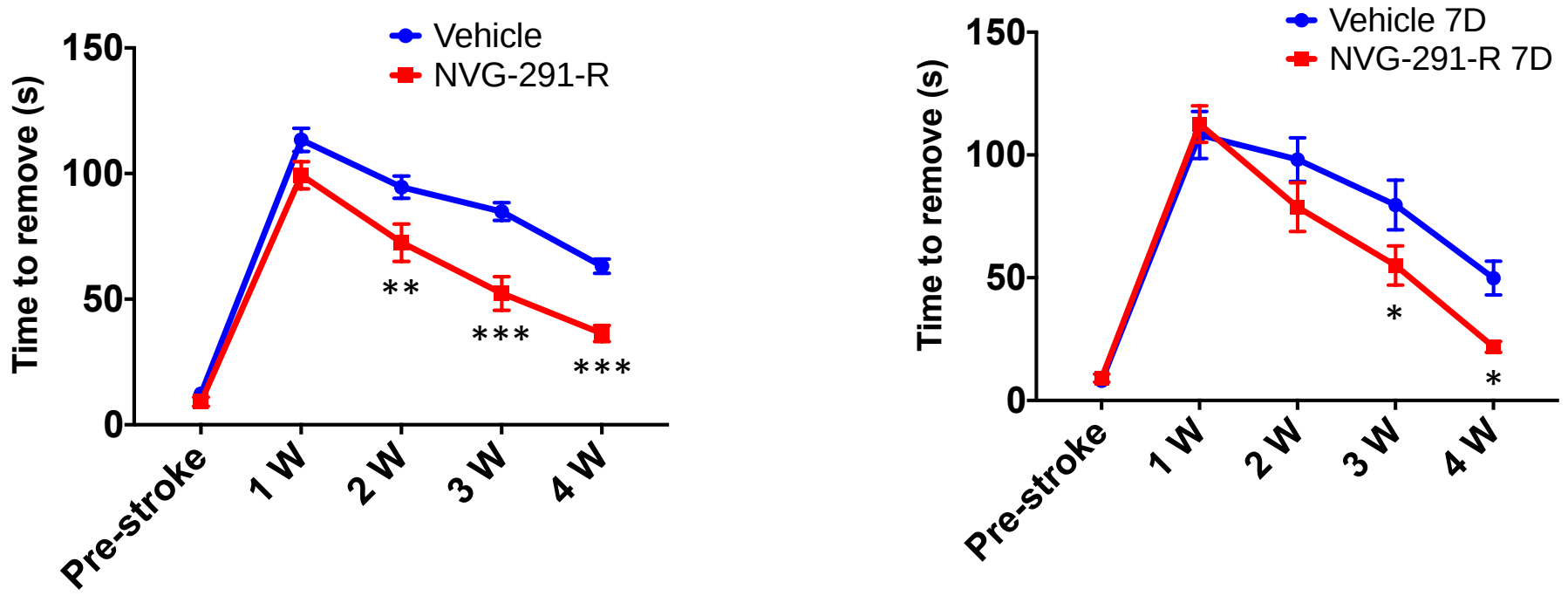


Image of axon fibers crossing the midline of the cervical spinal cord (marked with arrows). Note significantly more fibers are crossing the spinal cord in the NVG-291-R treated animals compared to placebo treated animals

Luo et al., Cell Reports Volume 40, Issue 4, 111137, July 26, 2022 (https://doi.org/10.1016/j.celrep.2022.111137)

Improved Sensory and Motor Recovery



Once daily subcutaneous injection of either placebo or 1 mg/kg of NVG-291, starting 24 hours (left graph) or 7 days (right graph) after the stroke until 4 weeks

Treatment with NVG-291-R significantly improved motor and sensory recovery measured by the time required to remove an adhesive tape from the animal's paw

Luo et al., Cell Reports Volume 40, Issue 4, 111137, July 26, 2022 (https://doi.org/10.1016/j.celrep.2022.111137)

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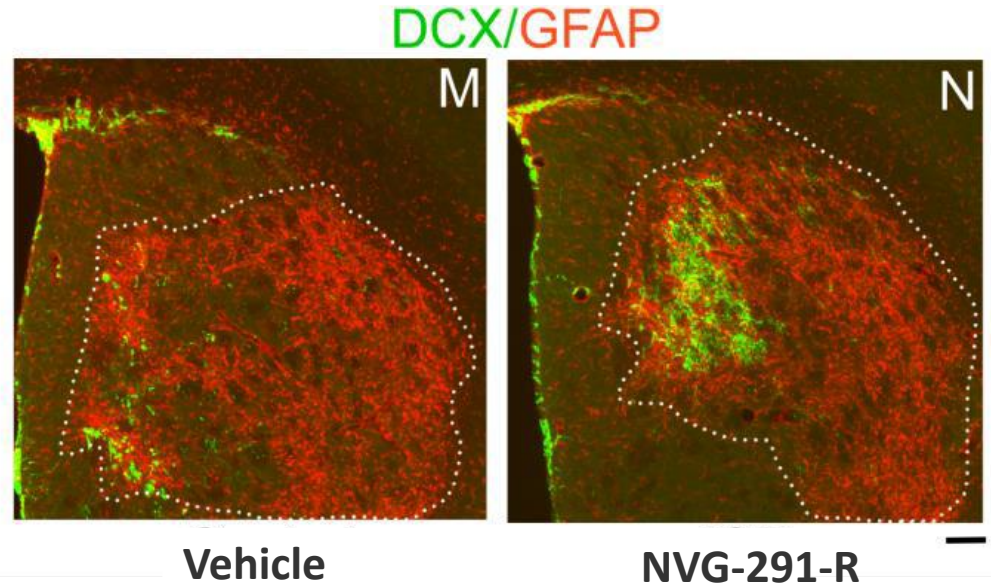
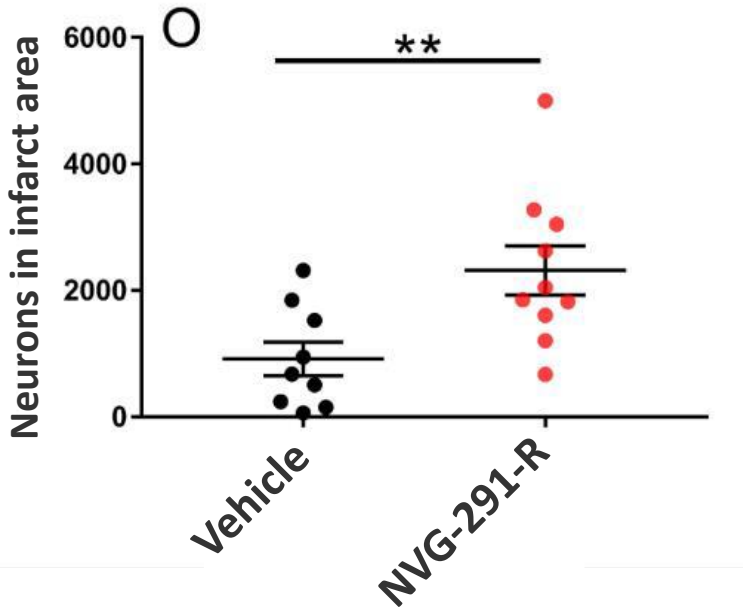
Enhanced Stem Cell Migration and Neurogenesis





Treatment with NVG-291-R promotes migration of newly created neurons derived from neuronal stem cells to the site of damage, differentiate into neurons and engraft into the lesion

Luo et al., Cell Reports Volume 40, Issue 4, 111137, July 26, 2022 (https://doi.org/10.1016/j.celrep.2022.111137)

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About NVG-291

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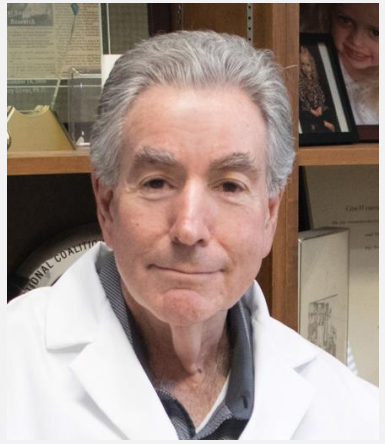
NervGen's Technology Was Invented by Dr. Jerry Silver

Known in the Spinal Cord Injury Field as the "Oracle"



Jerry Silver, PhD

Professor and Researcher,

Case Western Reserve University EST. 1826

Adjunct Professor,

Cleveland Clinic

Dr. Silver's Spinal Cord Research

- Discovered why the nervous system does not repair itself
- Identified the surprising molecules responsible

Dr. Silver Has Received Numerous Prestigious Awards Including

- Ameritec Prize
- Christopher Reeve-Joan Irvine Research Medal
- Jacob Javits Neuroscience Investigator Award

Dr. Silver's research revolutionized the understanding of the nervous system

STRONG IP PORTFOLIO

NervGen licensed the technology from Case Western and **owns global rights for all indications**

Intellectual property protection on NVG-291 until 2037

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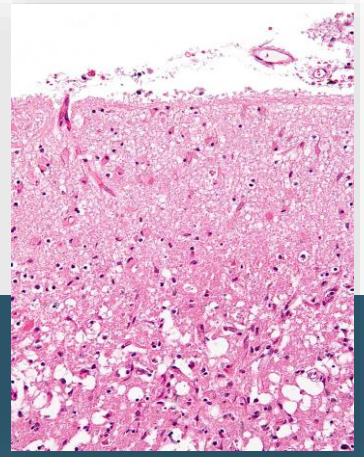
The Evolution of Our Proprietary Science

Pre 1990

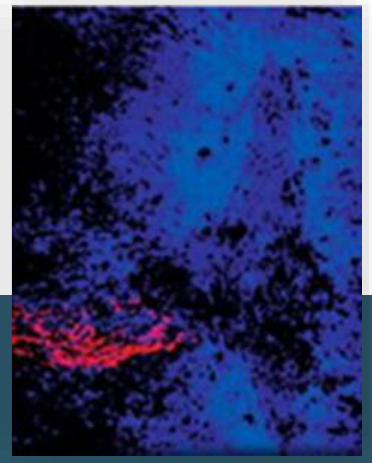
It was demonstrated that **glial scars** form at the site of injury to the nervous system and that scars in the brain cause neurons to be dysfunctional. Scars were later identified as the primary impediment of recovery



Micrograph of a glial scar

1990s

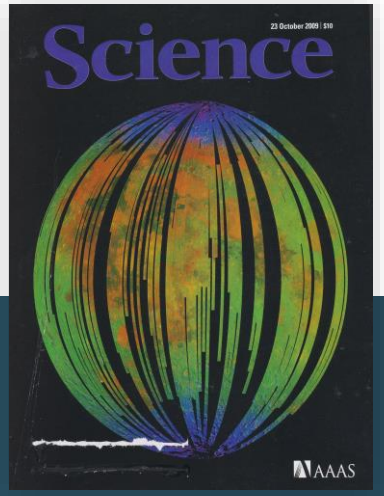
Dr. Silver identified a class of molecules called **CSPGs**, present in scars in the brain and spinal cord, that stop the body's natural repair mechanisms



Spinal cord nerve (red) trapped in the scar by CSPGs (blue)[1]

2009

Dr. Silver and collaborators from Harvard co-discovered that CSPGs bind with a receptor **(PTPσ)** present in the brain and spinal cord and that this interaction stops cells from repairing damage



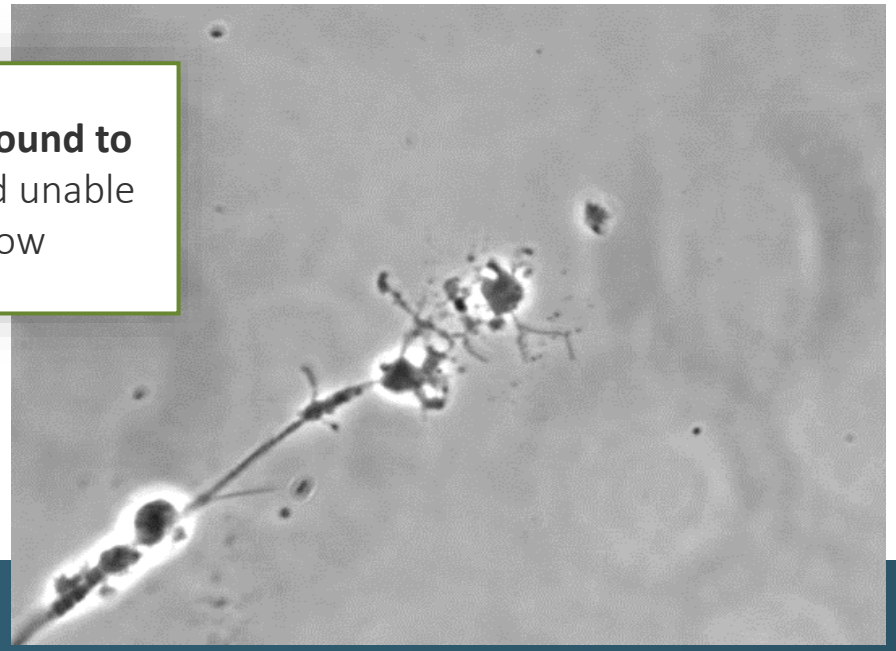
2015

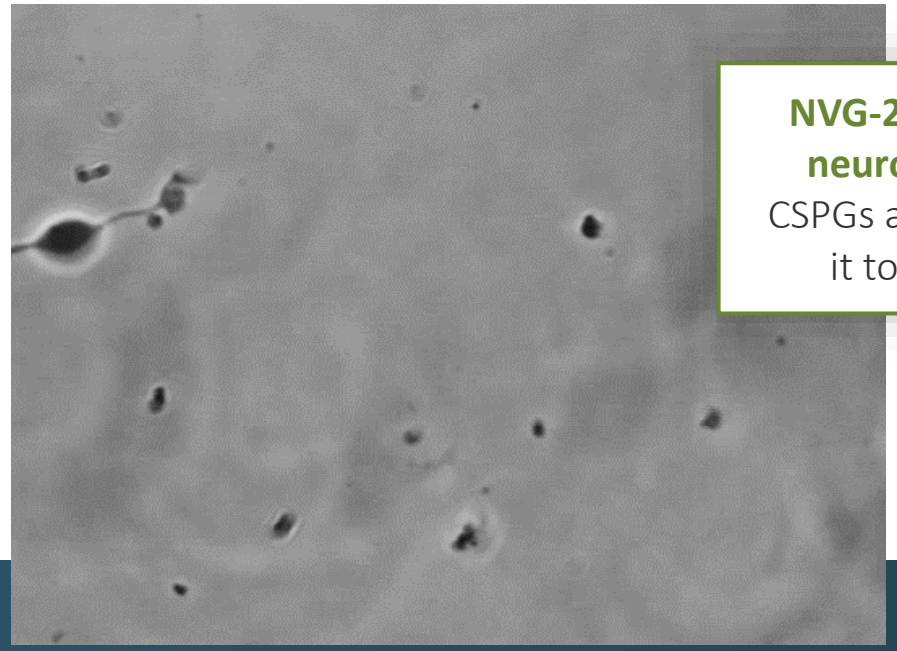
Dr. Silver's team then identified **NVG-291**, a drug that targets the interaction between CSPGs and PTPσ and allows the nervous system to repair damage

1. Shen, Y. et al. Science 326, 592–596 (2009)

NVG-291 Allows Neurons to Grow in the Scar

Neuron bound to CSPGs and unable to grow





NVG-291 frees neuron from CSPGs and allows it to grow

NVG-291, a 35 amino acid peptide, produced dramatic recovery in a spinal cord injury animal study:
the results published in Nature[1] are now cited in over 327 publications

Administered systemically by a
daily subcutaneous injection

Includes a transporter that
facilitates crossing the blood brain barrier

1. Lang, B. T. et al., Nature 2015 Feb 19;518(7539):404-8

YouTube CA

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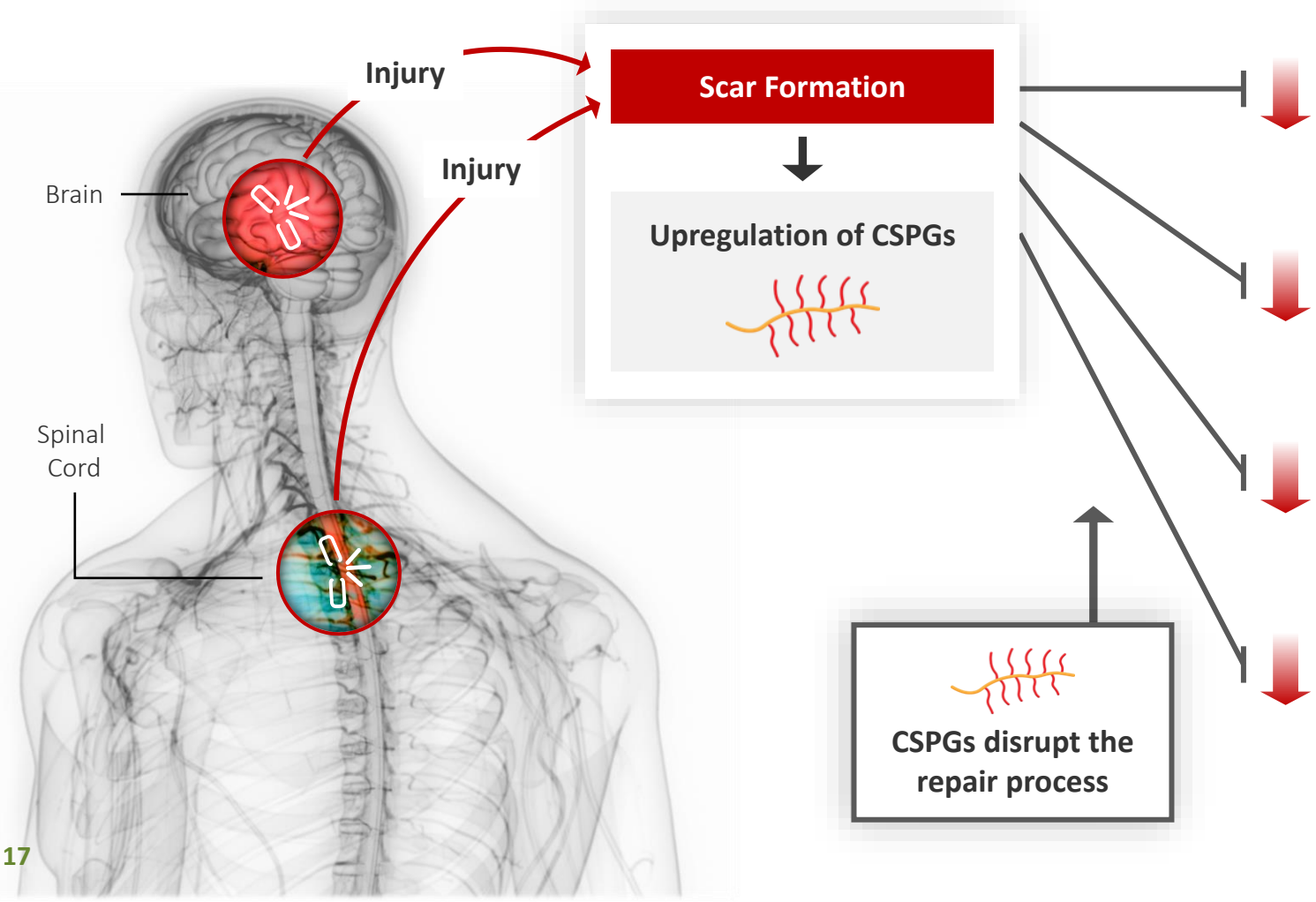
The Body's Powerful
Innate Repair Mechanisms
Disrupted by CSPGs



Repair Mechanisms:

Plasticity
The creation of new neuronal connections and rewiring of existing ones

Axonal Regeneration
The ability of a severed axon to reestablish connectivity with other neurons

Remyelination
The process of repairing damaged myelin – the fatty substance that protects axons and enables fast electrochemical transmission

Others
Stem cell preservation/migration
Autophagy
Microglial shifting

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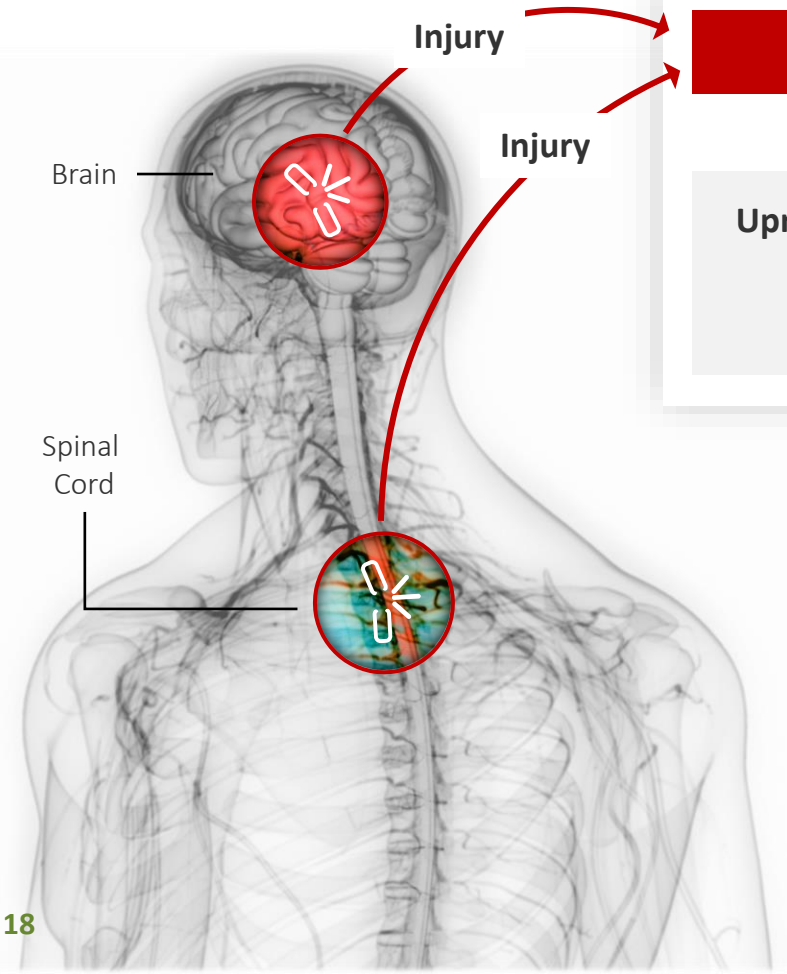
Takes the Brakes off Natural Repair Mechanisms



Scar Formation

Upregulation of CSPGs

NVG-291
Enables the nervous system to repair itself

Repair Mechanisms:

Plasticity

The creation of new neuronal connections and rewiring of existing ones

Axonal Regeneration

The ability of a severed axon to reestablish connectivity with other neurons

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Others

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More about Stroke

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Stroke – Long Term Complications

- The impact of a stroke can range from transient to devastating to fatal, depending on the location, size, and duration of the infarct
- A stroke with widespread impact can leave an individual in a vegetative state, while focal strokes leave damage that varies by location

Complications from stroke may include[1]:

- Paralysis or loss of muscle movement. You may become paralyzed on one side of your body, or lose control of certain muscles, such as those on one side of your face or one arm.
- Difficulty talking or swallowing. A stroke might affect control of the muscles in your mouth and throat, making it difficult for you to talk clearly, swallow or eat. You also may have difficulty with language, including speaking or understanding speech, reading, or writing.
- Memory loss or thinking difficulties. Many people who have had strokes experience some memory loss. Others may have difficulty thinking, reasoning, making judgments and understanding concepts.
- Emotional problems. People who have had strokes may have more difficulty controlling their emotions, or they may develop depression.
- Pain, numbness or other unusual sensations may occur in the parts of the body affected by stroke. For example, if a stroke causes you to lose feeling in your left arm, you may develop an uncomfortable tingling sensation in that arm.
- Changes in behavior and self-care ability. People who have had strokes may become more withdrawn. They may need help with grooming and daily chores.

[1] Mayo Clinic Website – August 2021

Stroke – Acute Treatments

Therapy for stroke can be divided into two components:

- **Acute** - where the goal is to limit the damage, and to rescue the penumbra
  - The penumbra is the brain tissue surrounding the center of the stroke, and vulnerable to permanent damage if the infarct evolves
- **Chronic** - where the goal is to regain function, predominately through physiotherapy, and to prevent a recurring stroke

In the acute setting, the therapy that should be applied depends on the type of stroke that has occurred (i.e., ischemic vs hemorrhagic). Thus, the first course of action in treating a stroke patient is to perform a CT scan, or MRI, to determine the type of stroke.

Acute Therapy for Ischemic Stroke

- In eligible patients
  - Thrombolytic (clot busting) and clot-preventing pharmaceuticals such as t-PA, aspirin, warfarin, heparin or clopidogrel*
  - Endovascular thrombectomy to remove clots

Acute Therapy for Hemorrhagic Stroke

- Endovascular procedures (ex. coils, stents) to repair damage
- Surgical treatment to prevent bleeding and relive pressure build-up

*t-PA is the only FDA approve treatment approved for stroke

Issues with Thrombolytic (Clot Busting) Drugs for Ischemic Stroke

Tissue plasminogen activate (t-PA), aspirin, warfarin, heparin or clopidogrel, also known as "clot busters" are used in the case of ischemic stroke

- t-PA is the only FDA approved treatment for stroke

To be effective, **t-PA must be used within 3 - 4.5 hours of the onset of a stroke**

- FDA labelling states t-PA must be used within 3 hours; however, benefit has been demonstrated to be beneficial in a select group patients up to 4.5 hours post onset[1]

There are several contraindications to using t-PA and other thrombolytics, including using t-PA in patients with hemorrhagic stroke

- The thrombolytic effects of t-PA can make a hemorrhagic stroke worse, and can be lethal
- As a result, patients must have a CT scan or MRI prior to treatment with t-PA

Given (i) the very narrow treatment time, (ii) the contraindication in hemorrhagic stroke, and (iii) the requirement for a patient to have a brain scan prior to treatment, very few patients are eligible to receive t-PA within the 3 - 4.5-hour time window

- **Less than 10% of all stroke patients receive t-PA2**

[1] American Stroke Association (ASA) 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke)
[2] Messe et al., Neurology 2016

Stroke – Impact on Society

Stroke is third only to Alzheimer's and Parkinson's in its scale as a neurodegenerative disease

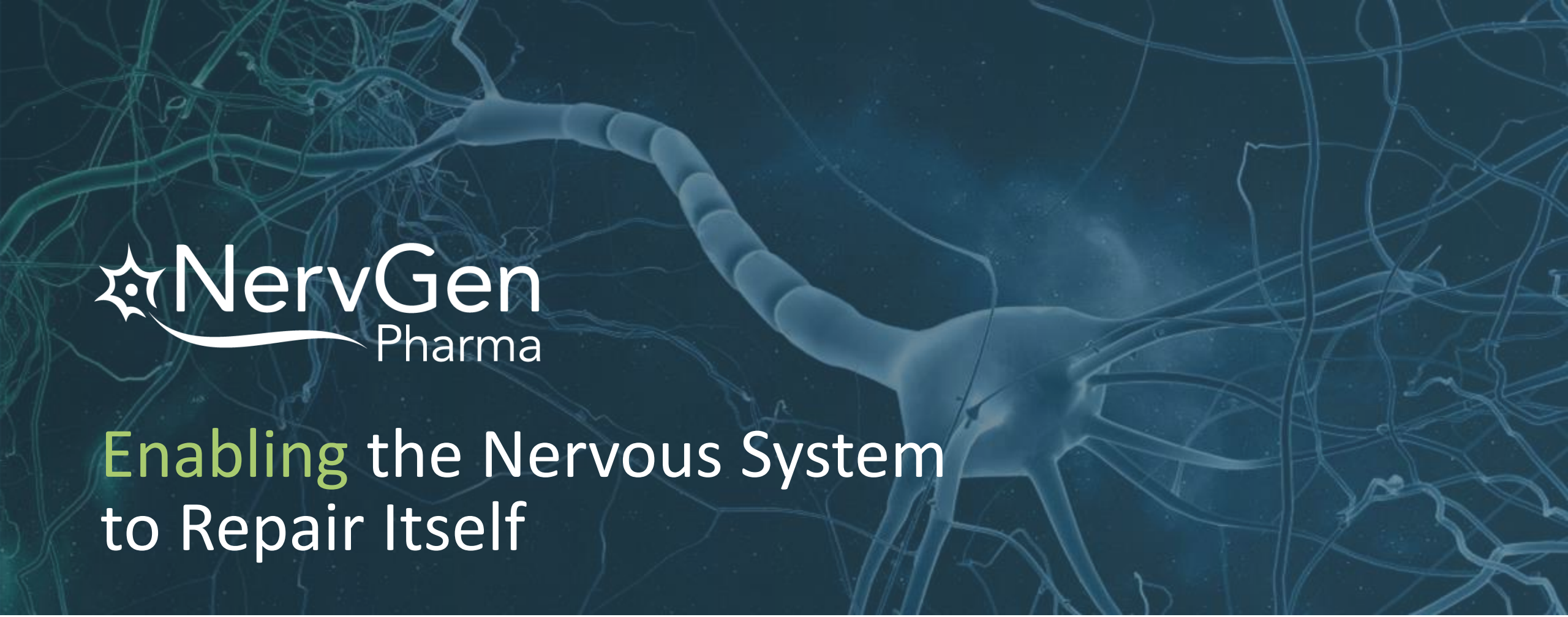
- Estimate of the annual incidence in the US is 800,000 (600,000 new patients, and 200,000 with repeat strokes)[1]
- Worldwide the annual incidence is estimated to be 16.9 million[1]

20% of individuals suffering a stroke die within a week, while another 13% die within a year

Although 80% of patients suffering from stroke return home within a month, **patients often need nursing care,** presenting a burden for both them and their family

- The economic burden of Stroke in the US in 2015 was is estimated by the CDC to be $34 billion[1]
- The total cost of stroke in 2035 (in 2015 dollars) is projected to be $81.1 billion[1]

1 Virani et al., Circulation 2020



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