ENCODE IDEAS

INITIATION REPORT

Encode Ideas

NervGen Pharma Corp. (OTC: NGENF, TSX-V: NGEN)

September 13, 2021

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FINANCIAL SUMMARY TABLE

Symbol	NGENF NGEN
Exchange	OTC TSX-V
Current Price	$1.65 USD $2.10 CAD
52 week Range	$0.90 - $2.43 $1.21 - $2.65
O/S	40.66mm*
Market Cap est	$67mm USD* $85mm CAD*
Average Volume (3M)	~40k
Cash (CAD)	~$9.699mm*
Debt	$0mm*

*pro forma estimate; 6/30/21 financials plus subsequent 8/4/21 raise of $2.34mm.

KEY CATALYST DATES

4Q 2021	Ph1 SAD Safety Data Release
4Q 2021	Alzheimer's Preclincial Data Release
1Q 2022	Full FDA IND Clearance
Mid 2022	Alzheimer's Ph1b Study Initiation

KEY DISCLOSURES

Encode Ideas, L.P. owns stock in the covered company. Encode Ideas, L.P. has been engaged by Nervgen to provide research coverage and awareness. Encode Ideas, L.P. intends to continue transacting in the securities covered therein, and we may be long, short, or neutral thereafter.

Nervgen is not an investment for the faint of heart, but for those investors who like to bet on trailblazing biotech companies with truly novel, disease-modifying, science, and moonshot potential, then Nervgen at a ~$70mm market cap should have plenty of appeal.

Encode Ideas is initiating coverage on NervGen Pharma Corp. (OTC: NGENF, TSX-V: NGEN) as a high conviction investment idea. Nervgen was founded off the work of Dr. Jerry Silver, a Professor of Neurosciences at Case Western Reserve University's School of Medicine (CWRUSM), whose research on glial scars and spinal cord injury (SCI) led to the discovery of chondroitin sulfate proteoglycans (CSPGs) as key inhibitory molecules obstructing nerve repair and regeneration in the central nervous system (CNS). CSPGs inhibition of nerve repair has profound implications not only for the treatment of physical insults to the CNS, such as SCI and traumatic brain injury (TBI) but also in neurodegenerative diseases, such as Alzheimer's Disease (AD) and Multiple Sclerosis (MS). For many years Dr. Silver struggled to get attention for his work on CSPGs, with medical research preferring to focus on other avenues for treating scars and plaques in the CNS, but a 2015 paper in Nature that demonstrated the druggability of CSPGs via a novel signaling molecule, protein tyrosine phosphatase sigma (PTPσ), suddenly brought his research to the forefront. Today CSPGs inhibitory impact on nerve repair in the CNS is widely accepted, and PTPσ is considered the most promising target to attenuate the impact of CSPGs. Nervgen, through its license with CWRUSM and collaboration with Dr. Silver, has the only drug in development, NVG-291, targeting PTPσ. Nervgen and Dr. Silver have generated a plethora of preclinical data across various models, demonstrating NVG-291's ability to attenuate CSPGs, thereby promoting nerve repair and growth. As stated above, the implications for a drug that mediates the impact of CSPGs are profound, ranging from orphan indications, like SCI, to blockbuster indications, like AD. Currently, the company is testing NVG-291 in a first-in-human Ph1 safety study, and from there will pivot into a Ph1b AD study mid-22. We believe the first-in-human safety data will be a symbolically important milestone for Nervgen, paving the path for an expansion into AD, an indication that has high investor appeal.

Novel Disruptive Science, Platform Potential Across Orphan Indication(s) & Neurodegenerative Indication(s) = ~$70mm Valuation?

Biotech companies working on novel disruptive science for orphan diseases (SCI) or large neurodegenerative indications (AD), like Nervgen, often earn lofty valuations based on provocative preclinical data alone. So why is Nervgen valued at a diminutive ~$70mm cap?

1. Dr. Silver and Nervgen's early focus for NVG-291 was SCI. One would think SCI, an orphan indication with no approved drugs, would have high investor appeal, but it doesn't. SCI has seen many clinical failures, hurting investors and leaving many hesitant to make additional bets on the indication. Although SCI lacks investor appeal, there is a strong mechanistic rationale for Nervgen to pursue this indication, and the company still intends to test NVG-291 in Ph2 for SCI later in 2022. However, Nervgen's first efficacy study will be in AD, ironically another indication with plenty of failures. However, AD, unlike SCI, has probably never had higher investor appeal, due largely to FDA's controversial recent approval of Biogen's (Nasdaq: BIIB) aducanumab. We believe Nervgen's valuation is still attached to the less appealing SCI indication and not to the more imminent and appealing opportunity in AD, where the company could have efficacy (biomarker) data by YE22.
2. NVG-291's path into human studies has been slower and bumpier than planned. Nervgen expected to have an Investigational New Drug (IND) for NVG-291 in 2020, but FDA placed it under a clinical hold pending further preclinical data. Nervgen submitted additional data to FDA in 2021 and NVG-291's IND was changed to a partial hold, allowing the drug to enter Ph1 studies in females only. Nervgen believes it will have the necessary preclinical data (reproductive toxicity data we assume) to remove the partial clinical hold by early-22 and allow NVG-291 to be tested in both genders. In the meantime, the company has started a Ph1 safety study in women. We believe the delays in getting full clearance for the IND have frustrated legacy investors and deterred some new ones, and once solved will remove a notable overhang on the stock.
3. Nervgen went public in Canada, and like many Canadian-listed peers, is tenuously financed. Canada is not the wasteland of hyper-diluted biotechs it once was, but accessing capital as an early-stage Canadian/OTC listed company, remains a challenge. Nervgen has recently completed a series of financings to bridge it through Ph1, but a larger capital injection is still needed within the next 6-9 months. We expect the company will be able to raise meaningful capital and list on Nasdaq in 2022 once it has an unencumbered IND and safety data in hand.

In our opinion, the above issues are already priced into Nervgen's modest market cap. Once these issues are addressed; Nervgen gets recognized for its programs outside of SCI most notably AD, FDA lifts the partial clinical hold, and the company is properly financed and listed on Nasdaq, all of which we expect over the next 12-months, the stock should rerate higher. There is no denying, Nervgen is not an investment for the faint of heart, but for those investors who like to bet on trailblazing biotech companies with truly novel, disease-modifying, science, and moonshot potential, then Nervgen at a ~$70mm market cap should have plenty of appeal.

Targeting CSPGs - Conceptually Groundbreaking, Preclinically Provocative, Clinically Unproven

Modulating CSPGs has groundbreaking medical potential. CSPGs are widely believed to be the predominant inhibitory molecules within a glial scar, and the associated extracellular matrix, known as the perineuronal net (PNN), that prevent nerve repair and regeneration. Targeting CSPGs pharmacologically, in essence inhibiting the inhibitor, offers the potential for nerve regeneration, nerve remyelination, and improved neuroplasticity. A drug capable of inhibiting CSPGs could have profound implications throughout the CNS, including the treatment of spinal cord injury (SCI), traumatic brain injury (TBI), stroke, Alzheimer's Disease (AD), Multiple Sclerosis (MS), and Parkinson's Disease (PD).

The scientific merit for targeting CSPGs has been proven through numerous preclinical experiments with chondroitinase ABC (ChABC), a bacterial enzyme that digests CSPGs. In preclinical SCI models, Dr. Silver was the first to show that treatment with ChABC dramatically reduced CSPGs at or around a glial scar and PNN, leading to functional recovery in animals. Treatment with ChABC has yielded positive results across several disease models, including SCI, AD, and MS, and across several species from rodents to non-human primates. As effective as ChABC has proven to be in animals, it is not a suitable drug candidate for humans due to the size of the molecule, short half-life, and toxicity profile. Nonetheless, ChABC provides exquisite validation that inhibiting CSPGs has real disease-modifying potential in the CNS.

Dr. Silver's discovery of PTPσ as the main receptor regulating CSPGs opened the possibility of a more viable mechanism than ChABC for inhibiting CSPGs. In a 2015 Nature paper, "Modulation of the proteoglycan receptor PTPσ promotes recovery after spinal cord injury", Dr. Silver elucidated how a novel peptide (now called NVG-291) developed in his lab was able to restore a substantial amount of functional recovery, both locomotor and urinary, in rodents with spinal cord injury. After the Nature paper, additional preclinical experiments and publications performed by Dr. Silver and Nervgen have demonstrated that PTPσ inhibition with NVG-291 has shown functional improvements in MS and stroke models among others. The depth and quality of preclinical data demonstrating that targeting CSPGs, whether with ChABC and NVG-291, has enormous potential across multiple CNS indications, is undeniable. Translating these undeniably positive preclinical data into human data is the task that is squarely in front of Nervgen now.

NVG-291 - Limps Into The Clinic But Could be Running Soon

NVG-291, Nergen's first-in-class PTPσ antagonist, is a peptide that is being dosed via daily subcutaneous injection. Nervgen has an open Investigational New Drug (IND) with FDA for NVG-291 under a partial clinical hold. The hold allows Nervgen to proceed into Ph1 with female subjects but requires additional preclinical data before including male subjects or premenopausal women in the multi-ascending dose (MAD) portion of the study. Nervgen is currently running the necessary reproductive toxicity preclinical studies to remove the FDA

partial hold and expects to have an unencumbered IND in early-22. In the meantime, the company is proceeding with the Ph1 study in Australia, enrolling healthy female volunteers in the single ascending dose (SAD) portion of the study and healthy postmenopausal women in the MAD portion. We are optimistic Nervgen should have data from the SAD portion of the Ph1 study late-21 and full data in 1H22. We also expect that once the FDA partial hold is removed, our estimate being early-22, that Nervgen will complete a bridging safety study with men and premenopausal women, allowing both genders to be included in subsequent efficacy studies scheduled to start mid-22.

In our discussions with Nervgen management, they have expressed a high level of confidence that they will be successful in addressing FDA's questions around reproductive toxicity, and have an unencumbered IND within the next 6-months. It is clear FDA's partial hold has weighed heavily on Nervgen equity and hurt their ability to raise meaningful institutional money. We believe the partial hold is fully priced into Nervgen's stock today, and a combination of early safety data from the SAD portion of the Ph1 study (budgeting for late-21) followed by removal of the FDA partial hold (budgeting for early-22) will have a positive impact on the stock and importantly allow for smart institutional money to participate in a validating financing.

Redefining Nervgen as an Alzheimer's Company

As we discussed, the narrative around CSPGs, PTPσ, and Dr. Silver has been heavily defined by the data derived in SCI. Although SCI will remain a key piece of Nervgen's clinical plans in 2022, we expect the majority of news from Nervgen over the near term to be pertaining to NVG-291's potential in neurodegenerative diseases, in particular AD. There is increasing evidence that CSPGs increase with age and are associated with AD. Since CSPGs bind and signal predominantly through PTPσ, it is thought that NVG-291 may be a potential treatment for AD. Supportive evidence for this hypothesis has been seen in preclinical studies with ChABC and knock-out models of PTPσ. Nervgen recently announced a collaboration with Dr. Ksenia Kastanenka at Harvard to perform preclinical testing of NVG-291 in validated animal models of AD. We don't want to put too much emphasis on further preclinical validation around NVG-291, but a steady stream of preclinical data in AD should be incrementally helpful in emphasizing Nervgen's increased focus on AD in advance of human data.

Nervgen, once it has completed all the requisite human safety work for NVG-291, will initiate its first efficacy study in AD patients. Although Nervgen has not guided to the design of its AD study, we assume they will follow the playbook that has proven to work for other AD-focused companies in their early studies; small sample size, open-label, with safety, pharmacokinetics (PK), and a plethora of AD-related biomarkers as endpoints. Biomarker data from these early-stage AD studies, although questionable in its clinical relevance, has proven to be jet fuel for valuations for AD companies. The case studies Ph1b / 2a biomarker-driven value creation for AD-focused companies are plentiful, including recent examples of Cassava Sciences (Nasdaq: SAVA) and Inmune Bio (Nasdaq: INMB). Both Cassava and Inmune added >$100mm in value off biomarker data from early-stage AD studies; Cassava in late-2019 from a 13-patient

Ph2a study and Inmune from a 6-patient Ph1b study in summer-2020. We expect Nervgen to be in a position to start a Ph1b AD study mid-22 and have preliminary data, including biomarker endpoints, by YE22.

Over the next 15-18 months Nervgen's AD program should rise in prominence with a steady cadence of preclinical data, Ph1b initiation, and preliminary human safety, PK, and biomarker data. As we have highlighted, there is significant investor appetite for AD companies, regardless of the stage of development. We believe, based on its foreseeable AD newsflow, that the company should receive increased investor recognition and value as this program progresses.

Additional Efficacy Studies

Later in 2022 Nervgen plans to initiate two additional efficacy studies with NVG-291, one in MS the other SCI. As we have discussed, Nervgen has robust preclinical SCI data for NVG-291 demonstrating the drug's ability to restore function, both locomotor and urinary, across a variety of SCI models. SCI is recognized as an orphan disease by FDA and the European Medicines Agency (EMA) and there are currently no approved therapies that promote nerve repair and regeneration. Nervgen has received orphan designation for NVG-291 from EMA and we would anticipate that it will receive the same from FDA. Nervgen has yet to outline its plans for a Ph2 SCI study, but we would anticipate a small single-arm proof-of-concept (PoC) study that could generate signs of NVG-291 activity as early as late-22 / early-23. Again, we recognize that there is currently limited investor appeal for SCI, but given the therapeutic void that exists for SCI, any hint of efficacy from a PoC study could allow Nervgen to rapidly advance NVG-291 in this orphan indication.

MS is second only to SCI in regards to the depth of preclinical testing and validation that has occurred for the CSPG/ PTPσ / NVG-291 approach. NVG-291's mechanism of action appears to promote remyelination, the restoration of the myelin sheath on nerves, which is considered by many as a key to slowing MS progression. Nervgen has guided they plan to start a Ph2 MS study with NVG-291 2H21 and we would anticipate top-line data sometime in 2023.

Non-dilutive Skunkworks

Nervgen's overt clinical focus is squarely on AD, MS, and SCI. However, there appears to be a growing, albeit understated, push to collaborate with government organizations like the U.S. Department of Defence (DoD), Biomedical Advanced Research and Development Authority (BARDA), and National Institutes of Health (NIH) for research projects in non-core indications such as traumatic brain injury (TBI) and stroke. In 2020 Nervgen entered into a consulting agreement with the former Director of the U.S. combat casualty care research program, Dr. Michael Davis, to help identify, prioritize and secure sources of non-dilutive financing. We have limited visibility on the timing of potential government research collaborations but wouldn't be surprised to see one or two announcements over the next 6-12 months.

Financial Considerations & Leadership

Nervgen has historically been financed through high-net-worth retail investors. The company has raised CA$7.25mm in 2021. We estimate the company's cash balance can support operations into 1H22, as such we expect another small financing before YE21 to extend their cash runway through to YE22. In the meantime, we expect the company to have resolved the FDA partial clinical hold, completed the Ph1 safety study, and be ready to initiate the Ph1b in AD, all of which should position Nervgen for an institutional financing and Nasdaq-listing in 1H22.

As we transition to leadership, we would highlight the existing executive team inherited some of the challenges that have weighed on Nervgen stock, most notably the decision to go public in Canada at an early-stage which has contributed to being tenuously financed. Nonetheless, we are confident this team can navigate Nervgen through the existing capital market and clinical challenges it faces. Paul Brennan, who joined as CEO in 2019, has plenty of experience in publicly traded development-stage biotech including senior roles with Tekmira / Arbutus BioPharma (Nasdaq: ABUS), Aquinox Pharmaceuticals (Nasdaq: AQXP), and Aspreva Pharmaceuticals (Nasdaq: ASPV). An impressive recent addition to the senior team is Dr. Dan Mikol, a neurologist, who joined Nervgen as Chief Medical Officer from Amgen (Nasdaq: AMGN) where he was Executive Medical Director, Global Clinical Development. We would highlight one other, under-the-radar, addition to the Nervgen team, that is a long-standing friend to the partners at Encode - Rich Macary. Macary, who recently became a strategic consultant to Nervgen, was an early investor in AVI Biopharma (Nasdaq: AVII) where he led two rounds of shareholder activism and was instrumental in putting the team and capital in place for what would become Sarepta Therapeutics (Nasdaq: SRPT).

Risks

We have outlined many of the challenges Nervgen has faced and continues to face, and how once solved, could unlock substantial latent value in the company. Of course, we need to acknowledge that these challenges may not be solved in a timely manner, or in some cases at all, and the serious risks associated with these scenarios. Below we highlight notable risks that face the company between now and YE22;

- FDA maintaining its partial clinical hold on NVG-291, bringing into question the viability of advancing the drug into efficacy studies
- Safety issues develop in the ongoing Ph1 study that brings into question the viability of NVG-291
- COVID related delays in patient accrual in the Ph1 study
- Inability to raise meaningful capital and list on Nasdaq

Scientific Summary

NervGen Pharma is a publicly-traded biotech company dedicated to discovering and developing treatments for patients suffering from medical conditions related to nerve damage, resulting from injury, neurodegenerative disease, or other causes. NervGen's core technology targets a novel receptor called protein tyrosine phosphatase sigma or PTPσ. PTPσ is present in the central and peripheral nervous systems and plays a key role when there is nerve damage since it impedes nerve regeneration, inhibits plasticity and remyelination.

NervGen's lead product NVG-291 is a specific and selective PTPσ inhibitor. Multiple studies in a variety of animal models have shown that treatment targeting PTPσ receptors promotes regeneration of damaged nerves and improves function. Currently, NVG-291 is being developed for the treatment of Alzheimer's disease, multiple sclerosis, and spinal cord injury, each of which has significant market potential.

NVG-291

Recovery after central nervous system injury is minimal, leading to substantial interest in potential strategies to overcome this challenge. After brain or spinal cord injury, a glial scar forms that poses a major impediment to central nervous system regeneration. It is now known that in the region of forming scar tissue, several classes of growth inhibitory molecules are upregulated, including the family of extracellular matrix molecules known as chondroitin sulfate proteoglycans (CSPGs), that appear rapidly after injury in the vicinity of blood brain barrier breakdown.

It is well-established that robust upregulation of CSPGs by activated glia including astrocytes, microglia, and oligodendrocyte precursor cells dramatically alters the composition of the extracellular matrix within the lesion. A plethora of data has demonstrated that CSPGs negatively regulate several aspects of the repair process including neuronal survival, synaptogenesis, axonal sprouting, regeneration, and conduction, as well as replacement of oligodendrocytes and remyelination. Given the multifaceted inhibitory role of CSPGs in the injured spinal cord, their manipulation has become a promising therapeutic approach for functional and physiological improvements following injury.

PTPσ has been identified as a receptor for the inhibitory glycosylated side chains of CSPGs. In the central nervous system, this receptor is expressed in neural stem cells, progenitor cells, astrocytes, oligodendrocytes and neurons and binds to the CSPGs with high affinity. PTPσ, as a functional receptor, mediates the inhibitory effects of CSPGs on axonal growth and its inactivation leads to increased repair of sciatic nerve in rats, improved regeneration of injured optics nerve, enhanced regeneration in face nerve, and reconstruction of corticospinal pathway.

Based on the structure of PTPσ and several related phosphatases, a highly conserved 24 amino acid intracellular wedge domain was identified. NVG-291-R a novel peptide-mimetic of the PTPσ wedge with a TAT domain (to facilitate membrane-penetration) was developed that can bind to recombinant human PTPσ. Systemic administration of NVG-291-R was found to penetrate the cell membrane and relieve the CSPG-mediated axonal sprouting inhibition in a spinal

cord injury model. More recently NVG-291-R enhanced remyelination in LPC-induced demyelinated spinal cord. In addition, another study indicated that NVG-291-R reversed the inhibitory effect of CSPGs on the ability of oligodendrocytes to myelinate axons, *in vitro*. NervGen's lead clinical product, NVG-291, is a close analog to NVG-291-R.

Alzheimer's Disease

Alzheimer's disease is the most common cause of dementia among older adults. Dementia is the loss of cognitive functioning—thinking, remembering, and reasoning—and behavioral abilities to such an extent that it interferes with a person's daily life and activities. Alzheimer's disease is a highly complex and progressive neurodegenerative disease. In the United States alone, approximately 5.3 million Americans have Alzheimer's disease, of which 5.1 million are aged 65 years or older.

There is increasing evidence that CSPG molecules increase with age and are associated with Alzheimer's disease. Since CSPGs bind and signal predominantly through PTPσ, it is thought that NVG-291 may be a potential treatment for Alzheimer's disease. Supportive evidence for this hypothesis has been seen in knock-out models of PTPσ. Genetic depletion of PTPσ in Alzheimer's disease models suppressed Aβ accumulation, tau aggregation, neuroinflammation, and synaptic loss while enhancing behavioral and cognitive function including spatial navigation and memory, and novel object recognition. Although NVG-291-R has not been directly tested in an Alzheimer disease model, preclinical studies have demonstrated that breaking down CSPGs using Chondroitinase ABC improves symptoms in Alzheimer's disease models.

Multiple Sclerosis

Multiple sclerosis is a chronic autoimmune-mediated demyelinating disease characterized by a dramatic loss of clusters of oligodendrocytes, demyelination, and irreversible neurologic disability. In the United States, multiple sclerosis affects approximately 400,000 individuals; worldwide, the disease affects 2.5 million individuals and varies greatly by geographic region. The age of onset of multiple sclerosis is between 20 and 40 years, and it is slightly later in men than in women; however, multiple sclerosis can present across a person's entire lifespan. Approximately 10% of multiple sclerosis cases begin before age 18. The incidence of multiple sclerosis peaks at age 30, and the prevalence peaks at age 50.

In multiple sclerosis, upregulated CSPGs have been detected within active demyelinating lesions. The effects of NVG-291-R have been studied in two different MS models, an EAE mouse model and a LPC induced acute focal demyelination model. Treatment of animals with NVG-291-R enhanced myelin repair in the LPC-induced demyelination model, enhanced protease-dependent enzymatic digestion of CSPGs, and increased MMP-2 secretion to enhance OPC remyelination. In addition, targeting PTPσ with systemically delivered NVG-291-R also enhanced functional recovery following chronic demyelinating EAE.

NVG-291-R was also tested in an LPC-induced focal demyelination of mouse optic chiasm model. Following injection of LPC, the most severe inflammation happens 2-3 days post injection, the maximum extent of demyelination in optic chiasm happens at 7 days post injection,

while at 14 days post injection significant remyelination occurs. Systemic administration of NVG-291-R reduced the extent of demyelination within the optic chiasm at 7 days post injection.

Spinal Cord Injury

Spinal cord injury is a major cause of long-term physical impairment. The overall annual incidence of spinal cord injury is estimated at 15–40 cases per million. The known causes of spinal cord injury are motor vehicle accidents (50%), fall and work-related injuries (30%), violent crimes (11%), and sports-related injuries (9%). As these causes are mostly related to physical activity, the second and third decades of life are the predominant ages of the affected patients. The second highest incidence of spinal cord injury was noted in the patients aged above 50 years. In this group, pre-existing spondylosis is associated with spinal cord injury, which results from a relatively low-energy trauma. Besides traumatic spinal cord injury, the number of patients with spinal cord injury due to other pathologic conditions, such as tumors or demyelinating diseases, is increasing.

Current spinal cord injury treatments are limited mostly to supportive measures. However, there is scientific evidence to support targeting PTPσ using NVG-291 as a possible treatment. Rodent animal models of spinal cord injury in three independent labs all showed that binding of NVG-291-R to PTPσ led to blockage of the signaling cascade associated with CSPG binding in turn leading to alleviation of the symptoms of spinal cord injury such as return of locomotor and urinary functions. The findings in spinal cord injury models have been bolstered with similar reversal of nerve injury and enhanced physiological recovery in acute myocardial infarction, ventral nerve root avulsion, dorsal nerve root crush, and spinal cord injury model, and immune modulation in spinal cord injury models.

Clinical Development

NervGen has an open Investigational New Drug (IND) for NVG-291 with the United States Food and Drug Administration (FDA) under a partial clinical hold, which still allows Nervgen to proceed with its Phase I program. The trial will consist of a single ascending dose portion in females, and a multiple ascending dose portion in postmenopausal females. FDA has asked for additional preclinical safety data before including males in the Phase 1 program, and before including premenopausal females in the multiple ascending dose portion of the trial.

NervGen has initiated a Phase 1 clinical trial in Australia under all of the conditions required by FDA. Pending a positive outcome of the Phase 1 in healthy volunteers, NervGen intends to initiate a multi-dose Phase 1b study in patients with Alzheimer's disease. The Company also plans to initiate Phase 2 trials in spinal cord injury and multiple sclerosis after completion of Phase 1 and after resolution of the partial clinical hold. NervGen currently expects it will be able to initiate these trials in mid-2022.

Conclusion

NervGen's core technology targets a novel receptor PTPσ. Studies in a variety of animal models have shown that treatments targeting PTPσ receptors promote regeneration of damaged nerves and improves function. Currently, NVG-291, a specific and selective PTPσ inhibitor, is being developed for the treatment of Alzheimer's disease, multiple sclerosis, and spinal cord injury, each of which has a significant potential market.

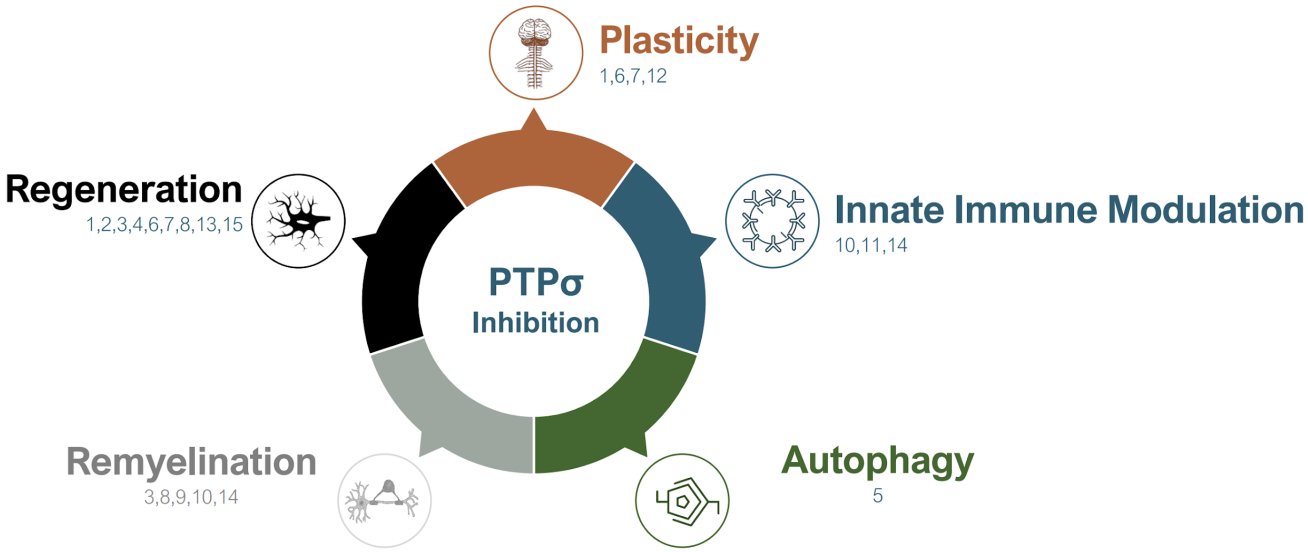
Detailed Scientific Summary

NervGen Pharma (NervGen) is a publicly traded biotech company dedicated to discovering and developing treatments for patients suffering from medical conditions related to nerve damage, resulting from injury, neurodegenerative disease, or other causes.

NervGen's core technology targets protein tyrosine phosphatase sigma (PTPσ), a neural receptor that impedes nerve regeneration, remyelination and plasticity. Multiple studies with animal models for several diseases and medical conditions have shown that treatment targeting PTPσ receptors with a compound developed by Dr. Jerry Silver and his research team, NVG-291-R, promotes regeneration of damaged nerves and improvement in function (Lang et al., 2015; Gardner et al., 2015; Li, H., 2015; Rink et al., 2018; Luo et al. 2018). NervGen licenced the intellectual property underpinning this research from Case Western Reserve University (CWRU) and is now developing NVG-291-R as the basis for its core technology. NervGen's lead product, NVG-291, is a close analog to NVG-291-R.

Various studies indicate that NVG-291-R's mechanism for nerve repair is mediated by a number of endogenous repair mechanisms, including regeneration, plasticity, remyelination, immune modulation and synapse formation (Figure 1).

Figure 1 Multiple Pharmacodynamic Responses of NVG-291-R Which Contributes to Nerve Repair



(NervGen Pharma, Corporate Presentation)

Furthermore, these repair mechanisms seem to help treat nerve damage associated with both nerve injury (spinal cord injury, peripheral nerve injury, traumatic brain injury, and stroke) and with neurodegenerative diseases (multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and Parkinson's disease). NervGen is currently developing NVG-291 as a potential treatment for Alzheimer's disease (AD), multiple sclerosis (MS), and spinal cord injury (SCI) (Table 1).

Table 1 NVG-291 Potential Lead Indications

	Spinal Cord Injury	Multiple Sclerosis	Alzheimer's Disease
Major Symptoms	Reduced motor control	Periodic symptoms, such as	Cognitive decline
	Reduced sensory function		
	Reduced bladder control	Progressive disability	
Unmet Need	There are no pharmaceutical treatments that either acutely reduce the damage at the time of injury or chronically promote recovery	Periodic symptoms are well treated	Current treatments are only symptomatic and do not address cognitive decline
		However, progressive disease and resultant disability are not well treated	
Potential Benefit	Preclinical studies demonstrate significant benefits in motor control, sensory function and bladder control	Preclinical studies demonstrate remyelination potential and reversal of disability	PTPσ inhibition has demonstrated PD effects (regeneration, plasticity, neuromodulation, autophagy) that can help slow, if not reverse, cognitive decline
PD = Pharmacodynamic; PTPσ = Protein tyrosine phosphatase σ			

(NervGen Pharma Website)

NervGen has an open Investigational New Drug (IND) for NVG-291 with the United States Food and Drug Administration (FDA) under a partial clinical hold, which allows Nervgen to proceed with its Phase I program. The trial will consist of a single ascending dose portion in females, and a multiple ascending dose portion in postmenopausal females. FDA has asked for additional preclinical safety data before including males in the Phase 1 program, and before including premenopausal females in the multiple ascending dose portion of the trial.

NervGen received ethics approval for the Phase 1 study protocol from Bellberry Human Research Ethics Committee in Australia. The Therapeutic Goods Administration in Australia has been notified of the study through the Clinical Trial Notification Scheme. The study protocol was also previously reviewed by FDA and is intended to support the progression of a clinical study in the United States in the future. The Phase 1 study is currently underway in Australia under all of the conditions required by the FDA partial clinical hold. Pending a positive outcome of the Phase 1 study in healthy volunteers, NervGen intends to initiate an Alzheimer's disease Phase 1b study. The primary objective for the Alzheimer's disease Phase 1b study is to assess the safety and pharmacokinetic (PK) profile of NVG-291 in both elderly and Alzheimer's disease patients. Additionally, NervGen plans to include various biomarker and cognitive tests to identify early signals of efficacy. The Company also plans to initiate Phase 2 trials in spinal cord injury and multiple sclerosis after completion of Phase 1 and after resolution of the partial clinical hold. NervGen currently expects it will be able to initiate these trials in mid-2022.

NVG-291 and Glial Scars

Recovery after central nervous system (CNS) injury is minimal, leading to substantial interest in potential strategies to overcome this challenge (Case and Tessier-Lavigne, 2005; Domeniconi and Filbin, 2005; Liu at al., 2006; Yiu and He, 2006; Lu et al., 2008). After brain or spinal cord injury, a glial scar forms that poses a major impediment to CNS regeneration (Silver and Miller, 2004). Formation of the glial scar occurs after the introduction of non-CNS molecules into the brain parenchyma as a result of blood brain barrier (BBB) disruption (Preston et al., 2001). The BBB remains porous to blood and serum components for up to 14 days after brain or spinal cord injury, and the areas of greatest glial scarring correlate well with areas of most extensive BBB breakdown, as well as the largest numbers of activated macrophages.

In the region of the forming scar tissue, the ends of the regenerating axons cease extending and become swollen and distorted into various bizarrely shaped "growth cones" that can remain for years within axon tracts (Li and Raisman, 1995; Houle and Jin, 2001; Kwon et al., 2002). Ramón y Cajal (1928) believed that these "sterile clubs" or "dystrophic endballs" were a relatively quiescent, final resting state of the frustrated growth cone. Thus, it has long been theorized that dystrophic axons are incapable of robust regeneration.

It is now known that in the region of forming scar tissue, several classes of growth inhibitory molecules are upregulated, including the family of extracellular matrix (ECM) molecules known as chondroitin/keratan sulfate proteoglycans (PGs), that appear rapidly after injury in the vicinity of BBB breakdown (Fitch and Silver, 1997; Morgenstern et al., 2002; Jones et al., 2003; Tang et al., 2003). It is well-established that robust upregulation of chondroitin sulfate proteoglycans (CSPGs) by activated glia including astrocytes, microglia and oligodendrocyte precursor cells dramatically alters the composition of the EMC within the lesion (Tran et al., 2018). A plethora of data has demonstrated that CSPGs negatively regulate several aspects of the repair process including neuronal survival, synaptogenesis, axonal sprouting, regeneration and conduction, as well as replacement of oligodendrocytes and remyelination (Karimi-Abdolrezaee et al., 2010; Tran et al., 2018). Given the multifaceted inhibitory role of CSPGs in the injured spinal cord, their manipulation has become a promising therapeutic approach for functional and physiological improvements following spinal cord injury.

PTPσ along with its sister phosphatase leukocyte common antigen-related molecule (LAR) and the nogo receptors 1 and 3 (NgR), have recently been identified as receptors for the inhibitory glycosylated side chains of CSPGs (Shen et al., 2009; Fisher et al., 2011; Dickendesher et al., 2012). PTPσ has a single transmembrane and two intracellular PTPase domains; the intracellular proximal domain (D1) is catalytic and the distal one (D2) is regulatory for the PTPσ signaling (Chagnon et al., 2004; Wallace et al., 1999; Yan et al., 1993). In the CNS, this receptor is expressed in neural stem cells (NSCs), progenitor cells, astrocytes, oligodendrocytes and neurons (Kirkham et al., 2006) and binds to the CSPGs with high affinity (Shen et al., 2009). PTPσ, as a functional receptor, mediates the inhibitory effects of CSPGs on axonal growth (Ensslen-Craig and Brady-Kalnay, 2004; Fry et al., 2010; Meathrel et al., 2002; Shen et al., 2009; Thompson et al., 2003) and its inactivation leads to increased repair of sciatic nerve in rats (McLean et al., 2002), improved regeneration of injured optics nerve (Sapieha et al., 2005), en-

hanced regeneration in face nerve (Thompson et al., 2003), and reconstruction of corticospinal pathway (Fry et al., 2010).

Lang et al. (2015) found that in rats that PTPσ had a critical role in converting growth cones into a dystrophic state by tightly stabilizing them within CSPG-rich substrates. Upon analyzing the structure of PTPσ and related phosphatases, Lang et al. (2015) identified a highly conserved 24 amino acid intracellular wedge domain. As wedge domains are known to regulate downstream signaling through a variety of mechanisms (Fisher et al., 2011; Xie et al., 2006; Jiang et al., 1999; Barr et al., 2009), they designed Intracellular Sigma Peptide (ISP, NVG-291-R), a novel peptide-mimetic of the PTPσ wedge with a Tat domain to facilitate membrane-penetration. NVG-291-R was able to bind to recombinant human PTPσ.

In rodent brain and spinal cord lysates, NVG-291-R was able to pull down both immature full length PTPσ and the mature functional complex (Aicher et al., 1997). In PTPσ null mice, only a very minor signal was detected which may reflect nonspecific binding to PTPδ, the third LAR family member (Wallace et al., 1998). No detectable binding was observed between NVG-291-R and other CSPG receptors such as LAR and NgRs. Interestingly, a LAR wedge-domain Peptide (ILP) (Xie et al., 2006) was also capable of binding PTPσ, but less efficiently than NVG-291-R.

In a study by Lang et al (2015) systemic administration of NVG-291-R penetrated the membrane and relieved the CSPG-mediated axonal sprouting inhibition in spinal cord injury model. More recently the same group reported, NVG-291-R enhanced remyelination in LPC-induced demyelinated spinal cord (Luo et al., 2018). In addition, another study indicated that NVG-291-R reversed the inhibitory effect of CSPGs on the ability of oligodendrocytes to myelinate axons, *in vitro* (Yao et al., 2019).

NVG-291 and Alzheimer's Disease

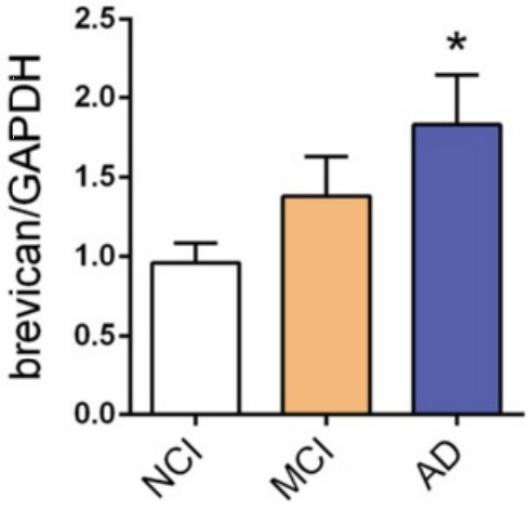
Alzheimer's disease (AD) is currently ranked as the sixth leading cause of death in the United States (U.S.), but recent estimates indicate that the disorder may rank third, just behind heart disease and cancer, as a cause of death for older people. AD is a highly complex and progressive neurodegenerative disease (Henry et al., 2010). In the U.S. alone, approximately 5.3 million Americans have AD, of which 5.1 million are aged 65 years or older (Alzheimer's, 2015).

AD is the most common cause of dementia among older adults. Dementia is the loss of cognitive functioning—thinking, remembering, and reasoning—and behavioral abilities to such an extent that it interferes with a person's daily life and activities. Dementia ranges in severity from the mildest stage, when it is just beginning to affect a person's functioning, to the most severe stage, when the person must depend completely on others for basic activities of daily living.

AD is a neurodegenerative and prominent protein-conformational disease (PCD) (Adav and Sze, 2016; Leandro and Gomes, 2016) primarily caused by the aberrant processing and polymerization of normally soluble proteins (Tran et al., 2015). When misfolded, soluble neuronal proteins attain altered conformations, due to genetic mutation, external factors, or aging, leading to abnormal neuronal functions and loss (Horwich, 2002).

Increasing evidence has demonstrated that CSPG molecules increase with age (Tanaka et al., 2009) and are associated with AD (Lendvai et al., 2013). Howell et al. (2015) assessed brevican content in superior frontal gyrus from no cognitive impairment (NCI), mild cognitive impairment (MCI) and AD subjects. A clear elevation of intact, full-length brevican core protein content was observed in AD superior frontal gyrus tissue compared to NCI individuals (Figure 2). Indeed, brevican in AD frontal gyrus was nearly double that of NCI tissue, and there was a clear trend of increased full length brevican in MCI subjects compared to NCI tissue.

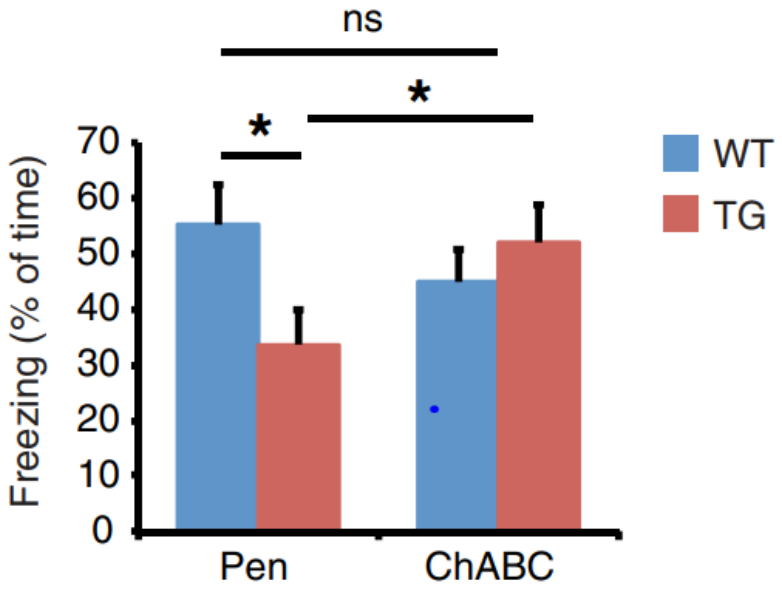
Figure 2 CSPG Levels in Human Brain with No Cognitive Impairment, Mild Cognitive Impairment and Alzheimer's disease



(Howell et al., 2015)

Preclinical studies have demonstrated that breaking down CSPGs using Chondroitinase ABC (ChABC) improves AD symptoms (Végh et al., 2014; Yang et al., 2015). Végh et al. (2014) examined whether local injection of ChABC into the hippocampus of 3 month old APP/PS1 mice could reverse the observed fear memory deficit. Control animals were injected with penicillinase (Pen), an enzyme with no endogenous substrate in mice. Animals were subjected to a fear conditioning task 24 hr after injection. APP/PS1 mice that were injected with Pen showed a significant reduction in fear memory compared with wildtype (WT) Pen treated mice (Figure 3), and this effect was comparable to untreated mice. ChABC treatment on the other hand restored memory function in APP/PS1 mice, and freezing levels were not significantly (NS) different from either ChABC or Pen treated WT mice.

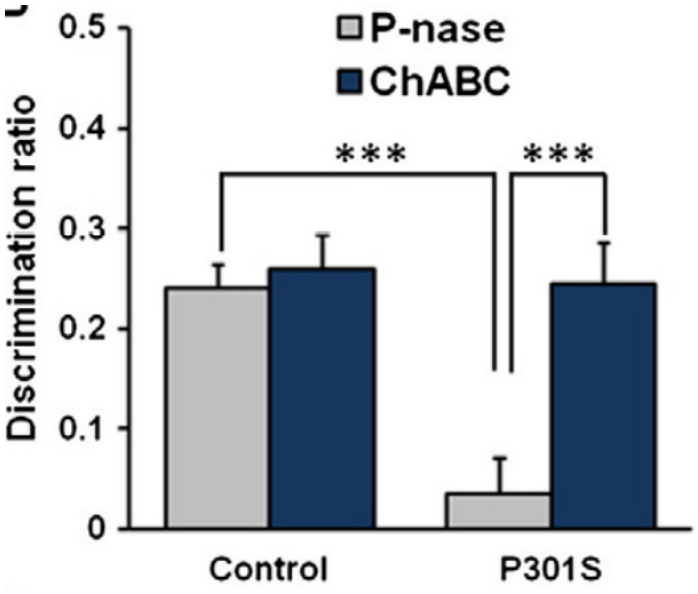
Figure 3 ChABC Treatment Restores Hippocampal Memory and LTP in 3 Months old APP/PS1 Mice



(Végh et al., 2014)

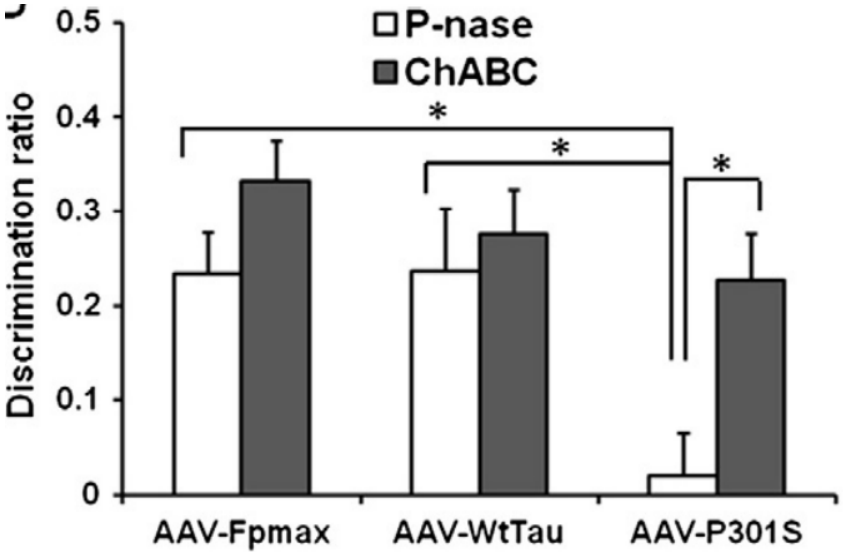
Yang et al. (2015) investigated two models with tau hyperphosphorylation, aggregation and neurodegeneration: a transgenic mouse model in which the mutant P301S tau is expressed in neurons (Tg P301S), and a model in which an adeno-associated virus expressing P301S tau (AAV-P301S) was injected in the perirhinal cortex, a region critical for object recognition (OR) memory. Both models showed profound loss of OR memory despite only 15% neuronal loss in the Tg P301S and 26% in AAV-P301S-injected mice. Recordings from perirhinal cortex slices of P301S transgenic mice showed a diminution in synaptic transmission following temporal stimulation. ChABC was injected into the perirhinal cortex and animals were tested for OR memory one week later, demonstrating restoration of OR memory to normal levels (Figure 4 and Figure 5). Synaptic transmission indicated by fEPSP amplitude was restored to control levels following ChABC treatment. ChABC did not affect the progression of neurodegenerative tauopathy.

Figure 4 Object Recognition Memory Recovery After ChABC Treatment in Tg P301S Mice



(Yang et al., 2015)

Figure 5 Object Recognition Memory Recovery After ChABC Treatment in AAV-P301S Injected Mice



(Yang et al., 2015)

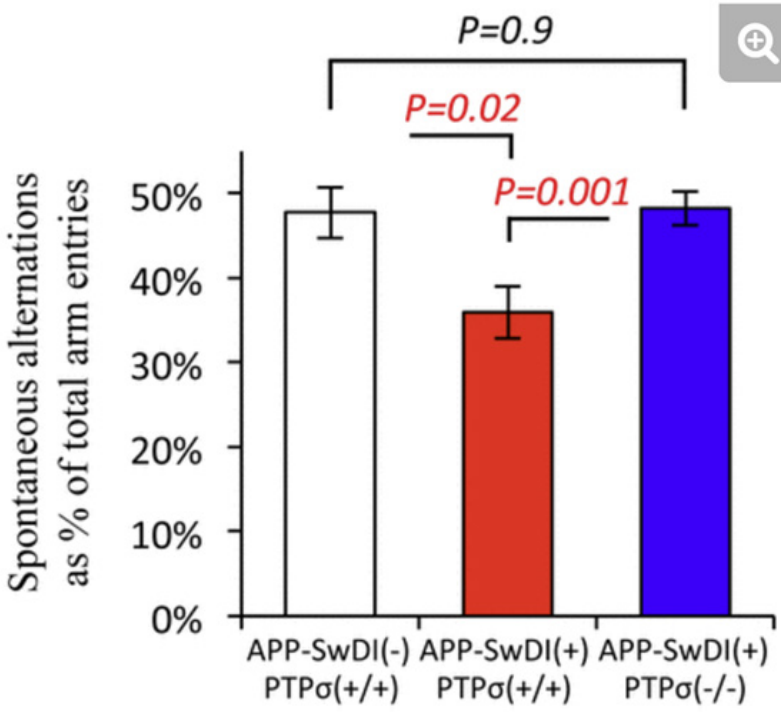
As discussed previously PTPσ is expressed in neural stem cells, progenitor cells including OPCs, oligodendrocytes, astrocytes, neurons and microglia/macrophages (Shen et al., 2009; Luo et al., 2018; Kirkham et al., 2006; Dyck et al., 2018a). CSPGs bind and signal predominantly through PTPσ, which in turn inhibits neuronal growth, sprouting, plasticity and regeneration (Shen et al., 2009). Supporting the potential role of PTPσ inhibition is evidence seen in knockout models of PTPσ. Genetic depletion of PTPσ in AD models suppressed Aβ accumulation,

tau aggregation, neuroinflammation, and synaptic loss, while enhancing behavioural and cognitive function including spatial navigation and memory, and novel object recognition (Gu et al., 2016).

Gu et al. (2016) assessed whether the alleviation of neuropathology's by PTPσ depletion was accompanied with a rescue from AD relevant behavioral deficits. The most common symptoms of AD include short-term memory loss and apathy among the earliest, followed by spatial disorientation amid impairment of many cognitive functions as the dementia progresses. Using a Y maze and novel object assays as surrogate models, they evaluated these cognitive and psychiatric features in the TgAPP-SwDI and TgAPP22 SwInd mice.

The Y-maze assay, which allows mice to freely explore three identical arms, measures their short-term spatial memory. It is based on the natural tendency of mice to alternate arm exploration without repetitions. The performance is scored by the percentage of spontaneous alternations among total arm entries, and a higher score indicates better spatial navigation. Compared to non-transgenic wild type APP-SwDI(-)PTP**σ**(+/+)mice, APP-SwDI(+)PTPσ(+/+) mice show deficit of short-term spatial memory, which is rescued by genetic depletion of PTPσ (Figure 6).

Figure 6 PTPσ Deficiency Restores Short-term Spatial Memory in TgAPP-SwDI Mice

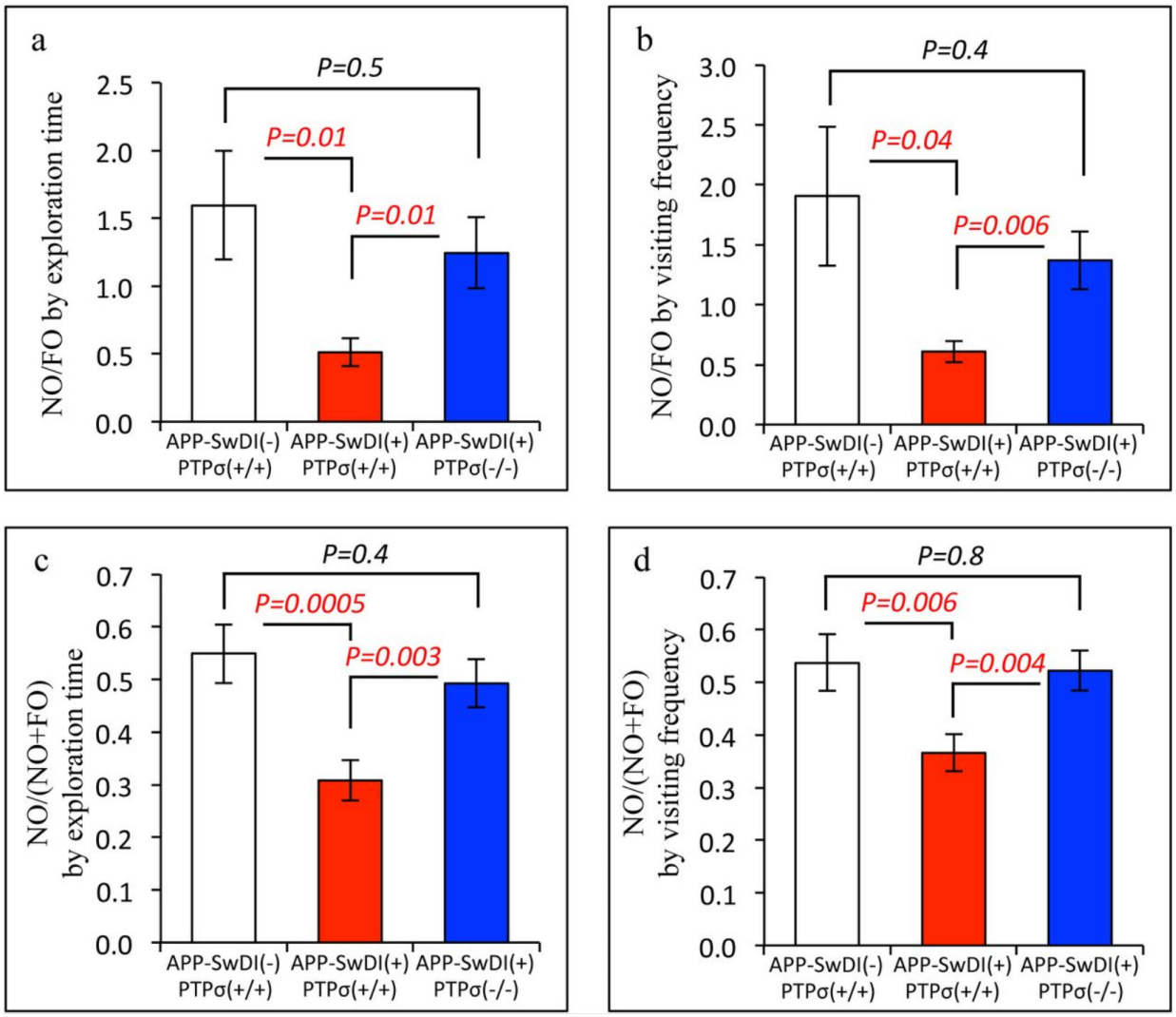


(Gu et al., 2016)

In the novel object (NO) test, NO preference is measured by the ratio between NO and familiar object (FO) exploration, where NO/FO >1 indicates preference for NO. Attention to NO is additionally measured by the discrimination index, NO/(NO+FO), the ratio of NO exploration to total object exploration (NO+FO). Mice of this colony showed a low baseline of the NO/

(NO+FO) discrimination index, likely inherited from their parental Balb/c line. For non-transgenic wild type APP-SwDI(-)PTP**σ**(+/+) mice, the discrimination index is slightly above 0.5 (chance value), similar to what was previously reported for the Balb/c wild type mice (Horn et al., 2012). Thus, a sole measurement of the discrimination index may not reveal the preference for NO as does the NO/FO ratio. Although not as sensitive in measuring object preference, the NO/(NO+FO) index is most commonly used as it provides a normalization of the NO exploration to total object exploration activity. While each has its own advantage and shortcoming, both NO/FO and NO/NO+FO measurements consistently show that the expression of TgAPP-SwDI gene leads to a deficit in attention to the NO, whereas genetic depletion of PTPσ restores novelty exploration to a level close to that of non-transgenic wild type mice (Figure 7).

Figure 7 PTPσ Deficiency Enhances Novelty Exploration by TgAPP-SwDI Mice

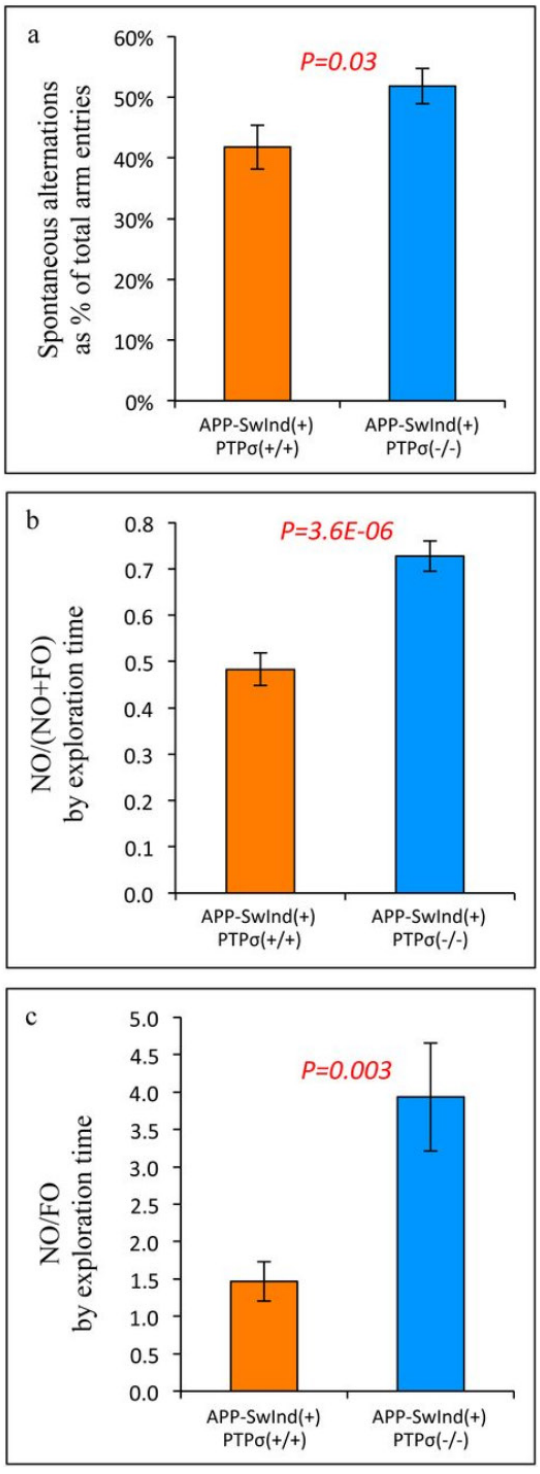


(Gu et al., 2016)

Performance of spatial navigation is scored by the percentage of spontaneous alternations among total arm entries in the Y-maze assay. Compared to APP-SwInd(+)PTP**σ**(+/+) mice, APP-

SwInd(+)PTPσ(-/-) mice showed improved short-term spatial memory (Figure 8).

Figure 8 PTPσ Deficiency Enhances Behavioral Performance by TgAPP-SwDI Mice



(Gu et al., 2016)

Since NervGen's lead compound NVG-291 targets the interaction between PTPσ and CSPGs, it may alter AD pathology by promoting regeneration at areas of nerve damage, plasticity in intact areas of the brain and by dampening Aβ production.

NVG-291 and Multiple Sclerosis

In the U.S., Multiple Sclerosis (MS) affects approximately 400,000 individuals; worldwide, the disease affects 2.5 million individuals and varies greatly by geographic region (Multiple Sclerosis Association of America Website). The disease is predominant in women, being more than three times more likely in women than men. Results from a systematic review by Alonso and Hernán (2008) showed that the female-to-male ratio in MS incidence has increased with time, from an estimated 1.4 in 1955 to 2.3 in 2000. They also reported an overall MS incidence rate of 3.6 cases per 100,000 person-years (95% confidence interval (CI), 3.0-4.2) in women and 2.0 (95% CI, 1.5-2.4) in men (Alonso and Hernán, 2008). The age of onset of MS is between 20 and 40 years, and it is slightly later in men than in women; however, MS can present across the lifespan. Approximately 10% of MS cases begin before age 18 (Hauser et al., 2015). The incidence of MS peaks at age 30, and the prevalence peaks at age 50 (Koch-Henriksen and Sørensen, 2010).

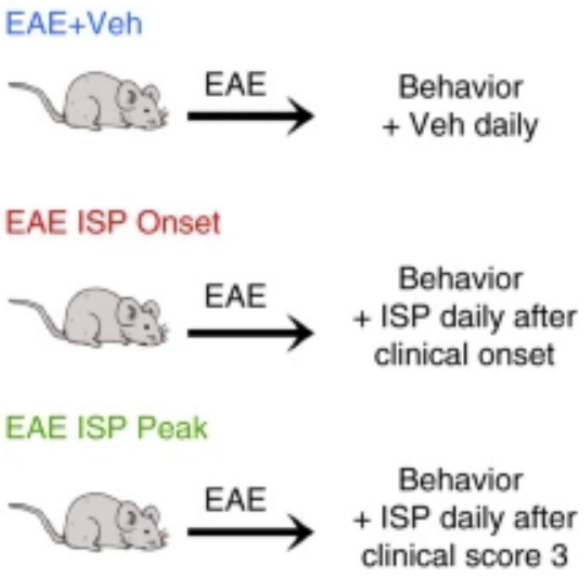
MS is a chronic autoimmune-mediated demyelinating disease characterized by a dramatic loss of clusters of oligodendrocytes (OLs), demyelination, and irreversible neurologic disability (Patrikios et al., 2006). Although remyelination can occur spontaneously, it ultimately fails in regions that develop scar-like, proteoglycan-laden plaques (Franklin et al., 2008). The underlying mechanisms of failed oligodendrocyte progenitor cell (OPC) differentiation, maturation, and remyelination are not well understood. Recent studies have identified the regulatory effects of CSPGs on OPC maturation and function (Keough et al., 2016; Pendleton et al., 2013). CSPGs have been identified as a negative regulator of regeneration and remyelination in many different CNS pathologies, including MS (Lau et al., 2012; Mohan et al., 2010; Sobel et sl., 2001).

In MS, upregulated CSPGs such as aggrecan and versican have been detected within active demyelinating lesions (Sobel et sl., 2001; Chang et al., 2012; Kippert et al., 2009). While permissive laminins promote the spreading, survival, and maturation of OLs (Colognato et al., 2005; Buttery et al., 1999), increased concentrations of CSPGs can outcompete growth-promoting ECM and curtail mouse or human OPC/OL migration, morphological process extension, and maturation (Pendleton et al., 2013; Siebert and Osterhout, 2011). CSPG inhibition could be relieved by enzymatic degradation through ChABC to enhance OL maturation *in vitro* (Siebert and Osterhout, 2011). *In vivo*, although CSPGs increase temporally in Lysolecithin (LPC)-induced lesions prior to the onset of remyelination (Lau et al., 2012; Fuller et al., 2007), improved remyelination can occur following CSPG-targeting treatments such as proteoglycan synthesis inhibitors β-d-xyloside (Lau et al., 2012) or flurosamine (Keough et al., 2016).

Luo et al. (2018) tested the effects of NVG-291-R in an experimental autoimmune encephalomyelitis (EAE) mouse model, which recapitulates chronic progressive demyelination disease processes. Following MOG_{35-55} immunization, animals received intraperitoneal (IP) NVG-291-R injections (20 µg/mouse, daily) for 41 days at the beginning (EAE NVG-291-R Onset) or the

peak of sickness (EAE NVG-291-R Peak) as determined by clinical scoring (Figure 9). In parallel, the control group was injected with 5% dimethyl sulfoxide (DMSO).

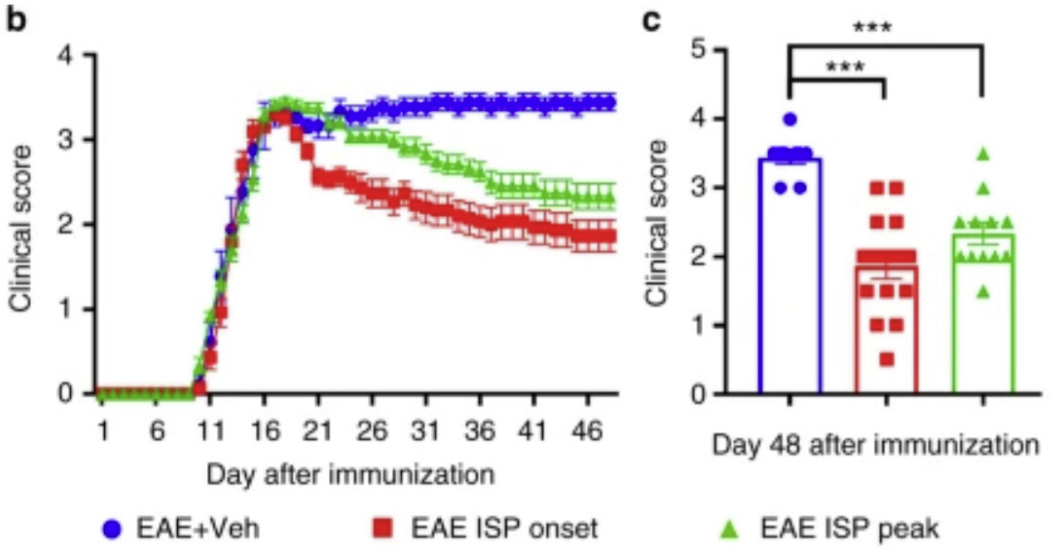
Figure 9 Experimental Design for Mouse EAE Model of Multiple Sclerosis



(Luo et al., 2018)

Functional recovery was initially observed in the Onset group after ~10–12 days of NVG-291-R administration (i.e., day 23 post immunization). NVG-291-R improved clinical scores from 3.5–4 (severe paralysis) to 2–1.5 (limp tail and hind limb weakness). After 20–22 days of NVG-291-R treatment (~33 days post immunization), several animals in the Onset group recovered with clinical scores improving to 0.5–1 (limp tail) (Figure 10). In contrast, control animals remained severely paralyzed with scores remaining around 3.5–4. EAE NVG-291-R Peak animals also improved significantly with NVG-291-R treatment; however, NVG-291-R given at the onset of disease allowed for better recovery (Figure 10) (Luo et al., 2018).

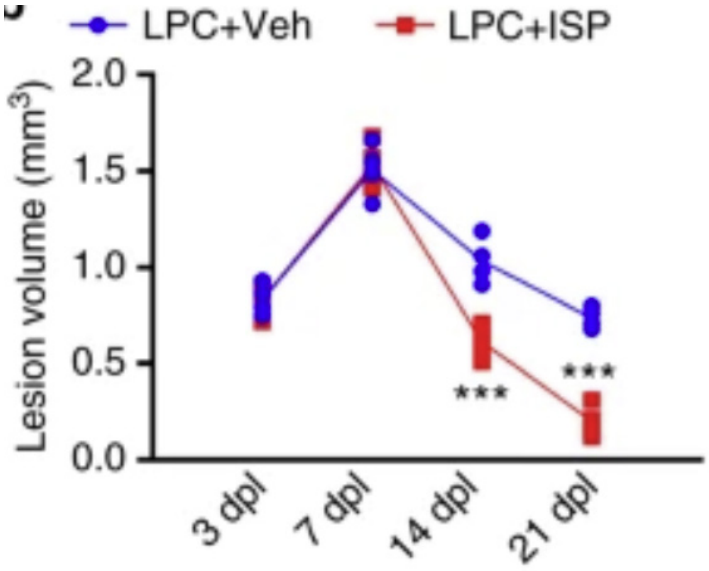
Figure 10 Effects of NVG-291-R on a Mouse EAE Model of Multiple Sclerosis



(Luo et al., 2018)

Luo et al. (2018) also examined whether NVG-291-R modulation of PTPσ-CSPG interactions had similar effects in acute focal demyelination induced by LPC injected into the dorsal column white matter of young adult C57BL6/J mice treated either subcutaneously (SC) with NVG-291-R (20 µg/day) or control vehicle starting at 1-day post-LPC injection. After NVG-291-R treatment, LPC-induced lesion volumes were significantly reduced at 14- and 21-days post lesion (dpl) compared with vehicle-treated animals as shown by Luxol Fast Blue (LFB) myelin staining. Vehicle-treated animals had an average lesion volume of 1.508 ± 0.069 mm^3, 1.035 ± 0.06 mm^3, and 0.738 ± 0.027 mm^3 after 7, 14, or 21 dpl, respectively. In contrast, NVG-291-R treated animals showed reduced lesion volumes from an average of 1.535 ± 0.058 mm^3 at 7 dpl to 0.613 ± 0.043 mm^3 at 14 dpl (Figure 11). By 21 dpl, they found extensive lesion repair and reduced lesion volumes in NVG-291-R treated mice (1.535 ± 0.058 mm^3 to 0.2 ± 0.041 mm^3) (Figure 11).

Figure 11 NVG-291-R 3 Promotes Remyelination in the Spinal Cord of Lysolecithin (LPC)-demyelinated Mice

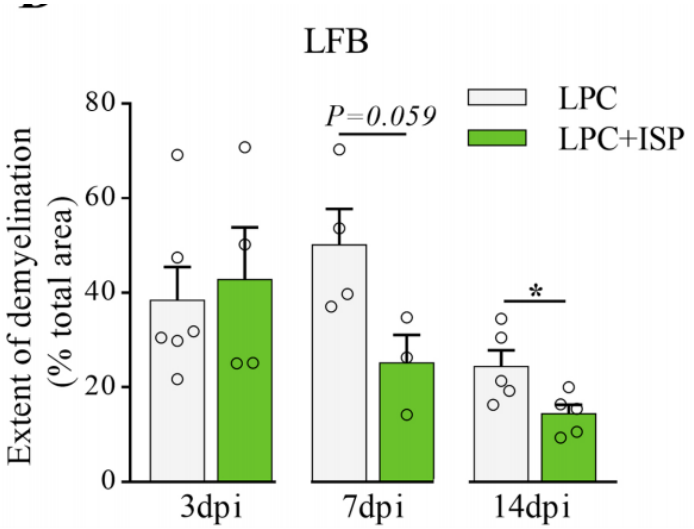


(Luo et al., 2018)

Subsequently, Niknam et al. (2019) examined the effects of NVG-291-R in an LPC-induced focal demyelination of mouse optic chiasm model. Following injection of LPC, the most severe inflammation happens on 2-3 dpi (Tourdias et al., 2011), the maximum extent of demyelination in optic chiasm happens on 7 dpi, while at 14 dpi a significant remyelination occurs (Dehghan et al., 2012; Pourabdolhossein et al., 2014). Accordingly, Niknam et al. (2019) measured the inflammation, demyelination, remyelination and functional recovery at 3, 7 and 14 dpi. Systemic administration of NVG-291-R reduced the extent of demyelination within the optic chiasm, as evaluated by LFB staining (Figure 12), FluoroMyelin staining (Figure 13), and myelin specific immunostaining against myelin basic protein (MBP) at 7 dpi (Figure 13).

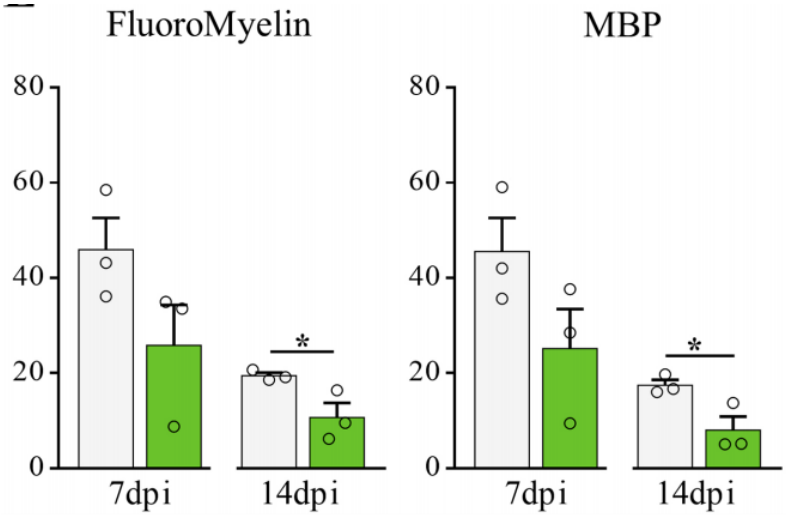
At 3 dpi the extent of demyelination was mostly similar for LPC and LPC+ NVG-291-R treated animals which shows that NVG-291-R does not affect the initial processes of demyelination induction by the LPC. Hematoxylin and eosin staining at 3 dpi also showed that NVG-291-R does not affect the severity of inflammation. At 7 and 14 dpi, the extent of demyelination was reduced by NVG-291-R treatment. The reduction in the extent of demyelination in NVG-291-R group may be due to reduced demyelination and/or enhanced remyelination. In the other words, different levels of demyelination at 7 dpi might be the consequence of myelin protection or accelerated myelin repair. Comparing the extent of demyelination at 7 and 14 dpi showed that NVG-291-R had potentiated the myelin repair process.

Figure 12 Attenuation of the Extent of Demyelination in the LPC-induced Focal Demyelinating Lesions with NVG-291-R (LFB Staining)



(Niknam et al., 2019)

Figure 13 Attenuation of the Extent of Demyelination in the LPC-induced Focal Demyelinating Lesions with NVG-291-R (FluoroMyelin and MBP Staining)



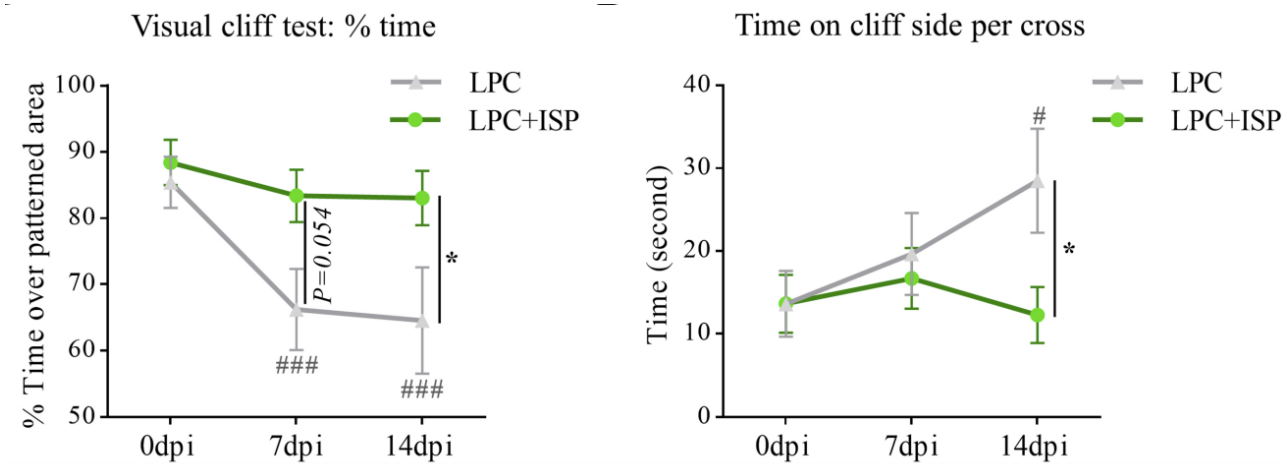
(Niknam et al., 2019)

These findings are in agreement with a previous report which showed NVG-291-R treatment reduced LPC-induced demyelination in mice spinal cord as well as in EAE animals.

To determine whether observed histological and electrophysiological improvements by NVG-291-R, functionally impacted the mice visual acuity, Niknam et al. (2019) performed a visual cliff test as a visually mediated behavioral task. Visual cliff test effectively measures the visual depth perception in animals (Leamey et al., 2007). Animals were placed in the center of the box, on the dividing line between the patterned area and cliff area and were allowed

to choose between the two sides for 5 minutes. The total amount of time spent in each half of the box as well as the time on cliff side per cross were measured. Before LPC injection, mice approached the border and inspected the cliff, then retreated to the patterned side. In contrast, after LPC injection, mice frequently walked over the border region onto the cliff side without pausing. At baseline (0 dpi), both groups of mice spent approximately more than 85% of the total time on the patterned side. Following injection of LPC, this percentage significantly decreased at 7 and 14 dpi, whereas less reduction was observed in NVG-291-R treated group. Visual cliff test analysis demonstrated that NVG-291-R treated mice spent more time on the patterned side compared to LPC. In addition, the average time spent on the cliff side of the box per crossing was lower in NVG-291-R treated mice (Figure 14). Together, these results suggest that NVG-291-R promoted visual acuity restoration following demyelination induction.

Figure 14 NVG-291-R Improved the Visual Acuity Following LPC-induced Demyelination in Optic Chiasm



(Niknam et al., 2019)

Taken together these results demonstrated the possibility of using NVG-291-R as a new strategy to inhibit PTPσ for myelin protection, myelin repair in demyelinated axons, and functional neural pathway conductivity restoration in patients suffering from MS.

NVG-291 and Spinal Cord Injury

Spinal cord injury (SCI) is a major cause of long-term physical impairment. The overall annual incidence of SCI is estimated at 15–40 cases per million (Sekhon et al., 2001). The known causes of SCI are motor vehicle accidents (50%), fall and work-related injuries (30%), violent crimes (11%) and sports-related injuries (9%) (Ho et al., 2007). As these causes are mostly related to physical activity, the second and third decades of life are the predominant ages of the affected patients. A recent study from the U.S. National Spinal Cord Injury Database found that 56% of all SCI cases occur in the cervical spine (Vialle et al., 2005).

The second highest incidence of SCI was noted in the patients aged above 50 years. In this group, pre-existing spondylosis is associated with SCI, which results from a relatively low-en-

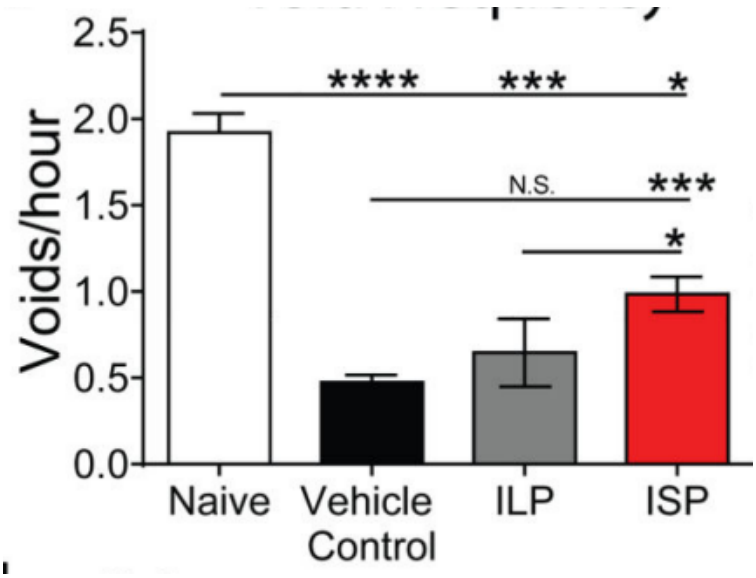
ergy trauma. Besides traumatic SCI, the number of patients with SCI due to other pathologic conditions, such as tumors or demyelinating diseases, is increasing. Metastatic epidural spinal cord compression (MESCC) is one of the causes of nontraumatic SCI. It is estimated that MESCC occurs in 5%–10% of cancer patients and in up to 40% of patients who have pre-existing nonspinal bone

Current treatments are limited mostly to supportive measures. Affected individuals often have life expectancies of decades with permanent disability (McDonald and Sadowsky, 2002; Anderson, 2004). To develop appropriately targeted repair strategies, there is a need for a better understanding of the broad cell biology of SCI and how that cell biology differs in different SCI lesion compartments. Normal function in the CNS requires interactions of many cell types, including neurons, neuroglia, and non-neural cells (Barres, 2008). Similarly, the response to CNS injuries involves complex multicellular interactions, and the activities of diverse cell types can influence SCI outcome (Burda and Sofroniew, 2014).

The scientific evidence of PTPσ as the target for nerve regeneration following axonal damage, and the potential for NVG-291 treatment to reverse it, is well supported by nonclinical efficacy models. Rodent animal models of SCI in three independent labs all showed that binding of NVG-291-R to PTPσ led to blockage of the signaling cascade associated with CSPG binding in turn leading to alleviation of the symptoms of SCI such as return of locomotor and urinary functions (Lang et al., 2015; Ham et al., 2020; Ham et al., 2019; Rink et al., 2018).

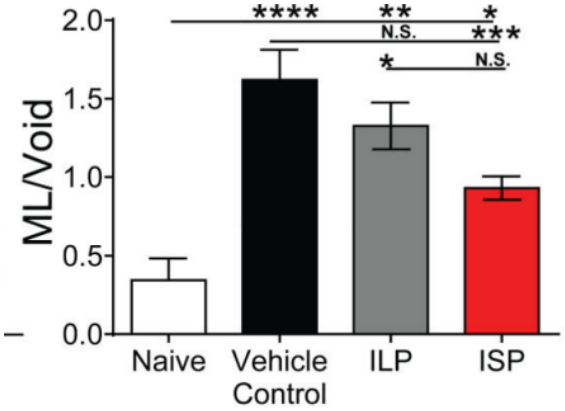
Lang et al. (2015) examined the modulation of PTPσ using NVG-291-R to promote recovery after SCI in mice. Beginning one day following contusive SCI, animals were treated with NVG-291-R (11µg/d), LAR wedge-domain Peptide (ILP; 11µg/d) or vehicle once daily for seven consecutive weeks. SCI disrupts connections between the bladder and brainstem micturition control center, leading to reduced void frequency and an accompanying increase in void volume (de Groat et al., 1990). Twelve weeks post injury, NVG-291-R promoted a significant 2-fold increase in void frequency (Figure 15) versus controls along with a significant decrease in void volume (Figure 16).

Figure 15 Functional Recovery following NVG-291-R Treatment – Void Frequency



(Lang et al., 2015)

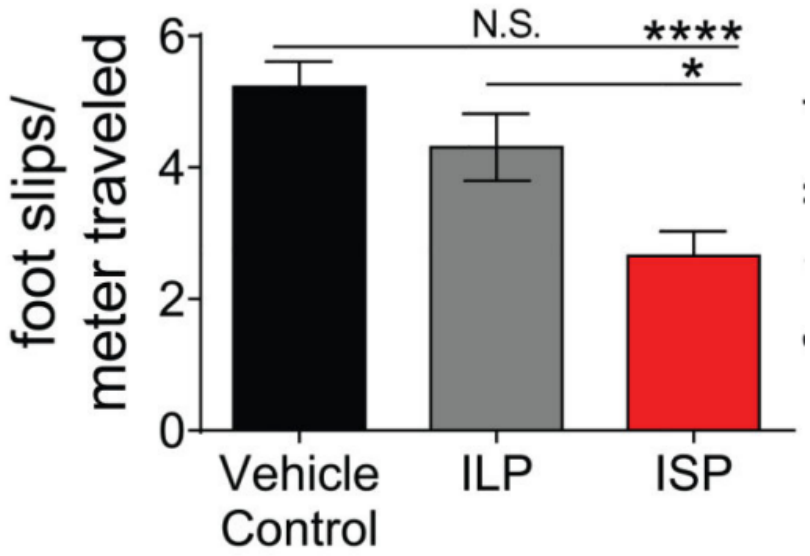
Figure 16 Functional Recovery following NVG-291-R Treatment – Void Volume



(Lang et al., 2015)

Lang et al. (2015) also measured locomotor recovery using the Basso, Beattie and Bresnahan (BBB) scale and a gridwalk test (Basso et al., 1995). Following SCI, vehicle and ILP treated animals recovered from hindlimb paralysis at day 1 to, on average, occasional weight bearing stepping at week 11. NVG-291-R treatment resulted in a significant progressive recovery of locomotion, which began several weeks after injury. Thirty percent of NVG-291-R treated animals (versus zero Vehicle/ILP treated) demonstrated, at least, frequent coordinated stepping (BBB≥13) with three animals achieving BBB scores ≥17.5. Furthermore, NVG-291-R treated animals made on average 58% fewer foot slips than control animals on the gridwalk test, suggesting recovery of sensorimotor coordination and balance (Figure 17).

Figure 17 Functional Recovery following NVG-291-R Treatment - Gridwalk



(Lang et al., 2015)

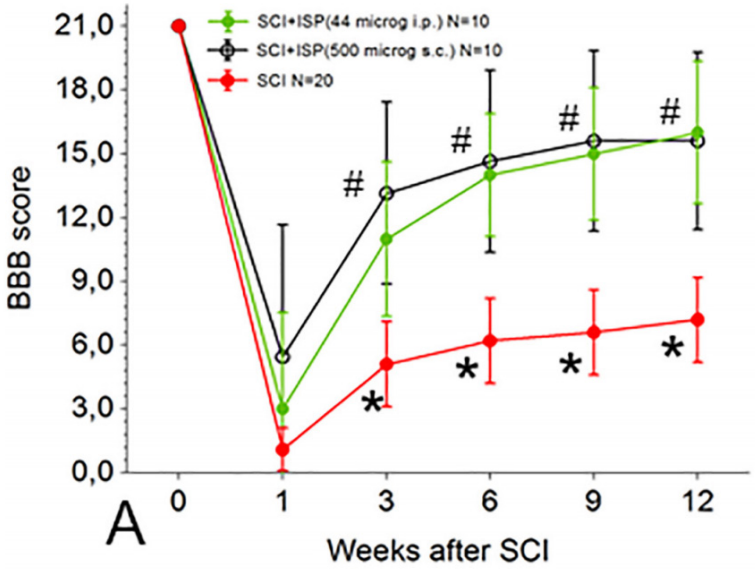
Rink et al. (2018) examined the recovery of rats after SCI by modulation of PTPσ using NVG-291-R. Following SCI at the Th10-segment, 40 rats were distributed in three groups. Animals in group 1 (20 rats) were subjected to SCI but received no treatment. Rats in group 2 were treated with IP injections of 44 µg/day NVG-291-R (SCI + ISP44) and animals of group 3 were treated with SC injections of 500 µg/day NVG-291-R (SCI + ISP500) for 7 weeks after lesioning. Recovery was analyzed at 1, 3, 6, 9 and 12 weeks after SCI by determining:

1. BBB-score,
2. Foot-stepping angle,
3. Rump-height index,
4. Number of correct ladder steps,
5. Bladder score, and
6. Sensitivity.

In normal intact animals, i.e. pre-injury, BBB scores were 21. At 1 week following surgery the scores dropped significantly in all groups (SCI: 1.1 ± 1.0; SCI + ISP44: 3.0 ± 4.5; SCI + ISP500: 5.4 ± 6.2) which showed that the model of spinal cord compression produced a severe injury. At first sight the BBB scores of 1.1 in the SCI group and 5.4 in the SCI + ISP500 group may suggest that NVG-291-R has had some neuro-protective effects or that both treatment groups were not injured to the same extent as the control groups. As far as the differences between 1.1. and 3.0 and 5.4 points is concerned, were not statistically significant, most probably due to the large standard deviations (SD).

The fact that mean BBB scores did not differ between the three groups at 1 week after SCI indicated, as expected, equivalence among groups in lesion severity. Thereafter, at 3, 6, 9 and 12 weeks, a statistically significant ($p < 0.05$) improvement occurred in groups SCI + ISP44 and SCI + ISP500 when compared to the control SCI group. No differences between both "all animal" cohorts with NVG-291-R treatment were detected (Figure 18).

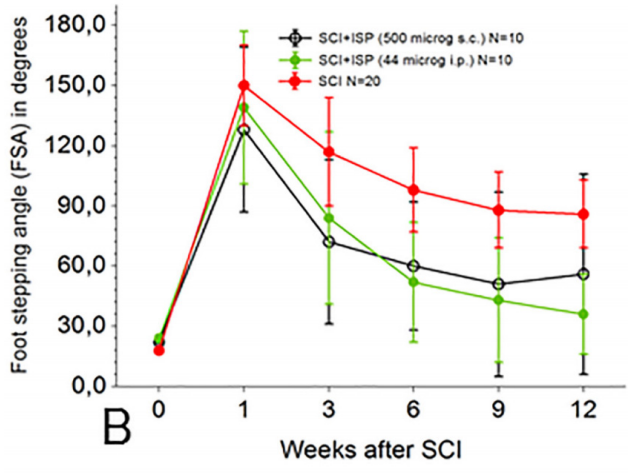
Figure 18 Time Course of BBB Motor Score Values Measured in All Animals



(Rink et al., 2018)

A foot stepping angle (FSA) larger than 90° indicates that the toes and the dorsal paw surface, rather than the plantar surface, touch the ground during normal ground locomotion. Compared to pre-injury values (~20°), at one week following surgery, FSA was significantly higher in all three groups (SCI: 150.0 ± 20.3°; SCI + ISP44: 139.0 ± 38.0°; SCI + ISP500: 128 ± 41.0°; $p < 0.001$). There was only a slight and gradual improvement in each group over time, but the mean values even at 12 weeks after SCI remained higher than those measured in intact rats. In addition, there were no significant differences between the three groups ($p > 0.05$); Figure 19).

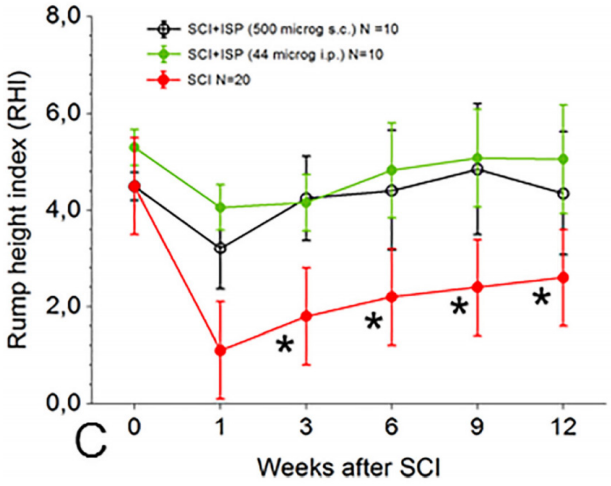
Figure 19 Time Course of Foot Stepping Angle Values Measured in All Animals



(Rink et al., 2018)

Rump height index indicates the ability of the hind limbs to support body weight during ground locomotion. After an initial postoperative drop in the values at one week after surgery, the rats of the untreated SCI group started a gradual recovery. However, the values measured for this group at 3, 6, 9 and 12 weeks remained significantly lower than those for groups SCI + ISP44 and SCI + ISP500 (Figure 20).

Figure 20 Time Course of Rump Height Index Values Measured in All Animals

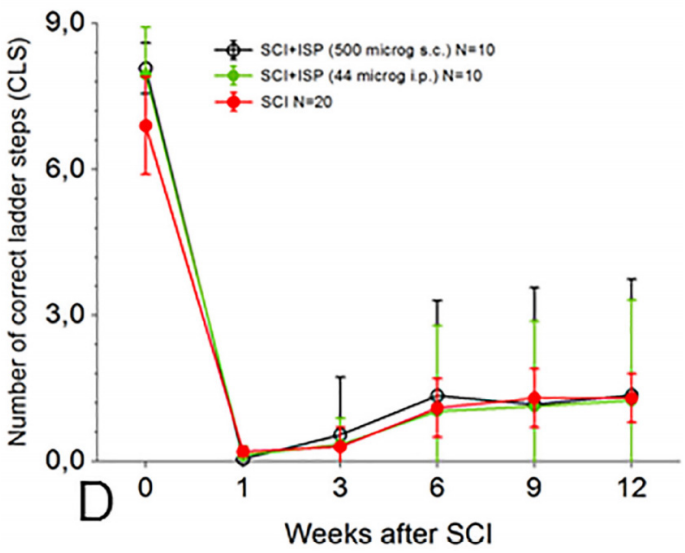


(Rink et al., 2018)

During inclined ladder climbing, proper paw placement and maintaining the paw on the rungs to support body weight require high levels of motor and sensory control. Compared to pre-injury values (7.0–8.0) the number of correct steps was significantly reduced at one week following surgery in all groups (Figure 21). There was no effect of treatment or interaction of time with treatment ($p > 0.05$). In other words, there was no significant improvement with time in either group, nor were there any significant differences in correct ladder steps (CLS) be-

tween groups ($p > 0.05$).

Figure 21 Time Course of Number of Correct Ladder Steps Values Measured in All Animals

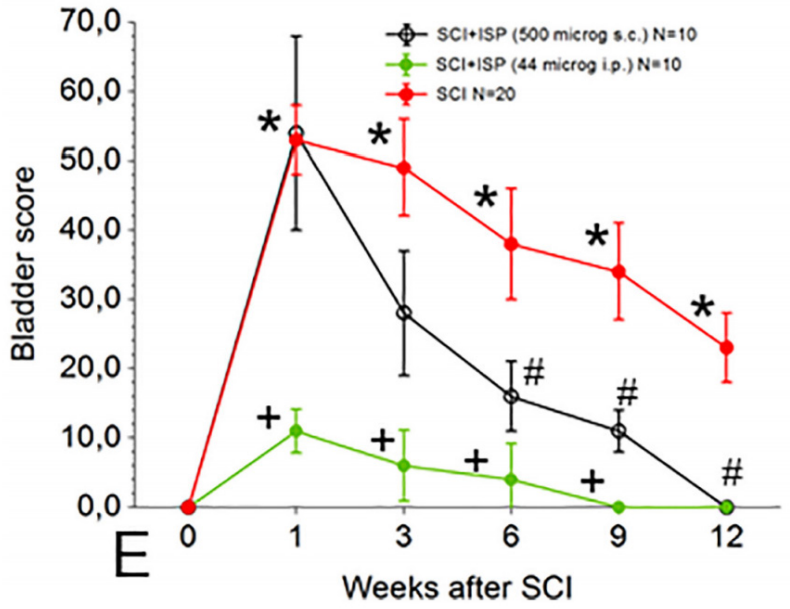


(Rink et al., 2018)

For bladder function, higher scores are indicative for worse function. Compared to pre-injury values (0), at one week following surgery, scores were significantly impaired in all groups; the majority of animals were unable to void the bladder spontaneously. Starting at the third week after SCI, all animals began to restore micturition control. However, the untreated group recovered most poorly but, interestingly, the SCI + ISP44 group improved bladder function better than the SCI + ISP500 group (Figure 22). A possible reason for this difference is unknown but could be related to the route of drug application (IP versus SC).

The dry wet (mean ± SD) of the untreated SCI group (lower row Figure 22) was 130.01 ± 91.48 mg and that of the SCI + ISP500 SC group (upper row Figure 22) – 61.71 ± 20.62 mg. Earlier own measurements on the dry weight of the urinary bladder in intact rats (though of another strain) showed an average mass of about 30 mg.

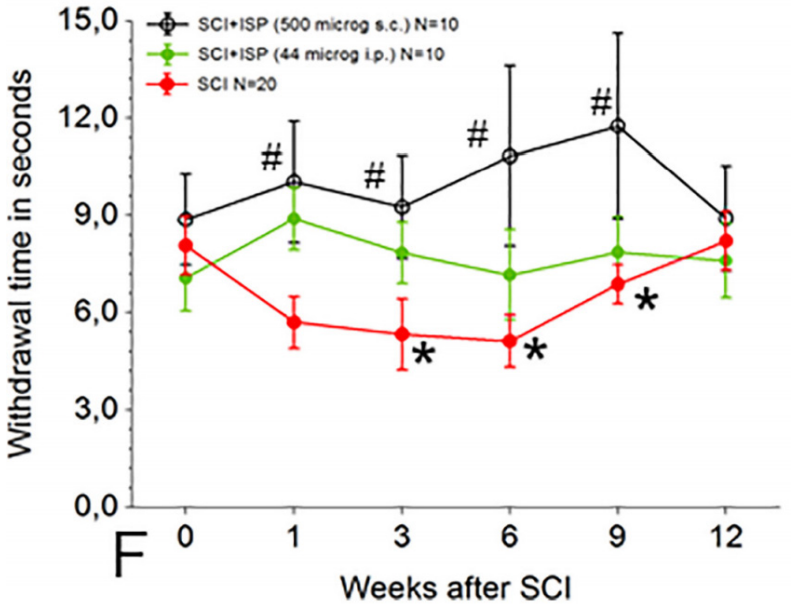
Figure 22 Time Course of Bladder Score Values Measured in All Animals



(Rink et al., 2018)

For the thermal sensitivity test, pre-injury withdrawal latencies were similar for the left and right paws as well as for the tail (range: 7.1 ± 1.0–8.9 ± 1.4 seconds). Following decreases in the withdrawal time at 3, 6 and 9 weeks, the rats from the SCI group recovered completely and reached the pre-operative average value of about 8 seconds at 12 weeks after SCI. In contrast, after an increase in time at 1, 3, 6 and 9 weeks, the rats from the SCI + ISP500 group also restored the average mean value of 8 seconds (Figure 23).

Figure 23 Time Course of Withdrawal Time Values Measured in All Animals



(Rink et al., 2018)

The first systematic study that independently evaluated and compared the effects of IP versus SC application of NVG-291-R following compressive SCI. They used an established palette of functional measures (all performed blinded) and also examined the number of serotonergic fibers in the vicinity of the lesion site. The results showed that, compared to SCI alone, SCI combined with NVG-291-R therapy has a clear beneficial effect. In fact, NVG-291-R therapy especially in the responding animals resulted in a definite improved locomotor and urinary function as assessed by the BBB score, rump-height index, bladder score, bladder hypertrophy and withdrawal latency. There was also confirmation that NVG-291-R increased serotonin expression in the preserved neural tissue bridges around the lesion.

The findings in SCI models have been bolstered with similar reversal of nerve injury and enhanced physiological recovery in acute myocardial infarction (MI) (Johnsen et al., 2016; Gardner et al., 2015; Sedaghat et al., 2017) ventral nerve root avulsion (Li et al., 2015), dorsal nerve root crush (Yao et al., 2019), enhanced remyelination in a rodent MS models (Luo et al., 2018; Niknam et al., 2019) and SCI model (Dyck et al., 2018b), and immune modulation in SCI models (Luo et al., 2018; Dyck et al., 2018a). NVG-291-R's modulation of PTPσ also has effects within the peripheral nervous system (PNS). The root avulsion and root crush models data as well as the acute MI data support the ability of NVG-291-R to facilitate nerve regeneration and functional recovery following peripheral nerve injury.

Conclusions

NervGen is a publicly traded biotech company dedicated to discovering and developing treatments for patients suffering from medical conditions related to nerve damage, resulting from injury, neurodegenerative disease, or other causes. NervGen's core technology targets a novel receptor called protein tyrosine phosphatase sigma or PTPσ. PTPσ is present in the central nervous system and the peripheral nervous system and plays a key role when there is nerve damage since it impedes nerve regeneration, inhibits plasticity and remyelination.

NervGen's lead product NVG-291 is a specific and selective PTPσ inhibitor. Multiple studies in various animal models have shown that treatment targeting PTPσ receptors promotes regeneration of damaged nerves and improves function. Currently NVG-291 is being developed to treat Alzheimer's disease, multiple sclerosis, and spinal cord injury, each of which has significant market potential.

Neuronal pathology and axonal injury are major contributors to progressive and permanent disability in AD patients. Modulating PTPσ has the potential to alter AD pathology by promoting regeneration at areas of nerve damage, plasticity in intact areas of the brain and by dampening Aβ production. NervGen is currently enrolling a Phase 1 safety study in healthy volunteers. Pending positive results in healthy volunteers, NervGen intends to initiate a Phase 1b AD study. The primary objective for including AD patients will be to study the safety and PK profile of NVG-291 in both elderly and AD patients. Additionally, NervGen plans to include various biomarker and cognitive tests to identify early signals of efficacy. The Company also plans to initiate Phase 2 trials in spinal cord injury and multiple sclerosis after completion of Phase 1 and after resolution of FDA's partial clinical hold. NervGen currently expects it will be able to initiate these trials in mid-2022.

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