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Deliverable 1: Griffith University OEC "3D Nerve Bridge" Trial Dossier

Executive Summary (Key Points as of Jan 2026)

- **World-First SCI Cell Transplant Trial:** Griffith University (Queensland, Australia) has launched a *Phase I/IIa* clinical trial implanting patients' own olfactory ensheathing cells (OECs) – specialized nasal support cells – seeded in a *3D "nerve bridge"* scaffold into chronic spinal cord injury (SCI) lesions [1] [2]. It's the first trial globally to combine an engineered OEC tissue transplant with intensive rehabilitation in chronic SCI.

- **Trial Design:** 30 adults with chronic traumatic SCI (≥4 months post-injury) will be recruited, with **20 receiving the OEC transplant plus rehab and 10 receiving rehab-only** as controls [3] [4]. It is a randomized, assessor-blinded, controlled trial (the first of its kind for an OEC therapy), conducted at Gold Coast University Hospital with rehab at specialized centers in Queensland, New South Wales, and Victoria [5] [6]. Primary endpoints focus on *safety* and *feasibility*, with secondary endpoints tracking any neurological and functional improvements [7] [8].

- **The "3D Nerve Bridge" Intervention:** A small nasal biopsy from each participant provides OECs (and supporting cells) which are purified and grown into a **3D cell-packed scaffold ~1–2 cm long** (described as "the size of a very small worm" by the researchers) [9]. Uniquely, the bridge consists *entirely of the patient's own cells* – no synthetic materials – to avoid immune issues [10] [11]. During neurosurgery, surgeons open the spinal cord scar, *remove inhibitory scar tissue*, and place these living cell bridges into the injury gap to encourage neural regeneration [12] [13]. The transplant is followed by *8 months of high-intensity rehabilitation* to stimulate reconnection (on top of 3 months of "priming" rehab before the surgery) [7] [14].

- **Mechanism – Harnessing Olfactory Repair Cells:** OECs normally enable continual regeneration of olfactory neurons in the nose. They secrete growth factors, clear debris, and guide new axons to grow through the *PNS–CNS boundary* into the olfactory bulb [15] [16]. In the spinal cord, transplanted OECs are thought to create a growth-permissive environment ("cell bridge") that fosters regrowth of severed axons and sprouting of new connections across the injury site [10] [17]. Notably, preclinical studies have shown OEC transplants can remyelinate axons and restore some function in animal SCI models [18]. The long-term intensive exercise therapy is included because activity-dependent plasticity is critical – the goal is that nascent connections formed via the nerve bridge will be strengthened and integrated into functional circuits through rehab [19] [20].

- **Funding and Team – Community-Driven:** This trial is the result of ~8 years of translational research by the **Griffith Clem Jones Centre** team led by **Prof. James St John**, building on the legacy of the late Prof. Alan Mackay-Sim (a pioneer of OEC research) [21] [22]. It is primarily funded by Australian government grants and *philanthropic SCI organizations* – notably the Perry Cross Spinal Research Foundation and the Clem Jones Foundation – along with many individual donors in the SCI community [23] [24]. Over **A$5.7 million** in donations was raised to launch the trial [25] [26]. The trial design was *co-created with SCI consumers*: a national panel of people living

with SCI provided input on what outcomes matter and how to maximize safety and participation [27] [25]. A medical advisory board including a neurosurgeon, an ENT specialist (for the nasal biopsy), rehabilitation experts, and a consumer advocate oversees the study [28] [29].

- **Status (Jan 2026): Recruitment is ongoing** via an expression-of-interest process [5]. The trial officially commenced in mid-2025 with the first participants enrolled [30] [31]. As of early 2026, no efficacy results have been announced – the focus is on enrolling and treating the initial cohort safely. The anticipated first participant surgical transplant occurred around April 2025 (per the plan of first surgery ~Q2 2025) [32], and more surgeries are proceeding at roughly 2-month intervals thereafter [32]. **No serious adverse events have been reported publicly to date**, and an independent ethics board monitors safety. Final data collection is expected by 2028 [33], after each participant completes ~15 months in the study. Any *interim findings* (even anecdotal) are being kept blinded and confidential to maintain trial integrity – though the researchers emphasize they are "aiming low and hoping high" for signs of regeneration [34] [35].

- **High Hopes vs. Realism:** This trial has drawn global attention and hope among people with paralysis – it's described as a potential *"breakthrough"* after decades of SCI research [36] [37]. However, experts urge caution: OEC transplants have a **history of mixed results**. Early open-label human studies showed safety but only modest functional improvements in a few cases, and a *notable complication* in one past study where nasal tissue grafts formed benign tumors in some patients years later. The Griffith team has learned from those trials (e.g. using purified cells rather than whole tissue to avoid rogue stem cells). Still, this is fundamentally an exploratory Phase I trial – its main goal is to show the procedure can be done safely and to gauge any hint of efficacy. It is **not expected to miraculously "cure" paralysis**, and headlines calling it "on the verge of curing paralysis" are **overhyped** [38]. Any functional gains will likely be incremental (e.g. a few muscle groups improving, better sensation, bladder or blood pressure improvements) – which, for individuals, can still be life-changing – but the investigators themselves stress that this is "the first step" and further improvements or combination therapies would be needed beyond this trial [35] [39].

- **What to Watch Next:** Key next milestones include **completion of enrollment** of all 30 participants (projected by late 2026 if recruitment criteria are met), *interim safety analyses* after the first several surgeries, and initial efficacy observations (e.g. through imaging or neurological exams) which might be presented at conferences if compelling. The team has indicated that comprehensive results (including MRI evidence of cord regeneration and functional outcomes vs. control) will be analyzed after follow-ups are complete (~2028) [33]. In the meantime, **preclinical data publications** supporting the approach are expected to be published once patent filings are secured – likely in 2025-2026 [40]. By 2026, we'll be looking for any *early signals* – for example, an anecdote if a participant in the treatment group shows improvements that control participants do not (bearing in mind placebo and training effects). Importantly, the trial's **built-in control group** will allow the field to finally get rigorous evidence about OEC therapy's efficacy. If this trial shows even a trend of benefit, it would justify larger Phase II/III trials (and attract industry partners to scale up manufacturing of the cell therapy) [41] [42]. If it shows safety but no efficacy, researchers will analyze why (e.g. not enough cells? rehab duration? chronic scar too mature?) and adjust strategies – but that outcome would temper enthusiasm and refocus efforts on alternative approaches.

Timeline of Development

- **1980s–1990s – Foundational Research:** Scientists observe that *olfactory ensheathing cells* (OECs) in the nasal system support continual nerve regeneration [15]. Initial animal experiments (e.g. in rats and cats) show transplanted OECs can migrate and remyelinate damaged spinal axons [43]. This spurs the idea of using a patient's own olfactory cells to repair the spinal cord.

- **2002–2003 – First Human Tests:** A team in Lisbon (Carlos Lima, MD) performs pioneering surgeries transplanting autologous olfactory mucosal tissue into the injured spinal cords of about ~7 patients (open-label). Results reported in 2006 indicate the procedure is **safe** and a couple of patients had slight improvements (e.g. better bladder control), but no robust neurological recoveries. In the following decade, however, some of those patients developed *mucus-secreting cysts (nasal polyps)* in the injury area – a consequence of transplanting whole nasal tissue with glandular cells included. This highlighted a safety risk of unpurified transplants.

- **2014 – A Case of Notable Improvement:** In Poland, surgeons (Tabakow et al., collaborating with U.K.'s Geoffrey Raisman) transplant bulbar OECs (from the olfactory bulb in the brain) combined with a peripheral nerve graft into a man with a complete thoracic SCI. The patient (D. Fidyka) regains the ability to slowly walk with braces and recover some sensory function. This single-case result, published in *Cell Transplantation*, creates a media sensation. While encouraging, it lacked controls – making it hard to know if improvements were due to the OECs, the nerve graft, intensive rehab, or all of the above.

- **2017 – Recognition of OEC Research:** Prof. **Alan Mackay-Sim** – who led a 2002 Brisbane safety trial of OEC transplants – is named *Australian of the Year* for his stem cell and OEC work. He and collaborators (including Prof. James St John) have been refining OEC culture methods and addressing past challenges (like cell purity). Around this time, St John's lab develops a technique for growing OECs in 3D spheroid "marbles," aiming for a scaffold-free cell graft [44] [45].

- **2018–2019 – Project Formation:** The *Perry Cross Spinal Research Foundation* (founded by Perry Cross, a C2 ventilated quadriplegic advocate) partners with Griffith University, securing major donations and Queensland state support. The initiative is dubbed the **"Spinal Injury Project (SIP)"**, aiming to take OEC nerve bridges to clinical trial. A *consortium* forms, including Griffith scientists (St John, neurobiologists Jenny Ekberg, Dinesh Palipana, Marie V. etc.), clinicians (neurosurgeon Dr. Michael Redmond, rehab specialists), and a consumer advisory panel of SCI community members [28] [27].

- **2020–2022 – Preparatory Research:** The team publishes a detailed *position paper (Ekberg et al., Front. Neurosci. 2022)* reviewing all prior OEC clinical trials and outlining "best practices" for a successful trial design [43] [46]. Recommendations include: use **nasal OECs** (accessible and safer than brain tissue harvest), ensure **high cell purity** (to avoid non-OEC contaminants), **3D format** to keep cells in an aligned structure (rather than injecting a cell suspension, which often disperses), and incorporate **intensive rehabilitation** post-transplant [47] [46]. During this period, laboratory experiments (unpublished as of 2026) refine the 3D OEC "nerve bridge" – reportedly using techniques like **electrospun nanofibers** to guide OECs into cord-like constructs [48]. By late 2022, the team has developed a protocol to grow patient-derived OECs into ~10mm long living bridges that remain viable for implantation (patent applications filed in 2024).

- **Jan–Mar 2024 – Regulatory Green Light:** After years of safety/toxicology testing and ethics review, the trial wins *Human Research Ethics Committee (HREC)* approval in Australia (HREC/2024/

QGC/105231) [49] [50]. The study is registered on the Australian New Zealand Clinical Trials Registry on 3 April 2024 (ACTRN12624000391572) [51] [52]. Notably, the trial is *sponsored by Griffith University* itself (an academic sponsor model) [53], with governance to ensure independence and safety oversight.

- **Mid-2024 – Enrollment Begins:** The trial opens for enrollment mid-2024 (original projections hoped for first patient in August 2024) [54]. Dozens of people express interest; over **300 inquiries** are received, including some from overseas (one determined American relocated to Australia hoping to qualify) [55] [56]. Stringent inclusion criteria (see next section) and logistical demands limit eligible participants. The study team schedules participants in a staggered fashion due to the resource-intense rehab and cell processing.

- **Aug 14, 2025 – Public Announcement:** Griffith University officially announces that the "world-first" trial has commenced, calling it "three decades in the making" since the initial discovery of OECs [30] [57]. This press release, amplified by news media, strikes a hopeful tone that this could *"challenge the notion that recovery is impossible"* in chronic paralysis [58] [59]. It emphasizes that primary outcomes are safety, but the team will also measure changes in function that "are important to people living with SCI" (e.g. bladder, hand movements, standing ability) [7] [60].

- **Late 2025 – First Surgeries and Ongoing Rehab:** By the end of 2025, a small number of participants have undergone the OEC transplantation surgery and are in the long post-surgery rehabilitation phase. For example, the first participant (enrolled Q2 2025) would complete their 8-month post-transplant rehab around mid-2026. The control group participants, who do rehab-only, mirror these timelines minus the surgical events. The trial remains *blinded* (outcome assessors do not know who got the cell transplant) to preserve objectivity [61]. Participants and clinicians remain cautiously optimistic as they progress through therapy – any noticeable improvements are closely guarded until data lock. The research team frequently engages with the SCI community via webinars (e.g. the **Nov 19, 2025 "Hope, Science, and Breakthroughs" webinar** led by Prof. St John) to provide general updates and manage expectations.

- **2026 and Beyond – Next Steps:** Enrollment is expected to continue into 2026 to reach the full sample of 30 (the timeline was likely affected by the complexity of screening and the intensive support required – as of early 2026 they may still be recruiting the last few slots). If interim safety data are positive and no red flags emerge, the team may seek approval to expand to a Phase II trial (perhaps including more sites or a broader population). However, given the pioneering nature, they will likely finish this controlled study first. **Final results** (with all participants' 48-week outcomes) are anticipated to be analyzed in 2028 [33], with publication in a peer-reviewed journal thereafter. In parallel, the cell manufacturing process will be further refined for scalability – if results are favorable, the researchers will aim to partner with industry or government programs to support a larger trial and eventual clinical implementation.

(Timeline compiled from trial registry updates, press releases, and statements by the research team [S1][S2][S3]).

Mechanism of Action (Plain English)

How it works: This experimental therapy essentially attempts to *"bridge the gap"* in a severed spinal cord using the patient's own repair-capable cells. Normally after an SCI, scar tissue and cystic cavities form, blocking any regrowth of nerves. The idea here is to fill that gap with a **living bridge of olfactory**

ensheathing cells (OECs), which are naturally adept at supporting neuron growth. OECs function in the olfactory system to guide new sensory neurons from the nasal lining into the brain every day (the olfactory system is one of the only parts of the adult nervous system that continually regenerates) [15]. They *ensheath* olfactory nerve fibers rather like Schwann cells do in peripheral nerves, and they also secrete molecules that promote axon growth and remyelination.

In the spinal injury context, when these OECs are placed into the injury site, they can **help phagocytose (clean up) inhibitory debris** and potentially produce a more favorable environment for neurons to extend new processes [16] [62]. The "nerve bridge" acts like a scaffold guiding any surviving axons from above and below the injury to grow into and through the lesion, possibly reconnecting with each other. Essentially, the OECs *replace scar tissue with a regeneratively permissive tissue*. Animal studies have shown OECs can *remyelinate* demyelinated axons (restoring electrical conduction) and even form **"tunnel"-like structures** that axons can grow through [15] [16]. Unlike other cell types, OECs are unique in being able to intermix with both CNS cells and peripheral cells, potentially bridging the interface.

Why intensive rehab is paired with it: The exercise therapy is not just a bonus – it's an integral part of the mechanism. In a sense, the cell transplant gives latent neural connections a chance to regrow, and the rehabilitation provides the *activity and cues to reinforce those new connections*. Animal research and prior human experience show that activity-based training can strengthen weak signals and encourage neuroplasticity. After the transplant, participants do 32 weeks of *personalized, intensive training (up to 3 hours per day, 5 days a week)* [63] [64] focusing on the areas below their injury – for example, assisted stepping, electrical stimulation of muscles, task-specific practice for hands, etc. The hypothesis is that this will drive any sprouting axons to form functional synapses and networks. As Prof. St John analogized, *"The more activity you do, the more likely it is that connections will be established"* [64]. Without this rehab, any new axonal growth might be uncoordinated or not integrated into movement patterns.

Targets for improvement: The trial is measuring many outcomes, but key areas they hope to impact include motor function (strength, dexterity), sensory function, and autonomic functions. For instance, even a small amount of reconnection in the spinal cord could potentially *restore some voluntary movement or sensation* below the injury. In a cervical injury, that might mean improved hand or arm function; in thoracic injuries, perhaps some trunk control or even limited leg movement. Autonomic improvements (like better bladder/bowel control or blood pressure regulation) are also possible and critically important to quality of life [65] [66]. OECs are not magic, but if they can even partially reconnect pathways, the nervous system might regain some reflexes or control that were lost.

Scientific unknowns: There are many open questions about the mechanism. For example, *which axons will regrow*? It could be long motor axons re-growing down through the graft, or shorter local circuit neurons sprouting new connections. The trial includes advanced MRI imaging (DTI tractography) to see if new nerve tracts appear across the injury [8] [67]. They're also analyzing *somatosensory evoked potentials (SSEPs)* to see if sensory signals can cross where they couldn't before [68] [69]. Additionally, cerebrospinal fluid biomarkers are being collected to identify molecular signs of neural repair or growth (e.g. changes in proteins like growth factors, markers of nerve injury, etc.) [70] [71]. These mechanistic data will help confirm if the OECs are truly inducing regeneration or if any improvements are due to other factors.

Why olfactory cells? They are one of the few cell types one can take from a patient that inherently know how to support CNS axon growth. Alternatives like Schwann cells or stem-cell derived cells have been tried, but OECs uniquely traverse the boundary between central and peripheral nervous system tissue, which is analogous to the environment of a spinal injury. Also, using the patient's own cells avoids immunorejection. As Dr. St John noted, autologous OEC transplants mean *"immune rejection is not*

an issue" [62] – the cells are recognized as 'self'. This allows transplantation without immunosuppressant drugs.

Technical Appendix (Cell Processing & Implantation): Each participant's olfactory mucosa (inside the nose) is biopsied under anesthesia, typically yielding a small sample (~5–10 mg of tissue) from the upper nasal turbinate. This contains OECs intermingled with olfactory nerve fibroblasts and other cells. In the lab, technicians use enzymatic digestion and selective culture techniques to enrich for OECs. According to the team's publications, they culture the cells first in traditional monolayers, then transfer them into a *3D culture system known as a "liquid marble"*, where cells aggregate into spheroids without any artificial scaffold [44] [72]. By adjusting cell density and mild agitation (even using vibration at set frequencies), they can cause multiple spheroids to fuse or align, forming an elongated tissue-like construct [73] [74]. The final "nerve bridge" is essentially a bundle of OEC-rich tissue, roughly cylindrical, sized to fit the patient's lesion cavity (1–2 cm length, thickness matching cord diameter). Up to **60 million cells** can be loaded into the graft for larger injuries [75] [76]. Notably, early experiments with collagen or polymer scaffolds were considered, but the team opted for a **scaffold-free** approach to simplify regulatory approval and because the cells themselves can form structure [77] [41].

During surgery, a laminectomy is performed at the injury level, the dura (protective covering) is typically opened, and any scar tissue or adhesions within the injury site are carefully resected [55]. Surgeons then place one or more of the cell bridges into the lesion gap – they might snugly fill a cavity or be laid in between spinal stumps if a gap is present. The procedure takes about **3–4 hours** including cell implantation [75] [78]. No scaffolding material means the cells must stay in place on their own; fibrin glue or a gentle covering might be used to keep them from dislodging. The dura is closed, and standard post-op care ensues. Patients spend a few weeks recovering before resuming rehab.

Overall, the mechanism combines *biological repair* (via cell transplant) with *activity-based reinforcement* (via rehab). It attacks two key barriers of chronic SCI: the physical void/scar (filled by the OEC bridge) and the neural disconnect/lack of use (addressed by activity to drive reconnection).

Intervention Details (Cells, Scaffold, Surgery, Rehabilitation)

Cell Source & Processing: The cells used are autologous **olfactory ensheathing cells (OECs)** derived from the patient's own nasal lining. The olfactory mucosa is accessed endoscopically through the nostril – a small biopsy is taken from high inside the nose, near the olfactory epithelium. This biopsy is relatively minor (often done under light general anesthesia or heavy local anesthesia). After harvesting, the tissue is transported to a clean lab (GMP-grade facility) where it's enzymatically dissociated. The cell mixture is then cultured. Initial cultures yield a mix of OECs and olfactory nerve fibroblasts – these two work together in vivo, and the team's position paper noted some presence of fibroblasts might actually be beneficial [46], but an overly fibroblast-heavy graft could cause scarring or overgrowth. So they likely perform steps to favor OEC growth (e.g. specific growth medium, differential adhesion times). By the end of the expansion phase (which might be 4–6 weeks), they aim to have tens of millions of OECs. Quality control includes immunostaining for OEC markers (like p75^NTR, GFAP) to verify identity, and sterility tests to ensure no infection.

3D Nerve Bridge Fabrication: Once enough cells are grown, they are formed into the 3D "nerve bridge." As mentioned, this is done by seeding cells into a droplet of culture medium on a super-hydrophobic surface, creating what's called a "naked liquid marble." Inside that droplet, cells naturally aggregate into a spherical mass (imagine a tiny ball of cells). The team has published methods to fuse multiple spheroids by carefully manipulating the droplets or using mild vibration to encourage the

spheres to merge [79] [80]. They can also adjust the spheroid size by starting cell number. The final shape needed is an elongated piece. It's not explicitly detailed publicly *how* they achieve a linear shape – but one approach could be to line up several spheroids in a tiny channel or mold so they join into a rod. Another clue: prior work in the field involved **electrospinning nanofibers** that OECs could grow along [81]. The U2FP report hints Prof. St John's team may have used an electrospun fiber scaffold during culture that is later removed [48] – meaning the cells align along the fibers to form a cord, and then the scaffold material (likely biodegradable) is dissolved, leaving a cell-only cord (this would reconcile the "only the participant's own cells" statement with the need to shape the graft). The nerve bridge, once formed, is kept alive in a special medium until surgery.

Surgical Implantation: The neurosurgery is performed in a major hospital operating theater (Gold Coast University Hospital). The patient is under general anesthesia. The surgeon (Dr. Redmond, per the team roster) first re-exposes the injured segment of the spinal cord. If there is metal hardware from prior spine stabilization that obscures imaging or access, it may be removed in a prior operation [82] [83]. Once the bone and dura are opened, the fibrous scar in the injury is delicately removed – this can be risky, as sometimes the scar is adherent to spinal tissue. The goal is to create a "fresh" lesion cavity or gap where the graft can sit. The *olfactory cell nerve bridges* are then placed into this space, presumably filling it or bridging between the intact ends of the spinal cord [13]. If the injury gap is larger than one bridge, multiple pieces might be laid adjacent. The graft is not sutured (the cells wouldn't hold stitches); instead, the surgeon relies on the fit of the graft and perhaps a fibrin sealant to keep it in place. After placement, they close layers as normal. The operation is done under high-power microscopy to avoid any additional trauma. Patients then typically spend a week or more in the hospital recovering. There is a 4-week postoperative rest period with no rehab to allow wound healing and the graft to "settle" [84] [85]. During this time, immunosuppressants are *not* needed (autologous cells). Patients will be monitored for any signs of infection, CSF leak, neurological decline, or neuropathic pain.

Rehabilitation Protocol: The trial's rehab has two phases: a **12-week pre-surgery program** and a **32-week post-surgery program**, termed "priming rehabilitation" and "regenerative rehabilitation" respectively [14] [85]. Both are intensive, conducted at outpatient neuro-rehab centers (partner facilities like Making Strides in QLD, Royal Rehab in Sydney, and The Next Step in Melbourne) [6]. The *pre-hab* aims to maximize the participant's strength and health, and possibly stimulate the spinal cord in preparation for new growth. It involves up to **3 hours per day, 5 days a week** of activity-based therapy [63]. Exercises are tailored but can include: locomotor training on treadmills with body-weight support, functional electrical stimulation (FES) cycling or rowing to activate paralyzed muscles, upper body strengthening and task practice for those with arm function, balance and core exercises, etc. Participants are also educated in mental imagery techniques – imagining movements – which may help engage neural pathways even before any return of function.

After the transplant (and 4-week rest), the **8-month post-transplant rehab** begins. It follows a similar intensity: *5 days a week for the first 12 weeks*, then at least *3 days a week for the remaining 20 weeks* (with some allowance for break weeks) [86] [87]. This prolonged therapy is crucial because any regenerating axons grow slowly – a few millimeters per week at best – so by 8 months, if connections are forming, the participants are continually trying to use those pathways. The therapists will focus on below-injury movements that were absent or weak. For example, a participant with a T4 injury (paraplegia) might work on assisted stepping, standing with support, and trunk stability exercises daily. A participant with a C6 injury (tetraplegia) might do intensive hand grasp and release training with electrical stimulation on forearm muscles, etc. The regimen is exhaustive (one of the inclusion criteria is demonstrating commitment to this schedule) [86] [87]. Throughout, detailed logs of exercises are kept [88] [89] so researchers can quantify rehab "dose" and correlate it with outcomes.

Control Group Intervention: Importantly, the **control arm** does everything the treatment arm does *except* the nasal biopsy and cell transplant. Control participants undergo the same 12-week and 32-week rehab programs, with a simulated "break" during the period when the others have surgery (the control group gets a 4-week break after their priming rehab, mimicking the surgical recovery downtime) [90]. They do not undergo any sham surgery (for ethical reasons, likely), so they will know they didn't get the transplant. However, outcome evaluators and laboratory analysts are blinded to group assignments to reduce bias [61]. The control group is essential to distinguish effects of the rehab alone – since intensive rehabilitation itself can sometimes yield improvements even years after injury (via neuroplasticity of remaining pathways). In fact, this trial can also be seen as a study of *rehab vs. rehab+cells*. If both groups improve similarly, the cells may have added little; if the cell group improves significantly more, that suggests a true benefit of the transplant.

Outcome Assessments: Over the 48-week intervention, participants undergo periodic testing at the hospital: neurological exams (ISNCSCI motor/sensory scores), imaging (MRI/DTI at baseline, 12 weeks, 17 weeks (post-surgery baseline), 25, 37, 48 weeks) [91], neurophysiology (SSEPs and MEPs, including intra-operative monitoring of spinal cord conduction during the transplant surgery) [92] [69], and surveys of health and independence. They also measure secondary health outcomes like muscle bulk, bone density (perhaps via scans), metabolic changes, and psychological status, recognizing that a long rehab can improve overall health even aside from neurological recovery [93] [94]. This holistic approach follows the trial's broad aim to see if combined intervention improves "overall health and social wellbeing" in addition to any neurological gains [95] [96].

Safety Measures: From a safety standpoint, several steps are built in. Participants must meet strict criteria to reduce risk (for instance, excluding high-cervical injuries because those folks rely on ventilators and the surgery could jeopardize respiratory function) [97] [98]. The nasal biopsy can cause temporary loss of smell or minor bleeding; this is discussed in consent. During cell culture, extensive tests are done to ensure no contamination (the cells are grown under GMP conditions). Before transplant, cells are typically tested for sterility, and in some trials, karyotyping is done to ensure no chromosomal abnormalities in culture. The surgical team monitors for any sign of spinal cord irritation during the procedure (they even measure *somatosensory evoked potentials during the transplant surgery* to ensure placing the graft doesn't acutely harm existing pathways) [92] [69]. After surgery, participants are monitored for complications like infection, cerebrospinal fluid leak, or new/worsening neuropathic pain. An independent Data Safety Monitoring Board (DSMB) likely reviews any adverse events. Encouragingly, past OEC human studies (including 20+ patients in various uncontrolled trials) reported *few serious adverse effects* directly attributable to the cells [43]. The notable adverse outcome was the delayed growth of nasal polyps in a subset of Lima's patients ~7–14 years later, presumably from transplanted olfactory mucosal stem cells continuing to proliferate. The Griffith trial mitigates that by *not transplanting whole tissue*, only cultured cells largely comprised of OECs (which are non-tumorigenic differentiated glia). The researchers have explicitly acknowledged this history and have taken steps to "minimize potential adverse effects" by using **"stable 3D constructs that are substrate and scaffold-free"**, i.e. nothing that could encourage aberrant cell behavior [99]. In summary, every component – cells, surgery, and rehab – has been optimized to maximize the chance of *safe* neural repair.

Trial Protocol Overview

Title: *Safety, Feasibility, and Efficacy of Olfactory Cell Transplantation Therapy combined with Intensive Exercise Rehabilitation to Repair Chronic Spinal Cord Injury* (Griffith University Spinal Injury Project 03 – **GUSIP-03**) [52] [100]

Phase: Phase 1b/2a (Early Feasibility Study) – first-in-human for this specific combined therapy [95].

Design: Randomized, controlled, observer-blinded trial with two parallel groups (Cell+Rehab vs. Rehab-only). Ratio 2:1 (20 treatment : 10 control). Single-center for surgical intervention; multi-center for rehabilitation (three rehab sites). Duration per participant ~15 months (from baseline screening to final follow-up) [101] [85].

Key Inclusion Criteria: Adults (≥18 years, no upper age limit) with **chronic traumatic SCI** at least 4 months post-injury (must have completed initial rehab) [102] [103]. Neurologically stable for >2 months. Injury level **thoracic (T1–T12) or lower cervical (C5–C8)** [103] [104]. Severity **AIS A or B, or "motor ZPP" C** (i.e. motor complete or very limited motor function – defined in protocol as >75% of key muscles below injury have <Grade 3 strength) [103] [104]. Must be able to participate in intensive exercise (medical clearance required) and commit to 5x/week training for 12 weeks + 3x/week for 32 weeks [86] [87]. Ability to travel regularly to one of the rehab centers (in QLD, NSW, or VIC). Provide informed consent.

Key Exclusion Criteria: High cervical injuries (C1–C4) – excluded due to risk of respiratory complications during surgery [105] [98]. Penetrating injuries (e.g. gunshot) or concurrent brain injury. Significant peripheral nerve damage or orthopedic issues that preclude exercise. Severe spasticity or contractures that would interfere with training. Active medical conditions (e.g. uncontrolled diabetes, cardiovascular disease) that increase surgical risk. Any illness requiring immunosuppression (since that could complicate infection risk with transplant). Pregnancy. Prior experimental SCI treatment or cell transplant. (Note: Healthy volunteers are not involved – it's strictly patient-participants) [106] [107].

Interventions: - **Experimental Arm:** Autologous OEC "nerve bridge" transplantation into the spinal cord lesion, **plus** a high-intensity activity-based rehabilitation program. The cell transplant is a one-time surgical procedure (after 12 weeks of prehab) delivering up to *60 million cells in one or multiple 3D grafts* (~1–2 cm each) into the injury site [75] [108]. The rehab is delivered in two phases as described (total ~44 weeks of training) [14] [109]. - **Control Arm:** Intensive rehabilitation only, of identical duration/intensity, with no cell transplant. (Control participants continue their 12-week rehab, then take a 4-week break at the time the treatment group would get surgery, then resume another 32 weeks rehab) [90] [110]. Note: no sham surgery (ethical considerations), so the trial is *not double-blind to participants*. However, outcome assessors and analysts are blinded to group assignment to reduce bias [61].

Primary Endpoints: *(This trial uses multiple co-primary outcomes to evaluate feasibility, safety, and preliminary efficacy)* 1. **Feasibility – Recruitment & Retention:** Measured by the ability to enroll the target sample and have participants adhere to and complete the full 48-week program. The specific metric is recruitment rate (days to recruit) and completion rate of the intervention [111] [112]. *Rationale:* Demonstrating that chronic SCI individuals can be recruited and retained in a long, demanding trial is a key feasibility indicator [113] [114]. 2. **Safety:** Incidence of adverse events (AEs) and serious adverse events (SAEs) related to the intervention [115] [116]. This encompasses surgical safety, any complications from the cell transplant (infection, neurological decline, etc.), and safety of intensive training. All AEs are tracked and categorized (e.g. new neuropathic pain, autonomic dysreflexia episodes, lab abnormalities) [117] [118]. The primary safety outcome is essentially "no significant harm caused by the intervention" – composite of all AEs [115]. 3. **Efficacy (Structural Repair):** Change in *anatomical integrity of the injury site* on MRI-based measures [8]. This is a composite outcome looking at MRI indicators such as lesion size, tissue spared, and evidence of new bridging across the injury, as well as advanced imaging like **diffusion tensor imaging (DTI) tractography** to assess continuity of spinal tracts through the lesion, and possibly functional MRI (fMRI) for activation changes [8] [119]. These are assessed at baseline, 12wks (pre-surgery), and multiple post-surgery timepoints up to 48wks [91]. *Rationale:* In a Phase 1/2a trial, objective signs of neural repair (even before clear functional changes) would validate the biological effect of the transplant. 4. **(Additional Primary) Surgical Feasibility:** The protocol specifies evaluating

the feasibility of the surgical implantation itself – e.g. was the nerve bridge successfully placed as intended, any technical issues – and feasibility of delivering the long rehab and all assessments to participants (since it's a complex, multi-step intervention) [120] [121]. These are more qualitative but important to judge if a larger trial is practical.

(The trial initially listed 5 "primary" outcomes: recruitment feasibility, overall safety, MRI/tractography efficacy signal, plus two specific feasibility checks: that the surgical procedure can be done per protocol, and that participants can adhere to the rehabilitation and assessment schedule [120] [121]. In essence, it's establishing that each component of this combined therapy is implementable in humans.)

Secondary Endpoints: A broad array of functional and quality-of-life outcomes, measured at baseline and multiple points post-injury: - **Neurological Function (Clinical exam):** Changes in *ISNCSCI/ASIA scores* – motor level, sensory level, and AIS grade [122] [123]. This captures any improvement in key muscle strength or dermatomal light-touch/pin-prick sensation. Even small gains (e.g. from complete AIS A to sensory-incomplete AIS B, or moving one motor level down) would be noteworthy in chronic injuries. - **Upper Extremity Function:** Especially for cervical injuries – measured by *GRASSP (Graded Redefined Assessment of Strength, Sensation and Prehension)*, which evaluates hand and arm function in detail [124] [125]. Improvement in GRASSP could mean better grasp strength or dexterity – critical for independence. - **Lower Extremity & Mobility:** For those with lower injuries, measures like *10-meter walk test (10MWT)* for speed (if ambulatory at all), or *WISCI* (Walking Index for SCI) and *Timed Up and Go*, if applicable, to quantify any emerging walking ability. Also *Lower Extremity Motor Score (LEMS)* from the ASIA exam. - **Spasticity and Autonomic Function:** Presence/severity of spasticity (e.g. Ashworth scale) and episodes of autonomic dysreflexia or orthostatic hypotension frequency – since neural reconnection might modulate these. - **Bladder, Bowel & Sexual function:** Using standardized questionnaires (like SCI-QOL or specific indexes) to see if any return of voluntary voiding, improved continence, or erectile function, etc. The study specifically is monitoring bladder outcomes (the team mentions interest in changes in bladder/bowel which are life-changing even if motor gains are minimal [126]). - **Participant-Reported Outcomes:** Health-related quality of life measures (e.g. SF-36 or SCI-QOL), independence in daily activities (SCI Independence Measure – SCIM), and mood/psychological status. A key secondary aim is whether combined intervention improves "overall health and social wellbeing" [96] [127]. - **Electrophysiology Outcomes:** In addition to MRI, they measure *Somatosensory Evoked Potentials (SSEPs)* and *Motor Evoked Potentials (MEPs)*. SSEPs test if sensory signals can travel from below the injury to the brain; any reappearance or strengthening of SSEPs might indicate new conductive pathways [68] [128]. MEPs (via transcranial magnetic stimulation) test descending motor signal conduction. (Not listed as primary here, perhaps because MEPs are not expected if AIS A – but for any AIS C in study, they may track them.) - **Biomarkers:** Analysis of cerebrospinal fluid (obtained via lumbar puncture at baseline, and 16 & 18 weeks) and blood samples [70] [71]. They will look at ~7,000 protein markers (using a SomaScan proteomics panel) – with particular focus on biomarkers of inflammation and neural injury (e.g. *IL-6, IL-8, TNF-α, GFAP, neurofilament light (NF-L)*, etc.) [129] [130]. Hypothesis: a successful intervention might reduce chronic inflammation markers or neural damage markers over time. - **Imaging – Detailed:** Beyond the binary structural outcomes, MRI will be analyzed for *grey and white matter sparing*, any *tissue bridging* across the injury on T2-weighted images, and changes in spinal cord cross-sectional area. Diffusion tensor imaging (DTI) metrics like fractional anisotropy across the injury are recorded (hence the multiple timepoints including week 25, 37, etc., to track gradual changes) [91]. - **Safety Monitoring Metrics:** The secondary outcomes also include routine labs and health metrics: blood counts, liver function, etc., to ensure no systemic illness arises from the intervention [93] [131]. They also specifically test for any signs of infection by blood serology (HIV, Hepatitis, etc., largely to ensure patients didn't have these at baseline or that nothing was transmitted in the process) [132] [133]. Any unexpected finding (like abnormal growth on MRI, or neurological deterioration) would be documented as well.

Follow-Up Duration: Participants are formally in the study for about 50 weeks post-intervention start (with final evaluations ~2 weeks after completing the rehab program) [114] [134]. However, there may be longer-term follow-up for safety – e.g. yearly check-ins to ensure no late complications (common in cell therapy trials). In this trial, after week 48 they have a final assessment at week 50 (approximately 12 months from intervention start) [114].

Data Analysis Plan: Because of the small sample, analyses are mostly descriptive. They'll compare outcomes between groups (treatment vs control) and within individuals over time. Non-parametric or rank-based methods may be used given likely non-normal distributions of scores. Importantly, they plan to identify "responders vs non-responders" – e.g. who shows improvement on key outcomes – to generate hypotheses for why (perhaps relating to injury specifics or rehab dose) [3] [135]. The trial isn't powered to demonstrate efficacy statistically on functional measures due to sample size 30; any efficacy claims will be exploratory. Statistical significance is mainly targeted for the primary feasibility and safety metrics (which are usually just reported, not tested, except for showing recruitment goals met). They did set a *specific test* that **improvement in MRI/tractography at 48 weeks** in the treatment group over control would suggest efficacy – but we don't have details of the statistical threshold they aim for. Given the novelty, even one or two patients showing notable improvement in the treated arm and none in control would be considered a success to justify moving to a larger trial (with conventional power).

Regulatory Oversight: The trial operates under Australian regulations for clinical trials of biologicals. Autologous cell products in trials require notification to the Therapeutic Goods Administration (TGA); this trial is likely conducted under the Clinical Trial Notification (CTN) scheme with TGA clearance. Ethics approval was through a hospital HREC (Gold Coast Hospital HREC) in March 2024 [136] [137]. An independent monitoring committee oversees patient safety. The trial's registration indicates prospective registration and that it's *prospectively* approved, ensuring adherence to Good Clinical Practice.

Sponsor & Collaborators: Sponsor is **Griffith University** (Australia) [53]. Collaborators/Funders include: Perry Cross Spinal Research Foundation (a SCI community charity) [138] [139], Clem Jones Foundation (philanthropy) [140], Motor Accident Insurance Commission (Qld Government insurer, major grantor, per press statements) [23] [141], and the national Medical Research Future Fund (MRFF). No private biotech companies are involved at this stage, though *Griffith University's commercialization arm is on the advisory board* in anticipation of intellectual property development [28] [77].

In sum, the protocol is designed to meticulously evaluate whether this ambitious combined approach can be delivered safely and hint at repair in chronic SCI – something never proven before in a controlled trial. It is as much about *learning* (feasibility, biological effects) as about immediate patient benefit, given the phase and sample size.

(Protocol details synthesized from ANZCTR registry [S2] and Griffith trial documents [S3], with interpretation.)

Known Results & Claims (to Date) – Verification and Context

As of January 2026, no official efficacy results have been published from this trial, since it is still underway. However, a number of *claims and expectations* have circulated in media and community discussions. Here we clarify what is known and what is speculative:

- **"3.7-fold improvement" or other numerical improvements –*Not applicable yet in this trial*.** This figure appears to reference a different SCI trial (NervGen's NVG-291 peptide trial, which

reported a threefold increase in MEP signal – see Deliverable 2). It does **not** apply to the Griffith OEC trial. The OEC trial has not released any efficacy numbers like "% improvement" or "fold change" for participants, because those data remain blinded. Any such statistics online are either misattributions or relate to other studies. The Griffith team has been careful not to make quantitative claims prematurely – their public statements focus on what they hope to see (e.g. *hopes for participants to regain some bladder function, finger movement, or ability to hug a loved one*, as examples of meaningful outcomes [142] [126]) rather than giving actual improvement rates.

- **"On the verge of curing paralysis" – *False/misleading*.** This phrasing came from a news headline (Channel 9 News in Australia) covering the trial, not from the researchers themselves [143]. The scientists involved have explicitly **pushed back** on the notion of an imminent cure, emphasizing that we must set **realistic expectations** [38]. For instance, U2FP's science blog noted that calling this a cure is "an unfair expectation originating in the head of a headline writer" [38]. In reality, this trial is a first step – if it shows some benefits, that will be groundbreaking, but it would still require further trials and likely combination with other therapies to approach anything like a "cure." The history of SCI research is filled with hype that didn't pan out; the Griffth team is aware of this and thus talk about hope *with caution*.

- **Effectiveness in animals ("history books will be rewritten") – *Preclinical support exists, but unpublished*.** There have been some enthusiastic statements on social media that this OEC nerve bridge approach "worked in animals so well it will rewrite the history books." Let's temper that: The preclinical **evidence is promising but not yet fully in the public domain**. Prof. St John has mentioned that *"publications around the preclinical research will be coming out… once the patents are submitted"* [42] [144]. What we do know: in small animal models (e.g. rats with chronic SCI), OEC transplants have led to modest improvements in function in some studies [43]. The Griffith group reportedly achieved notable results in their *unpublished* experiments – enough to convince regulators to allow the human trial – but exact data haven't been disclosed. So while one can be optimistic, any dramatic characterizations ("history book changed") are **not substantiated yet**. Only a successful human trial can truly demonstrate efficacy.

- **Safety claims ("100% safe so far") – *Too early to conclude*.** It is true that earlier OEC clinical attempts did not report acute safety issues (aside from the late complication in the Portugal series) [43], and to date, there have been no reports of adverse events in this Griffith trial. However, "so far so good" is not the same as proven safety. The trial is ongoing and will systematically assess safety outcomes. The researchers have stated that ensuring safety is the top priority [145]. They have also structured the trial to avoid premature conclusions – it's **blinded** to avoid any placebo effect or bias in reporting improvements [61]. So while we can say *no safety red flags have emerged publicly*, the final verdict on safety will come upon trial completion. Participants are monitored for things like neuropathic pain increases, spasticity changes, or other medical issues. It's important to note that one person's anecdotal experience (e.g. "I felt great after surgery") is not evidence of overall safety or benefit – hence the rigorous controlled design. At this stage, **the known data are simply that the procedure has been performed in humans with no immediate complications reported**.

- **Community excitement ("Game-changer for chronic complete injuries") – *Understandable hope, but unproven*.** The SCI community is understandably excited because this trial targets chronic injuries, including motor-complete ones (AIS A/B), which have seen almost no recovery historically. If the OEC bridge triggers any neurological return in such cases, it would indeed be game-changing. But to date, **no results confirm this**. The Perry Cross Foundation's communications have been hopeful that their improved therapy will yield *"greater response"* than past attempts [146]. Perry Cross himself said he'd join the trial if he were eligible because "it's not

often we get to start human trials" and some prior participants in similar trials had promising outcomes [146] [147]. These statements convey optimism but should not be mistaken for actual results. The **proof of concept** remains to be demonstrated. In summary: a "game-changer" remains a *possibility*, not a reality as of 2026, and we will need to see the controlled data.

- **Interim observations ("One participant started moving X…") – *No official reports*.** Sometimes rumors circulate about trial participants noticing improvements. It's crucial to approach such anecdotes carefully. Participants in the treatment arm are highly motivated and undergoing intensive rehab; some may report subjective changes ("I feel stronger," "I have tingling in my toes," etc.). These could be real or could be placebo effect or even just the result of rigorous training. The trial is designed to capture these changes with objective tests and to compare them against the control group to see if they are truly due to the transplant. The team has not released any individual stories of recovery at this stage (likely intentionally, to maintain scientific rigor). If you see a sensational story on a blog or video claiming a participant regained major function, **check if it's verified by the trial investigators**. So far, none such claims have been officially verified or released. The first credible indication might come if the researchers present preliminary data at a conference (none announced yet aside from community webinars).

In conclusion, **no efficacy claims can be confirmed yet** for the Griffith OEC trial. The excitement around it is based on its strong scientific rationale and preclinical groundwork, not on actual human results (since those are not in yet). All sides are trying to avoid the mistakes of previous "hyped" cures. As Prof. St John said in late 2024, this trial should be seen with *"hope… above all, hope" but grounded in evidence and not false expectations* [148] [59]. The coming years will tell us if those hopes translate into tangible outcomes.

(Sources: Griffith press release [S1], U2FP Headline Patrol analysis [S4], trial registry [S2].)

Safety and Risks

Surgical Risks: Any spinal cord surgery carries significant risks. The procedure involves reopening an old injury site, which can trigger bleeding or further trauma to the cord. There is a risk of *worsening neurological function* if the manipulation injures surviving axons. For example, removing scar tissue could inadvertently damage nerve fibers that were intact. The surgical team mitigates this by using intraoperative monitoring (SSEPs during surgery to ensure signals remain) [69] and by only operating on chronic stable injuries, not acute fragile ones. Another risk is *infection* – introducing a cell graft and having hardware (if instrumentation is removed or if any is left) raises infection risk. All surgeries are done under sterile conditions, and patients receive prophylactic antibiotics. The nasal biopsy is a minor surgical step but can cause *CSF leak* or infection if it penetrates too deeply (the olfactory mucosa is near the cribriform plate, a thin bone by the brain). However, the biopsy is done carefully by an ENT surgeon. A known side effect of nasal biopsies is a reduction or loss of the sense of smell (anosmia) – because some olfactory nerves are removed. In past OEC trials, a number of patients did experience partial anosmia; participants are counseled about this possibility. It's considered a tolerable side effect given the potential gains elsewhere.

Cell Transplant Risks: Using autologous cells avoids graft-vs-host immune rejection, but there are still safety concerns: - **Tumor Formation:** Perhaps the biggest concern, stemming from the Portugal experience, is that transplanted cells could form an abnormal growth or tumor over time. In that case, nasal stem cells within the graft proliferated into benign but problematic masses after several years. In the Griffith trial, by using cultured cells that are primarily OECs (which are a mature glial cell, not a stem

cell), the risk is substantially reduced. OECs are not known to be tumorigenic. Nonetheless, the investigators will monitor via MRI long-term to ensure no unusual tissue growth at the transplant site. Any hint of a mass or cyst would be a serious safety event. - **Migration/Misplacement:** There's a risk that the transplanted cells don't stay put. They could potentially migrate along the spinal cord or into the brain. OECs in theory could travel (they do so in the olfactory system). If they migrate, they might carry with them any potential to cause ectopic growth or inflammation. To monitor this, MRI will be done – e.g., if a gadolinium-enhanced MRI at follow-up showed a new lesion distant from the injury, it would raise questions. So far, prior human OEC transplants didn't report harmful migration; OECs tended to stay in the implant zone or close by. - **Immune/Inflammation Reaction:** Even autologous cells can cause local inflammation simply by the act of transplantation. The procedure introduces biological material, possibly some cell culture additives, etc., into the cord. This could theoretically trigger or exacerbate *arachnoiditis* (inflammation of the spinal cord covering) or chronic inflammation around the graft. The trial is measuring inflammatory cytokines in CSF to see if there's an immune response [129]. Dexamethasone or similar steroids are usually given around the time of surgery to minimize inflammation. If severe inflammation occurred, it could cause pain or even spinal cord compression (via swelling). - **Neuropathic Pain:** A known phenomenon in some SCI interventions is that new sensory connections or changes can trigger neuropathic pain or spasms. There's a risk that if some sensory fibers regrow abnormally, patients might experience *increased pain below the injury* or painful sensations (dysesthesia). Conversely, some hypothesize that restoring more normal circuitry could reduce pain. It's unpredictable. The trial will document any changes in pain scores or spasticity. So far, no alarm has been raised, but the sample treated is still small. - **Autonomic Dysreflexia:** In high injuries, manipulation of the cord or new inputs could potentially provoke autonomic dysreflexia (dangerous spikes in blood pressure). This is one reason high cervical injuries were excluded (in addition to breathing issues) [98]. For thoracic-level patients, AD is still possible if, say, the bladder signals start coming through differently. Participants will be closely watched for episodes of AD during rehab.

Rehabilitation Risks: The intensive exercise regimen itself can pose risks. Five days a week of 3-hour sessions for months on end could lead to *overuse injuries* – e.g. shoulder strain in wheelchair users, or skin breakdown (pressure sores) if not carefully managed during therapy. The trial has allowances for breaks (participants can take a couple weeks off during prehab, and 4 weeks off during the long rehab, to rest or attend to life events) [86] [87]. There's also risk of *falls* during gait training or *fractures* if someone osteoporotic stands or steps – the rehab centers involved are experienced with SCI clients and use harnesses and spotting to prevent falls. Another risk is *fatigue and burnout* – doing this much exercise can be exhausting and mentally challenging, potentially leading to depression or dropout. The research team included psychology support and careful periodic evaluations to ensure participants are coping. They even plan on measuring participants' social and mental well-being as part of outcomes [96].

General Medical Risks: Because participants likely have chronic SCI, they may have underlying issues like UTIs, kidney stones, etc. The trial's intense schedule could exacerbate some health issues (for example, frequent UTIs could interrupt training). The medical team monitors and treats intercurrent illnesses promptly. There is also a small risk that drawing CSF (for the biomarker lumbar punctures) could cause headaches or bleeding, but that is routine procedure risk.

Ethical Considerations: The trial went through ethics approval, meaning risks were weighed against potential benefit. One ethical aspect is that control participants must commit to a burdensome rehab knowing they are not receiving the experimental therapy. They do at least get the benefit of free, intensive rehab which could help them (and indeed intensive rehab is arguably an "active" control, not an inert placebo). Another ethical point is the **informed consent** process had to ensure participants understand the unproven nature of the intervention – that they may undergo surgery and hard work and possibly see no improvement. Given the SCI community's understandable desperation for progress,

managing therapeutic misconception is important. The inclusion of a consumer panel in designing the trial likely helped make sure the participant perspective (including desire for honesty about chances of benefit) was incorporated [27] [149].

Regulatory Safeguards: An independent ethics board (and possibly external SCI research monitors) can halt the trial if serious adverse events occur. For example, if any participant had a significant neurological deterioration attributable to the transplant, the trial would likely pause to investigate. As of now, no such halting has occurred.

Interim Safety Update: Although no official data, Prof. St John indicated in late 2024 that *over 300 people applied but only 30 can be in the trial, and at least one person from abroad moved to try to join* [55] [150], which underscores that people are willing to accept the risks for a chance at improvement. To date, reported adverse events have been minor – e.g., *mild injection site reactions* (for growth factor injections used during cell culture? Actually, that pertains more to NVG-291 trial) – sorry, scratch that, wrong trial. For OEC trial, minor events might include things like nasal discomfort from the biopsy or some neuropathic pain flares during rehab. But no moderate/severe AEs have been publicized. The careful stepwise approach (starting with a small number of participants first, reviewing, then continuing) likely contributed to the safe progress so far.

In summary, the **anticipated risks** of the Griffith OEC trial are: surgical complications (infection, cord damage), cell-related issues (abnormal tissue growth, increased pain), and the stresses of intense rehab. The team has taken comprehensive measures to minimize these risks. Ultimately, only when the trial concludes will we fully know the safety profile – but given the trial's meticulous design and prior OEC experience, it's reasonable to expect the procedure can be done *safely*, with the main unknown being whether it *helps*. Safety will continue to be monitored for years (they will likely track participants beyond the formal trial for any late effects).

(Citations: U2FP blog on trial design [S4], ANZCTR criteria [S2], Position paper on OEC trial pitfalls [S6]).

Evidence Appraisal (Strengths, Limitations, and Ratings)

Let's appraise the key evidence underpinning this OEC "nerve bridge" approach, tagging each item by evidence type and scoring its strength and relevance to **chronic SCI** on a 1–5 scale (5 = highest):

1. **Preclinical Animal Evidence – OEC Transplant in SCI (Rat, 2015)** – *Peer-reviewed animal data.* In a notable rodent study (Keyvan-Fouladi et al., 2003, and others), OECs transplanted into partially injured rat spinal cords showed axonal sprouting and some sensory improvements. Strength: 3/5 (well-controlled lab studies, reproduced by multiple groups, though some studies had only modest effects) [43]. Relevance to chronic SCI: 4/5 (OECs were tested in both acute and chronic injury models; they demonstrated ability to integrate into scar tissue, which is relevant to chronic human injuries). One limitation: rodent spinal cords are smaller and the injuries often less severe than human complete injuries. Some follow-up studies (e.g. Ramon-Cueto et al. 2000) claimed dramatic results in rats, but later attempts (e.g. Steward et al. 2006) raised questions about functional significance. Overall, animal data suggested safety and biological activity of OECs, but functional recovery was variable and usually partial.

2. **Previous Human OEC Transplant Trials (2001–2014)** – *Peer-reviewed human case series.* e.g., Mackay-Sim et al. (Brain, 2008) transplanted autologous nasal OECs in 3 chronic thoracic SCI individuals: they reported it was safe (no adverse effects up to 3 years) but with *no* notable

neurological improvement (Strength: 2/5 – very small sample, no control) [43]. Lima et al. (J. Spinal Cord Med, 2006) treated 7 chronic complete patients with olfactory mucosal grafts: reported slight improvements in 2 patients (bladder/ASIA sensory) but no others; long-term follow-up (Ferreira et al., 2014) revealed 4 of 7 developed intramedullary mass lesions (nasal polyps) ~years later requiring surgical removal. Strength: 2/5 (small open-label series; positive findings not consistent; serious late complication reduces perceived safety). Relevance: 5/5 (chronic motor-complete injuries, directly the target population). These early trials taught important lessons (need for cell purification; importance of rigorous outcome measures). They show that *simply putting nasal tissue in the cord is not a cure*, but provided safety justification to proceed with refined methods. The variability in outcomes (some minor gains in some patients) gave a hint that OECs might help under the right conditions.

3. **Case Study – Darek Fidyka (Cell Transplant, 2014)** – *Peer-reviewed human case report.* A single 38-year-old male with chronic T9 complete SCI received autologous bulbar OECs injected around a peripheral nerve graft bridging the gap (Tabakow et al. 2014). Over 2 years, he went from no voluntary movement to being able to walk with a frame and recover some sensation. Strength: 1/5 (n=1, no control; could be an outlier or influenced by extensive rehab). Relevance: 4/5 (chronic SCI, although used olfactory bulb cells and nerve graft – a slightly different approach). While this was touted as "proof of concept" that OECs can enable functional recovery, it's anecdotal in scientific terms. Still, it provided inspiration and some procedural insights (like combining a graft with OECs). The Griffith trial differs by using nasal OECs (safer to obtain) and a 3D cell bridge instead of a nerve graft.

4. **Position Paper & Preparatory Studies (Ekberg et al. 2022)** – *Peer-reviewed analysis/expert opinion.* This comprehensive review analyzed why past OEC trials had mixed results and outlined the rationale for the current trial's design [43] [46]. It's essentially expert consensus backed by decades of lab work. Strength: 3/5 (not original data, but high-quality synthesis by field leaders; moderate evidentiary weight). Relevance: 5/5 (directly addresses chronic OEC therapy design). It's a strength that the trial is built on identified best practices: autologous cells, ensuring cell purity/identity, scaffold-free grafts, and intensive rehab. A limitation is that some recommendations (e.g. 3D liquid marbles) are new and not extensively proven – they are logical extensions of prior work, not yet evidence-backed themselves.

5. **Unpublished Preclinical "Nerve Bridge" Data (2020–2023)** – *Non-peer-reviewed preclinical data.* The Griffith team has indicated they did extensive lab and possibly large-animal testing of the nerve bridges, including **unpublished rat or sheep studies** showing OEC bridges leading to reconnection and functional improvement [144]. Strength: 2/5 (since not published, we must rely on the researchers' accounts; likely internally reviewed for ethics approval). Relevance: 5/5 (directly the same product being used in humans). According to statements, these studies are slated for publication post-patenting; they presumably gave the go-ahead for human trial (e.g., showing no harm and some efficacy in chronic models). We have to be cautious – often animal results can look encouraging (e.g., "rats improved their BBB locomotor score by a few points") but not translate fully to humans. The limited transparency here is a weakness in evidence – however, ethics committees did vet those results. We'll score it low for now, pending peer review.

6. **Trial Design Itself (GUSIP-03 Protocol)** – *Registered protocol / methodological evidence.* The fact that this is a *randomized controlled trial* is itself a big plus for evidence generation. By including a control group and blinding assessors [61], it will yield far more rigorous evidence than previous studies. While the trial results are not in, the design mitigates many limitations that plagued earlier trials (lack of control, heterogeneity, short follow-up). Strength: 4/5 (as evidence, a protocol isn't "results," but it demonstrates high-quality methodology that will produce credible

evidence). Relevance: 5/5 (targeting exactly chronic SCI). If this trial is completed as planned, regardless of outcome, it will significantly inform the field – a positive result will have strong credibility; a negative result will be taken seriously as well because of the robust design.

7. **Community and Expert Consensus:** Many SCI researchers and clinicians have cautiously endorsed the trial's rationale. For instance, the independent Unite2FightParalysis "Headline Patrol" by Sam Maddox (Nov 2024) critically examined the trial and concluded "this is serious work, based on strong science fundamentals… Is it promising? Yes. On the verge of cure? No – that's hype" [151] [38]. This external critical appraisal supports that the trial's foundation is sound scientifically (score this as expert opinion evidence). Strength: 3/5. Relevance: 4/5. It's not data per se, but it indicates the trial passes scientific muster within the SCI research community. Limitations: expert opinion can be wrong; consensus doesn't guarantee results, but it's reassuring that this isn't seen as a fringe or unsafe experiment.

Overall Evidence Strength (pre-trial): *Moderate.* The idea of using OECs for SCI has *some of the strongest preclinical support among cell therapies*, and safety in humans has precedent, but efficacy evidence in humans is *weak so far*. The Griffith trial is explicitly designed to address that evidence gap.

Relevance to Chronic SCI: *High (5/5).* This intervention is tailored to chronic injuries, unlike many therapies that only target acute phase. People living with long-term paralysis are the focus, which is exactly what the community has been seeking (most previous trials excluded chronic cases or only saw them in uncontrolled contexts).

Limitations in Current Evidence: - All prior human data lacked control groups. Thus, we don't truly know how much recovery observed (if any) was due to treatment versus spontaneous or rehab effects. - Sample sizes were tiny; the Griffith trial is also relatively small (n=30), which is enough to flag safety and maybe large effects, but it could miss subtle benefits. - Outcome measures historically were not standardized (some earlier studies relied on patients' self-reports or non-quantitative measures). This trial improves on that with robust outcomes (ASIA scores, MRI, etc.) [122] [123]. - Chronic SCI in humans is a tougher environment than in lab animals (e.g., humans have larger gaps, more complicated injuries). So even though OECs showed some success in lab models, it's possible they won't overcome the barriers in an old human injury scar that might be several centimeters with cysts, etc. - Publication bias: many OEC studies with less favorable results might not be widely known. For instance, a trial in China or Iran (if any) might not have been reported in English literature. The position paper identified variability – meaning not all attempts showed success [47]. - We also don't yet know if intensive rehab alone can produce similar benefits. The control group in this trial will clarify that. But until results are out, one could question: perhaps it's the rehab that will do most of the heavy lifting. If that's the case, focusing on cells might be less impactful than simply providing more rehab access to patients. This trial's outcome will directly inform that question.

What Would Increase Confidence: - Seeing peer-reviewed publication of the Griffith team's *large animal studies* demonstrating the 3D nerve bridge leads to robust axon regeneration and functional improvement in chronic SCI models (e.g. in a dog or non-human primate). That would boost evidence strength (to maybe 4/5). - Early trial signals: If, say, at a conference the investigators report that MRI tractography showed new continuity in treated patients or an ASIA grade conversion in a treated patient and none in controls, that would strongly suggest efficacy. - Independent replication: If another center (perhaps in Europe or North America) can repeat an OEC transplant with similar approach and see improvements, that would turn anecdote into solid evidence. Right now, all eggs are in this one trial's basket.

To summarize, prior evidence gives a **rationale** to try this in humans (hence the ethical go-ahead) but does **not guarantee it will work**. This trial itself will become a critical piece of evidence. If it meets even some of its efficacy endpoints (e.g. shows improved motor evoked signals or improvements on MRI in the treatment group), it would represent a significant evidence leap – likely moving evidence strength to 4 or 5 (with confirmatory studies).

(References: Mackay-Sim 2008 (Brain) [mentioned in S6], Lima 2006 & Ferreira 2014 [summarized in S4], Tabakow 2014 case [news reports S4], Ekberg 2022 [S6], U2FP analysis [S4]).

Frequently Asked Questions (FAQ)

Q1: Who is eligible for this trial? Can high quadriplegics or those with very old injuries participate?
A: The trial is open to adults with *thoracic or lower cervical SCI* (injury at T1 through T12, or C5–C8) [103]. High cervical injuries (C1–C4) are excluded mainly for safety – the surgery could endanger breathing, and those patients often have more medical complications [105]. You must be between 4 months and roughly 10 years post-injury (at least 4 months out to be "chronic," and the trial didn't state an upper limit, but they do require a "stable" injury) [102]. People decades post-injury might be considered if healthy, but practically most recruits are in the 1–10 year range. Importantly, you need to be **motor-complete or near complete** (AIS A or B, or a C with very weak motor function) [103], since the therapy is intended for those who have little voluntary function to lose but potentially much to gain. Also, you must be medically fit to handle hours of exercise daily – so someone with severe pressure sores, unmanaged diabetes, or other serious conditions would not be eligible [152] [105]. Each candidate goes through extensive screening including cardiac checks, etc., to get clearance for intense rehab and surgery.

Q2: I'm in the U.S./Europe – can I join or get this treatment?
A: Currently, this trial is *single-site in Australia*. Participants must travel to the Gold Coast for surgeries and assessments, and attend rehab regularly at one of the partner centers in Australia [6]. The trial organizers did not outright ban foreigners, but they *strongly* encourage only those who can reside in Australia for the trial duration to apply (and they did not actively encourage medical "tourism" for it) [56]. One American did move to Australia hoping to join [56] – that shows how motivated people are – but keep in mind the trial had far more applicants than spots. If this trial proves successful, it could pave the way for similar trials or treatment programs internationally in the future, but as of 2026, it's not available outside the study. Your best bet if abroad is to follow the trial's progress and watch for any expansion or new trials (or consider other experimental studies in your region).

Q3: What exactly is done with the cells? Are they stem cells?
A: The cells used are *olfactory ensheathing cells (OECs)*, a type of specialized support cell from the olfactory (smell) system. They are not pluripotent stem cells – they are more like cousin cells to Schwann cells (which support peripheral nerves). They do have some "stem-like" qualities in that they can divide in culture and secrete growth factors, but they are considered differentiated glia. In this trial, after a piece of your olfactory mucosa from your nose is taken, technicians isolate OECs from that tissue. The cells are then *expanded in the lab for several weeks* to get a sufficient number (tens of millions). During this time, they may also remove other cell types (like olfactory gland cells or stem cells) to purify the OEC population. The OECs are then formed into a 3D "bridge" – essentially a living tissue made of your cells. Nothing artificial (no plastic scaffold or matrix) remains in the final product [10] [11]. So, the product is your own cells, grown outside your body and then placed back into your spinal cord at the

injury site. The OECs then ideally do what they normally do in the nose: help nerve fibers grow through tissue.

Q4: Will the participants in the control group eventually get the cell transplant?
A: This trial is *not* designed as a crossover study, so the control group does not automatically get the transplant later. They receive rehabilitation only. Ethically, one might hope that if the treatment proves beneficial, control patients could be offered it in a follow-up study. The researchers have expressed empathy for control participants' commitment; in the informed consent, controls understand they might not directly benefit but contribute to knowledge. If the trial has positive results, the next phase would likely allow *all* participants access to the treatment (either in an open-label extension or in a new trial). But until efficacy is proven, there's no plan for control folks to receive the transplant within this study. They will, however, have gotten an equivalent amount of intensive rehab, which itself can be beneficial for health and function.

Q5: What kind of improvements are realistically expected?
A: The researchers are careful not to promise any specific improvement – this is experimental. But they've given examples of what *even small improvements* could mean: *regaining some bladder or bowel control*, *a bit of hand function*, or *the ability to stand with assistance and hug someone* [142] . Those would be huge quality-of-life gains even if the person isn't walking independently. In terms of clinical measurements, we might consider an improvement of one AIS grade (say from AIS A to B, or B to C) as a meaningful change – that could mean going from no sensation to having some, or from no voluntary movement to some trace movements. Restoring the ability to sweat or regulate blood pressure could also greatly improve daily living. While Hollywood might imagine someone going from wheelchair to fully walking, that's not the typical expectation. We should think in terms of incremental recovery: a few muscle groups below the injury turning "on" again, some sensation returning, improved trunk stability, reduction in spasms, etc. Animal studies hinted at improved *locomotor scores and urinary function* [153] ; translated to humans, that might correspond to slightly better walking with aids or reduced catheterization frequency. The trial will consider it a success if they can detect any statistically significant improvement in the treatment group that isn't seen in controls – even if it's modest. As Prof. St John put it, *"we are aiming low and hoping for high outcomes"* – meaning they'd be content with small wins, and anything more would be a bonus [35] .

Q6: If it doesn't work, what are the next steps?
A: A negative or neutral result would be just as important to know. If the transplant plus rehab shows *no difference* compared to rehab alone, the team (and the field) will analyze why. It could mean that OECs by themselves aren't enough to overcome chronic spinal cord damage. It might suggest combining therapies – e.g. adding a growth stimulant drug, or electrical stimulation – could be necessary. The researchers have mentioned they are "already planning how to improve it" for next steps, but they can't test those variables in this first trial [154] [39] . So, if it doesn't work, one next step might be a trial of OECs *plus* a drug like chondroitinase (to dissolve scar) or *plus* epidural stimulation, etc. Or they might decide to try the approach in subacute injuries (earlier after injury when there's more innate potential) rather than chronic. Also, a negative outcome in terms of no functional improvement, but with proven safety, might still encourage trying a *higher dose* of cells or multiple transplant sites. On the flip side, if it clearly doesn't help, resources could be shifted to other promising avenues (like bioengineered scaffolds with growth factors, or gene therapies). Essentially, even a "failure" provides data: it tells us what doesn't work, which is crucial for science. Remember, this is a Phase 1/2 trial – its purpose is partly to inform the design of future, hopefully more effective, interventions.

Q7: Is any participant *worse off* because of the intervention?
A: So far, no. The priority of a Phase 1 trial is do no harm. All participants (including controls) get intensive rehab, which is generally beneficial for fitness and health. The surgical participants of course

take on surgical risk, but to date there have been no reports of a transplant causing deterioration. In previous OEC studies, *no participant became neurologically worse* as a result of the cell transplant (barring the few who developed those late-onset mucus cysts a decade later). In this trial, they have multiple safety checkpoints. If a participant did show any new deficits post-surgery (like weakness above their prior injury level, or new severe pain), the investigators would report that and investigate if it was due to the procedure. The question of being worse off can also include time/effort: participants invest a lot of time in the trial, which could be seen as burdensome, but they are compensated and they volunteered knowing this. Psychologically, if it doesn't give improvements, some might feel disappointed – that's something the team's psychologists will help with, ensuring participants have support. But strictly physically, as of now, there's no evidence anyone has been harmed or is "worse off." The trial's independent monitoring would likely stop it if clear harm was occurring in the treatment arm.

Q8: How is this different from other stem cell therapies I've heard about (like bone marrow stem cells or embryonic cells)?

A: It's quite different. First, OECs are not pluripotent stem cells; they are a specific glial cell tailored to supporting neurons. Many clinics worldwide have given injections of bone marrow stem cells or adipose (fat) stem cells into people with SCI – but those are mostly unproven and typically the cells are just injected systemically or into the CSF, *not engineered into a structured bridge*. The Griffith approach is more like tissue engineering: creating a piece of living tissue to graft into the cord. That's fundamentally more complex than a simple cell injection. Also, it uses the patient's own cells from a tissue (nose) that has a natural connection to the nervous system. Embryonic or induced pluripotent stem cells, in contrast, have the potential to become many cell types, but also carry higher risk (e.g. tumor formation, rejection if not autologous). Some trials with fetal cells or others in SCI had safety issues in the past. By using autologous OECs, this trial avoids immunological issues and uses a cell with a specific intended function (guiding axons). In short: *this is not a generic stem cell shot* – it's a customized cell transplant that also addresses the structural gap in the cord. It's also combined with rehab, which those "stem cell clinic" treatments usually aren't. That synergy might be key. Lastly, the trial is rigorously controlled and scientifically driven, unlike many off-the-grid stem cell offerings. That means outcomes (good or bad) from this will be credible.

Q9: What is the 3D scaffold made of? Does it stay in the cord?

A: Interestingly, the "3D nerve bridge" isn't a synthetic scaffold at all. It's made *entirely of the participant's cells*. Early on, the team experimented with collagen or polymer scaffolds to hold the cells [155] [156], but they decided to go scaffold-free for the clinical product [77]. The manufacturing process results in a cell-packed structure that has enough integrity to be handled and implanted. Once in the cord, it's just living tissue – over time, one would expect it either integrates with the host tissue or partly gets remodelled by the body. There's no permanent artificial material. This is good for avoiding foreign-body reactions. It does mean the OECs themselves provide the "framework." Think of it as a little *biological bridge* that may eventually blend in and become part of the patient's spinal cord architecture. Because there's no non-biological scaffold, there's nothing that needs removing later; the cells either survive long-term or naturally die off after doing their job (if they do die, ideally by then any new axon growth is stabilized by the host's own glia). The trial will use MRI to see if the graft is visible – sometimes a cell graft can show up initially as a distinct area on MRI and then becomes less distinct as it assimilates.

Q10: How will we know if it worked? What outcomes would count as success?

A: The trial has multiple endpoints, but from a lay perspective, a *"success"* would be if the treated group shows improvements that the rehab-only group does not. For example, if several treated patients regain some voluntary movement below the injury and none of the control patients do, that's a clear sign of efficacy. Another sign would be on MRI: if scans show new nerve tracts bridging the once-gap in treated patients. Or electrophysiologically, if treated folks have signals passing through the injury (measured by evoked potentials) that weren't there before, whereas controls remain flatlined – that's a

strong indicator [8] [119]. The researchers set specific primary outcomes: they considered it an efficacy success if they see *"anatomical changes to the injury site"* on MRI/DTI indicating repair [8]. So, one concrete measure might be an increase in spared tissue volume or connecting fibers. On functional measures, success could be: an average improvement in ASIA motor score in the treatment group significantly higher than in controls by week 48. Even changes in things like *GRASSP hand scores* or *walking speed* (for those who have some walking ability) will be looked at. It's possible only a subset (responders) might improve – so they will also examine how many individuals improve in each group. If, say, 50% of treated patients improve in some clinically meaningful way vs 0–10% of controls, that's a win. Also, safety is part of "worked" – if it yields improvements *without causing serious harm*, that's a success. On the other hand, if both groups improve similarly, then the cells didn't add value (meaning the result is negative for efficacy). The final determination will come from statistical analysis after all patients complete the trial. They will likely report something like: *"Injury site connectivity improved on DTI in X% of cell-treated vs Y% of controls, and treated participants had on average a Z-point improvement in [some functional scale] vs minimal change in controls."* If those differences are significant and clinically meaningful, that would be hailed as a positive result.

Q11: What is the long-term plan if this trial shows positive results?
A: Should this Phase 1b/2a trial show safety and a hint of efficacy, the next steps would involve scaling up to larger, multi-center trials to truly establish effectiveness. Likely a Phase 2b or Phase 3 trial would be planned. That could mean **hundreds of patients internationally**, randomized to OEC transplant vs. control, possibly stratified by injury level, etc., to see if the results hold in a broader population. The researchers will also be keen to optimize the therapy – for instance, maybe adding a *second dose of cells* or combining with electrical stimulation to amplify outcomes (they hinted they have ideas to improve it but held off to keep this trial focused) [154]. On the regulatory side, positive results would prompt discussions with agencies like the Australian TGA, FDA, EMA about designating this a breakthrough therapy and guiding a path to approval. Manufacturing capacity would need to be increased – currently cells are grown at a university facility; for widespread use, a commercial GMP facility or cell bank might be needed. The team's commercialization office is already involved, anticipating patents and investor partnerships if it works [77] [41]. So the long-term plan is: *verify it works, then industrialize and distribute.* However, realistically, that's years away. On an individual level, if it works, those in the SCI community will want access sooner. There might be pressure to set up *expanded access* programs or treatment centers under experimental protocols. For example, if this one trial is a success, perhaps a government-funded program could treat say 100 people as a next step while awaiting Phase 3 results. All that will depend on how clear-cut and large the benefits are.

Q12: Are there any controversies or skeptics about this trial?
A: Yes, as with any bold "first", there are skeptics. Some scientists note that previous OEC efforts didn't pan out, and question whether this attempt will be any different. The main skeptical view is that *the trial moved to humans without published proof that the 3D nerve bridges dramatically outperform past methods* [77]. Usually, one expects to see a slew of animal studies before a human trial, but the Griffith team, to protect IP, hasn't published all yet. They defended this by saying they needed to start the trial to get real data and patents are being filed in parallel [77] [41]. Some in the field might quietly worry that if this trial fails, it could set back SCI research optimism (the so-called "one more failed cure" scenario). Another controversy is the role of intensive rehab – critics might say *"if you just gave all these patients a year of intensive rehab without any transplant, maybe they'd improve too."* That's why the control group is so important to address that. And indeed, the trial might end up proving the value of rehab as much as the cells. There were also small murmurs about the *media fanfare*: The term "world-first" and high-profile promotions raised eyebrows, with concerns about hype. The U2FP blog piece titled "Does it pass the smell test?" was a good-natured critique pun – ultimately concluding it's grounded in science, but cautioning against the media hype [151] [38]. Another ethical question raised: is it okay to ask SCI participants to commit to such an onerous regimen (almost a year of near-daily exercise) for an

unproven therapy? The counterargument is they are fully informed and many are eager to do whatever it takes. On the whole, most SCI experts are *hopeful but waiting for data*. The trial itself hasn't drawn major ethical criticism since it was approved properly and involves the SCI community in design. If anything, the skepticism is a healthy "let's see if it truly works; previous attempts didn't, so manage your expectations."

Reality Check (Managing Expectations)

Reality Check: It's important to put this trial in context – it is a *Phase 1/2 safety and feasibility trial*, not a guaranteed treatment. While it's absolutely a breakthrough to even attempt a rigorously controlled regenerative therapy in chronic SCI, we must recall that **decades of SCI research have seen many hopeful experiments yield modest or no functional gains**. This approach, using OECs, is actually not entirely new – what's new is the 3D engineered bridge and the combined aggressive rehab. Past attempts with OECs did not lead to people with chronic complete injuries walking again or getting out of wheelchairs. Some participants in those earlier trials had *small improvements* (e.g. better sensation or bladder control), others had none. So, a likely scenario is that this trial might show **safety** and maybe *some* improvements in some individuals, but not miraculous recoveries.

In chronic SCI, even a tiny improvement can be valuable: for instance, regaining the ability to sweat below the injury or slight finger movement can increase independence. The team has said as much – they're looking for *"the ability to regain some sense of function"* as a win [142]. So our expectations should be set at that level. It's not going to instantly "heal" a severed spinal cord like flipping a switch. Neural regeneration is a slow, gradual process; any functional changes might be subtle at first and require careful testing to even detect. Additionally, because this is the first in-human trial of this exact method, the dose and technique might not be optimized. They might discover later that, say, they need more cells, or a different rehab protocol to get better results. That's why they already plan improvements for future trials [154].

It's also possible that the intensive rehabilitation will yield improvements regardless of the transplant – i.e., participants in both groups might improve. If that happens, it might be disappointing from the cell therapy perspective, but it underscores something important: even chronic SCI can sometimes see gains with extensive training (it's rare, but not impossible). The design will help distinguish that.

Another reality: **timeline to impact**. Even in the best case where this trial shows great results, it won't become an available therapy overnight. There would need to be larger confirmatory trials, regulatory approvals, funding, etc. We're talking several years at minimum. For someone living with SCI reading about this: it's inspiring, but it's not something you can sign up for tomorrow (unless you fit criteria and happen to be near the trial site, and even then the slots are limited). So, it's a step on a long road.

Furthermore, we must remember that the spinal cord is highly complex. **Multiple barriers** hinder recovery: scarring, lack of growth factors, cell death, inhibitory molecules, etc. This intervention addresses some of those (fills the gap with supportive cells, provides activity stimulation) but not others (it doesn't directly modify the glial scar chemical environment except locally, it doesn't replace lost neurons, etc.). It may be that a *combination* of approaches (cells + gene therapy + electrical stimulation + rehab) will ultimately be needed for more substantial recoveries. If this trial is a modest success, the logical next step is to integrate it with other advances.

Who might this realistically help first? If effective, the *initial beneficiaries* would likely be people with mid-thoracic to lower-cervical motor-complete SCIs (those very similar to the trial population). For

example, someone with a T6 complete injury a year out who currently has no lower body movement might, after such a treatment, gain some lower abdominal muscle control or sensation – which could improve balance or reduce caregiving needs. It might help a C7 quadriplegic improve hand grip to go from needing assistance to perhaps feeding themselves. These improvements could be life-changing to them, even if they aren't walking. Over time, if proven, it could be offered to others with chronic SCI. Probably those who are healthy and not too many decades post-injury would benefit most (since long-term disused muscles and nerves atrophy, and complications can accumulate). The trial's age limit is open, but intensive rehab might be tough on older folks – likely early beneficiaries would be *younger, fitter individuals with chronic SCI*.

People with *incomplete* injuries (AIS C/D) might also benefit, but ironically the trial didn't include many of them because they wanted clearly measurable outcomes. In the future, if OEC grafts really restore pathways, incomplete folks could perhaps go from some walking to much better walking, etc. But initial focus will be on those who have no other therapeutic options.

Bottom Line: This trial is a beacon of hope – carefully conducted and the culmination of years of work by scientists and advocates – but it is not a guarantee. It's best approached with *optimism balanced by patience*. The phrase often used is "cautious optimism." If it succeeds even partially, it opens a door that's been closed a long time. If it fails, that too is invaluable knowledge guiding the next strategy. As observers or potential future patients, we should support the effort, be grateful for the participants risking much to advance science, and understand that medical breakthroughs come stepwise. This is one such step.

As U2FP's review concluded: is this *"on the verge of a cure"*? No, that's an unfair overstatement [38] . But is it a well-founded attempt that could *"challenge that notion [that recovery is impossible] with evidence, ambition and hope"*? Yes – it's the best shot yet taken at a very hard problem [58] . The history books won't be rewritten overnight, but this trial is writing an important new chapter.

Who Might This Realistically Help First?

If successful, the profile of individuals who would likely benefit first from this OEC nerve bridge therapy are:

- **Those with chronic, motor-complete SCI at mid-levels**: e.g. thoracic paraplegics and lower cervical tetraplegics who have stable injuries but little or no voluntary function below the injury. These are exactly the people in the trial. They currently have very limited options – rehabilitation can maximize what they have, but it can't make new movements appear years after injury. For them, a small return (like some hip flexion or some finger movement) can make a large functional difference. They also have "room" for improvement (unlike someone who's already walking, where gains might be marginal).

- **Injury duration probably 1 to 10 years**: The trial requires minimum 4 months post-injury, but realistically they want chronic, so likely those 1+ year out. The process of scarring stabilizes by around a year. If someone is too recent (<1 year), they might still be in spontaneous recovery phase or have less established scar – in future they might try it earlier, but first evidence will come from well-established injuries. On the other end, if someone is 20+ years out, it's not clear how well their body would respond; muscles severely atrophied, etc. However, because they didn't cap the max years in the trial, it implies they believe even long-term injuries could benefit

if otherwise healthy. Likely initial real-world use (if proven) would focus on those maybe up to 10-15 years post injury, where some neuromuscular capacity remains.

- **Patients able to engage in intensive rehab**: This therapy isn't a one-off that magically works – it requires commitment to rigorous physiotherapy. So the first beneficiaries will be those who have the support, endurance, and resources to do many months of rehab. In practice, that might favor somewhat younger individuals (20s to 50s age) and those with access to good rehab facilities. The trial itself provides the rehab free, but outside a trial, one would need coverage or funding for so much therapy. It might also favor those who already maintain good fitness, since they'll tolerate the program best.

- **Those without contraindications**: People with certain complications might not be ideal candidates initially. For example, someone with uncontrolled spasticity or severe contractures may need those addressed first or might be excluded because it could hamper rehab. The ones this helps first will likely be folks who, aside from paralysis, are in stable medical condition (no active infections, manageable spasticity, etc.).

- **In terms of functions regained**: The "first" improvements we might see (if it works) could be in trunk control for paraplegics (allowing sitting balance), improved hand grip for tetraplegics, partial sensory return (e.g. being able to feel pressure or temperature below the injury). Bladder control might show improvement (maybe being able to void with less assistance). These functional domains (hand function, core stability, autonomic control) are often cited by SCI community as top priorities – even above walking in many cases – for independence. Those are realistically the kinds of functions that might come back first if new connections form, because they don't require every single pathway to regrow, just some reconnection in the spinal segments responsible for those functions.

- **Notably, complete thoracic injuries aiming for bowel/bladder improvement**: Many T2–T12 complete injury individuals can't feel or control bladder/bowel. If the nerve bridge allowed even partial signals through, one might regain sensation of a full bladder or some voluntary voiding ability. That alone would be a huge benefit to that population. So I suspect that's a target group that could see life-changing (if not obvious externally visible) improvements first.

- **Cervical injuries aiming for upper limb function**: For C5–C7 complete injuries, being able to extend the wrist or use fingers even a little can be the difference between needing full-time care and doing many tasks independently. That group might be the first where any motor improvement leaps out as clearly attributable to the therapy, since normally, years after a C5 injury, you'd never spontaneously start moving your fingers if you couldn't before. If a few transplanted patients do, that's a clear win. So one could say early beneficiaries, if it works, would be *people like a C6 quadriplegic who post-therapy might open/close their hand where they couldn't before*.

- **Eventually, incomplete injuries too**: If it works in motor-complete, it almost certainly could benefit motor-incomplete folks by adding redundancy and strength to their connections. But incomplete folks already can improve with other means, so the initial push is for those who have no other chance. But down the line, yes – someone who is AIS C (e.g. has some leg movement but can't walk) might, with a graft, gain enough additional fibers to walk, for example. But that's speculative until they test it there.

- **Psychosocially, who it helps**: Those who have strong support systems (family, caregivers) to help them through the intense process will benefit more. The trial's success requires a village – e.g. some participants temporarily relocated to be near rehab centers, needing accessible housing, etc. People with that support will fare better initially.

In summary, the realistic initial beneficiaries are the *subset of chronic SCI individuals for whom paralysis is currently most complete and permanent – mid-level, stable injuries – who are healthy enough to undergo an intensive combined procedure and therapy.* These are folks who've perhaps been told for years "there's nothing more we can do," and now finally there is something new to try. It won't instantly make them normal, but it could move them from *complete dependence to partial independence*, or from *no sensation to some sensation*. Those changes will first help them – and set the stage to broaden the reach to others if confirmed.

What I'm Watching Next (Milestones & Upcoming Developments)

Over the next 1–3 years (2026 onward), here are the key **milestones and indicators** to watch regarding the Griffith OEC Nerve Bridge trial and its progress:

1. **Enrollment Completion (Milestone ~2026):** Keep an eye on announcements from Griffith or the ANZCTR registry updates indicating all 30 participants have been enrolled. Full enrollment is needed to properly assess outcomes. If they struggle to fill slots (perhaps due to strict criteria or the burden of participation), that would be notable – but given interest, they likely will reach 30. A related milestone: if they decide to *expand enrollment* (say add more participants), that could happen if early safety is great and funding allows – but as of now, 30 is the cap.

2. **Interim Safety Analysis (Milestone 2025–2026):** Trials often have predefined interim analyses. By mid-2025 they had a few patients treated; by 2026 perhaps half the cohort could have completed their follow-ups. I'm watching for any conference presentations or press releases about safety. For example, if at a scientific meeting (like the ISCoS – International Spinal Cord Society annual meeting) they present "Interim safety data on first 10 subjects: no serious adverse events," that bolsters confidence. Conversely, if any serious safety issues occurred, one might see a pause or modification of the trial. No news is generally good news on safety here.

3. **First Efficacy Signals – Conference Presentation (Expected 2027):** Even though the final data won't be until 2028, researchers may share preliminary efficacy observations at conferences. They actually indicated that primary outcomes would be assessed at 48 weeks and presented at a major meeting. For instance, the press release mentioned results will be presented at the American Spinal Injury Association (ASIA) meeting (the 2025 date was for the NVG-291 trial) [157], but possibly ASIA 2026 or 2027 could see a presentation from the OEC trial. I'll be watching the program of ASIA or ISCoS annual meetings for any abstract by St John or colleagues reporting results. That will be a huge moment: if they show a graph of, say, MRI changes or ASIA score gains in treated vs control, that's when we'll know if it's trending positive. Conference abstracts often come out a bit before journal publication, so that's the one to watch around mid-2027.

4. **Publications of Preclinical Studies (2025–2026):** Prof. St John mentioned that their preclinical research would be published over the next year once patents were in place [42]. Look out for papers in journals like *Journal of Neurotrauma* or *Frontiers in Neurology* or similar, authored by members of the team (e.g., J. Ekberg, D. Palipana, etc.). Titles might include phrases like "Olfactory cell bridges" or "3D OEC culture in spinal injury model." These publications will give us

details on how the nerve bridges performed in animals, which will either increase our optimism or reveal challenges. They might, for instance, show histological images of axons growing through the graft in a rat – something that would be exciting to see confirmed.

5. **Trial Completion and Results Release (~2028):** The big milestone – when the trial ends and results are analyzed. According to the registry, last data collection is anticipated August 2028 [33]. Possibly by late 2028 or 2029, we'll see the *full trial results published in a top journal*. At that time, I'll look for:

6. Did it meet its primary endpoints of safety and feasibility? (Likely yes, unless something unexpected happened.)
7. And importantly, any efficacy differences? This will be where we see p-values comparing the treatment vs control for things like MRI changes or ISNCSCI improvements.
8. They'll also report how many adverse events occurred – hopefully mostly mild (like some increased spasms or minor infections).

9. That paper will be the first Level I evidence of its kind for chronic SCI cell therapy.

10. **Follow-on Funding/Phase II Announcement (2026–2027):** If early signs are encouraging, I expect to hear about new funding to scale up. For example, the team might apply for a larger grant or attract industry partnership. The Perry Cross Foundation and others will surely continue support, but a Phase II/III could cost significantly more. If results look good, perhaps government funding (MRFF or international sources like CIRM in California) might come in. So, news of a **Phase 2 trial planning** would be a huge positive milestone. That could be announced as early as 2027 if interim results merit it – they won't want a big gap if it works, they'll want to move to the next trial design.

11. **Regulatory Designations (2026+):** In the wake of positive signals, watch for the therapy getting special designations – e.g., *FDA Orphan Drug status* or *Fast Track* in the US, or similar in Europe. Although the trial is in Australia, if it's promising, the team might engage with FDA to pave a path for US trials. Getting, say, an FDA Breakthrough Therapy designation for chronic SCI cell transplant would be groundbreaking (the FDA would require some evidence first, though). Any such regulatory news would indicate global interest and smoothing of the path to eventual approval.

12. **Expansion of Rehab Network (Ongoing):** For practical implementation, the rehab component is huge. I'll watch if more rehab centers partner with the project to build capacity. For instance, if they announce adding a site in another Australian state or more centers, that suggests they might be preparing for a larger rollout. Also, if they standardize and publish their rehab protocol (which could become a model even for other treatments), that will be an outcome to monitor.

13. **Interactions with Other Research (2026–2028):** It will be interesting to see if the OEC trial intersects with other developments. For example, there's parallel work on *electrical epidural stimulation* enabling functions in chronic SCI. A milestone could be a combined approach – perhaps a small pilot of OEC transplant *plus* epidural stim in one or two individuals as a case study. Or even combining with a drug like NVG-291 (from NervGen, our other deliverable) – though that's far off, one could envision a future where removing inhibitors (like NVG-291 does) plus providing OEC bridges yields a synergistic effect. Any news of collaborative research in that direction would be notable as a sign of the field converging therapies.

14. **Community Outcomes/Testimonials (2026–2029):** As participants finish the trial and the blind is broken (likely after all have completed to preserve study integrity), I'd watch for participants speaking out about their experiences. For instance, a participant might choose to share "I was in the treatment group and I improved X amount." Real-world stories (tempered by the scientific analysis) can provide color. If many participants say "this changed my life for the better" – that's a strong informal indicator of success. Conversely, if we hear mostly "it was worth trying but I didn't regain anything significant," that will also filter out. I expect some will share their journey in SCI forums or media once allowed.

15. **Intellectual Property and Commercial Moves (2025–2027):** Griffith's commercial office and possibly a startup entity might file patents (some already filed) [41]. Watch patent databases for filings on "OEC nerve bridge" or similar around 2024–25. Also, they might spin this out into a company or partner with an existing biotech to commercialize. If a biotech invests or goes public around this tech, that's a sign of momentum. For example, if, hypothetically, a cell therapy company licenses the tech in 2027, that means they see market potential and are gearing up for larger trials and eventual therapy launch.

Each of these milestones will incrementally answer the big question: *Is this therapy moving the needle for chronic SCI?* By 2028, we should have a clear answer from the trial. And if it's positive, the milestone beyond would be seeking regulatory approval – which would be unprecedented (no cell therapy is approved for chronic SCI yet). The timeline for that is likely mid-2030s if all goes well (given needing a Phase 3, etc.). It's a long road, but these near-term milestones will be crucial checkpoints along it.

Deliverable 2: NervGen NVG-291 and CONNECT-SCI Program Dossier

Executive Summary (Key Points as of Jan 2026)

- **NervGen's NVG-291:** NVG-291 is a *first-in-class peptide drug* developed by **NervGen Pharma** targeting the protein tyrosine phosphatase sigma (PTPσ) pathway to promote neural repair [158]. It's designed to counteract the inhibitory effects of the glial scar and other factors that block regeneration after CNS injury. Mechanistically, it's derived from a molecule ("ISP") invented by neuroscientist Dr. Jerry Silver, which in animal models enabled damaged neurons to regrow and form new connections, restoring functions like bladder control and movement [153]. NVG-291 aims to replicate that in humans by *disinhibiting neuronal growth and plasticity* in the chronically injured spinal cord [159] [160].

- **CONNECT-SCI Trial (Phase 1b/2a):** In 2023–25, NervGen conducted the **CONNECT-SCI study** – a placebo-controlled trial with 2 cohorts: **chronic SCI** (injuries 1–10 years old) and **subacute SCI** (injuries 1–3 months old) [161] [162]. All participants have *cervical, motor-incomplete* injuries (AIS B, C, or D; some preserved function) [163] [164]. NVG-291 is given by **daily subcutaneous injections for 12 weeks**, with extensive outcome testing up to 16 weeks [165] [166]. **20 subjects per cohort** (with randomization, approx. 2:1 drug vs placebo in chronic cohort, 1:1 in subacute). The trial's co-primary endpoints are electrophysiological: improvement in *motor evoked potential (MEP) amplitudes* in key muscles (hand and leg) as objective markers of restored corticospinal connectivity [167] [168]. Secondary outcomes include clinical function (e.g. GRASSP hand function, walking tests) and MRI measures of spinal cord integrity [169] [170].

- **Positive Phase 1b Results (Chronic Cohort):** In June 2025, NervGen announced *positive topline results* from the chronic cohort of CONNECT-SCI [171] [172]. NVG-291 **met one of two co-primary endpoints**: treated patients showed a **3-fold increase** in motor evoked potential (MEP) amplitude in an intrinsic hand muscle (first dorsal interosseous) compared to baseline, which was significantly greater than the change in placebo ($p \approx 0.015$) [173] [174]. This indicates **heightened electrical connectivity** from brain to hand, suggesting new or strengthened neural pathways [167]. The second co-primary (MEP in tibialis anterior, a leg muscle) did *not* reach significance [175]. Secondary outcomes showed a *positive trend* in hand function: NVG-291 patients improved more on the GRASSP prehension strength subscore (+3.7 points vs +0.4 in placebo) [176], though sample size limited statistical power. Other clinical measures (walking speed, etc.) showed no clear drug-placebo separation at topline [177]. Crucially, **no serious safety issues** emerged: NVG-291 was well-tolerated over 3 months, with the most common side effect being mild injection site reactions [178]. There were *no drug-related serious adverse events or discontinuations*. These results mark the **first ever demonstration of a pharmacological agent enhancing motor signal conduction in chronic SCI humans** [179] [180] – a significant scientific milestone.

- **Expanded Data – Real-World Impacts:** In Nov 2025, NervGen released further analyses showing *durable and broader benefits* in NVG-291-treated chronic patients up to 12 months post-study [181] [182]. Blinded interviews revealed that patients on NVG-291 reported **notable functional gains in daily life** compared to placebo [183]. Examples included improved arm/hand usage (e.g. being able to perform self-care tasks like brushing hair, opening jars) [184], better lower body movement, and importantly, improvements in *bladder control and reduced muscle spasticity* [181] [185] – none of which were explicitly measured in the initial 16-week outcomes but manifested later. Objective neurophysiology also confirmed a **reduction in pathological reflex activity**: NVG-291 recipients had significantly lower hyperactive reticulospinal signals (measured via startle-evoked MEPs) than placebo [186]. This suggests the drug not only strengthens voluntary motor pathways (corticospinal) but also *tamps down maladaptive reflex pathways*, which correlates with reduced spasticity. Collectively, these expanded results indicate NVG-291's effects are **broad (impacting upper & lower limbs, motor & autonomic function)** and *persistent well beyond the dosing period*, reinforcing that actual neural repair/plasticity is occurring [187] [188]. Patients described regained independence and quality of life improvements, painting a compelling picture of real-world impact beyond the lab scores.

- **Mechanism – PTPσ & CSPG Inhibition:** NVG-291 works by mimicking the *intracellular "wedge" domain of PTPσ*, a receptor on neurons and support cells that binds to chondroitin sulfate proteoglycans (CSPGs) in the scar [159]. After injury, CSPGs accumulate in the glial scar and perineuronal nets, halting axon regrowth and plasticity [160]. By binding to PTPσ's regulatory site, NVG-291 essentially **unsilences the regenerative capacity** of neurons – axons can sprout and grow past the scar, and oligodendrocytes can remyelinate axons that were demyelinated [153]. Preclinical studies by Dr. Silver's team showed systemic delivery of the peptide (called "ISP") in paralyzed rodents led to **axon regeneration, new circuit formation, and recovery of functions** like walking and bladder voiding [189] [153]. NVG-291 is a refined, clinical-grade version of ISP. It is a therapeutic peptide (with a cell-penetrating moiety) that is injected under the skin; from there it circulates and crosses into the nervous system to reach injury sites. Its action is not injury-specific – it potentially enhances plasticity wherever CSPGs impose inhibition, which is why it's being explored for **other conditions** like multiple sclerosis (demyelination) and Alzheimer's (where CSPGs and PTPσ also play roles). The key concept: NVG-291 **releases the brakes** that the scar and certain inhibitory proteins put on the nervous system, allowing the body's natural repair processes to progress [190] [191]. This can lead to axonal regrowth, synaptic reconnection, remyelination of axons, and formation of new pathways to bypass damaged areas.

- **Safety Profile:** NVG-291 has thus far shown a *favorable safety profile*. In a Phase 1 trial in 2021–22, healthy volunteers (including both men and women) tolerated escalating doses well [192] [193]. A partial FDA hold initially limited exposure in premenopausal women (due to some preclinical reproductive findings), but that was lifted once additional data showed no safety signal [192]. In CONNECT-SCI's chronic cohort, as noted, no serious adverse events were attributed to the drug [178]. Injection site reactions (redness, mild pain) were the most frequent complaint [178]. There were no signs of drug-related systemic toxicity – vital signs, blood tests, etc., were comparable to placebo [171] [194]. No participants had to stop the drug due to side effects. Notably, NVG-291 did not increase spasticity or pain – in fact, spasticity tended to decrease [181] [185]. This contrasts with some concerns that promoting new growth could lead to aberrant pain circuits; that was not observed. Long-term safety (beyond 1 year) remains under study, but the durable functional improvements with no late complications reported up to a year post-dosing are very encouraging [187] [188]. The drug is also being tested in individuals with multiple sclerosis in a separate Phase 1b, with no major issues reported so far (as of Jan 2026).

- **Evidence Appraisal:** The evidence for NVG-291 is now at a solid Phase 2a level. We have: robust *preclinical animal data* (multiple peer-reviewed rodent studies, e.g. Nature 2015 by Lang et al. showing "ISP" restored locomotion and bladder function in chronic SCI rats [153]), *mechanistic validation* (studies confirming PTPσ is a key receptor mediating CSPG inhibition [160]), *Phase 1 safety data* in humans, and now a *randomized controlled human trial* showing objective and subjective improvements [167] [181]. The chronic cohort results provide Level 2 evidence of efficacy (small sample RCT). The strength of evidence is bolstered by the statistically significant MEP finding – an objective endpoint less susceptible to placebo effect – and the consistency with what was seen in animals (e.g. improved conduction and function). Limitations: the sample size was small (n=10 treated, 10 placebo in chronic cohort), so some functional outcomes only showed trends. Also, results are so far only in *motor-incomplete cervical* injuries – we don't know if it helps motor-complete or thoracic injuries yet. Nonetheless, experts have reacted very positively; achieving any significant improvement in chronic SCI with a drug has never been done before, so this is considered a big step forward [179] [180]. Dr. Monica Perez, the trial's principal investigator, noted that a threefold MEP increase is "substantial" and indicates real new connections [195] [196]. The fact that NVG-291 got FDA Fast Track designation for SCI underscores the FDA's recognition of its potential [197] [198].

- **Next Steps:** *Subacute Cohort & Phase 2:* As of Jan 2026, the subacute cohort of CONNECT-SCI (injuries 20–90 days old) is still **enrolling and dosing** [199]. The first subacute patient was dosed in Feb 2025 [199]. Results from this cohort (another ~20 patients) are expected in 2026. If subacute results also show positive trends or significance, it would broaden the use-case (treating people soon after injury to further improve recovery). Meanwhile, NervGen is preparing for larger trials: planning is underway for a **Phase 2b/Phase 3 trial** in a larger population, potentially as a pivotal trial for approval. They've raised additional funding (including listing on NASDAQ in late 2025 [200]) to support these trials. Anticipated next milestones: by late 2026, release of combined chronic+subacute data; in 2027, initiation of a multi-center trial with a few hundred SCI patients (possibly focusing on cervical incomplete injuries initially, as that's where data is strongest). Another watch item: NVG-291's testing in other conditions – a small trial in Multiple Sclerosis is planned or started, and preclinical work in traumatic brain injury, stroke, peripheral nerve injury, and even a model of *hearing loss* (where NVG-291 restored hearing in rats) [201]. These indicate the drug's mechanism has broad applicability in nerve repair. But SCI is the lead indication, and NVG-291 is on track to potentially become the **first drug treatment for chronic spinal cord injury** if Phase 2/3 trials confirm these early results and it gains regulatory approval in the coming years.

Timeline of NVG-291 Development & CONNECT-SCI

- **Late 1990s–2000s – Foundational Discovery:** Research by Dr. Jerry Silver (Case Western Reserve University) and others identifies *chondroitin sulfate proteoglycans (CSPGs)* in the glial scar as major inhibitors of axon regeneration after CNS injury [202]. By early 2000s, Silver's lab finds that receptors like PTPσ on neurons bind CSPGs, halting growth [160]. In 2003, PTPσ is first reported as a crucial receptor for CSPGs [160]. Silver conceives of a peptide to interfere with this receptor's inhibitory signaling, nicknamed "Intracellular Sigma Peptide" (ISP) because it mimics part of PTPσ's intracellular domain.

- **2015 – Breakthrough Animal Study:** Silver's team publishes a landmark paper in *Nature* (Lang et al. 2015) demonstrating that **systemic injections of ISP** allowed *chronically paralyzed mice and rats* to recover significant function [153]. Over 4–7 weeks of daily injections, treated animals showed *regenerated serotoninergic fibers* below the injury and regained bladder control and some walking ability [189] [153]. This was revolutionary: chronic SCI (several weeks post-injury) was thought irreversible, yet ISP-treated rodents urinated voluntarily and improved locomotion. The study also noted the peptide was not toxic and could be delivered systemically. This provided the proof-of-concept that blocking PTPσ can unlock plasticity and repair in the adult spinal cord.

- **2017 – NervGen Pharma Founded:** Recognizing the therapeutic potential, **NervGen Pharma Corp.** is founded (in Vancouver, Canada) to license and develop ISP for human use [203]. Dr. Jerry Silver and business partners including Bill Radvak form the company. They secure licensing of key patents from Case Western Reserve University on the ISP peptide technology. The drug is designated NVG-291 (with NVG-291-R referring to rodent version used in experiments, and NVG-291 human version). Early focus is spinal cord injury, but the company also eyes multiple sclerosis and other indications where scar or inhibitory molecules limit recovery.

- **2018–2019 – Preclinical & Manufacturing:** NervGen conducts preclinical studies to refine ISP into a clinical candidate. They optimize the peptide for stability and manufacturability (the peptide is ~39 amino acids with a TAT domain for cell penetration). They also perform toxicology studies in animals. Meanwhile, additional animal studies show NVG-291 (rodent version) helps in models of peripheral nerve injury and demyelination. For instance, a study sponsored by US DoD finds NVG-291 improved nerve regeneration in a sciatic nerve injury model [201]. Manufacturing processes (peptide synthesis) are established under GMP. By mid-2019, NervGen files an IND (Investigational New Drug) application with the FDA to start human trials in SCI.

- **2020 – Regulatory Hurdle:** In March 2020, the FDA places a partial clinical hold on NervGen's IND due to a preclinical finding: high doses of the peptide had effects on the female reproductive cycle in animal studies (extended estrus cycles in rodents). The FDA mandates additional studies before including women of childbearing potential. NervGen proceeds with Phase 1 in a stepwise manner: first in healthy males and post-menopausal females, deferring younger females.

- **2021 – Phase 1 Healthy Volunteer Trial:** The Phase 1 single- and multiple-ascending dose trial begins in Australia (under the streamlined Aussie regulatory system, with FDA oversight). By late 2021, NervGen reports completion of single-dose cohorts and initiation of multiple-dose cohorts [204]. Doses escalate without serious issues. In Q3 2022, NervGen announces it completed dosing in its third MAD (Multiple Ascending Dose) cohort with no safety flags [204] [205]. Eventually, they include healthy premenopausal women once FDA lifts the partial hold in mid-2022 [192]. Phase 1 results: NVG-291 is safe and well-tolerated up to the highest planned doses; pharmacokinetics

support once-daily dosing subcutaneously. Minor injection site reactions and some reports of mild tingling were noted, but no dose-limiting toxicities.

- **2022 – Trial Planning and Fast Track:** Based on Phase 1, NervGen designs the Phase 1b/2a trial "CONNECT-SCI." The trial protocol is developed in consultation with SCI experts, like Dr. Monica Perez of Shirley Ryan AbilityLab. They decide to target *cervical motor-incomplete* patients for two reasons: (1) these individuals have some preserved pathways that can be strengthened (so more measurable changes likely), (2) improving hand/arm function is a high priority outcome. In late 2022, the FDA grants **Fast Track Designation** to NVG-291 for treatment of spinal cord injury [197] [206], recognizing the serious unmet need and promising mechanism. This designation will facilitate quicker FDA interactions and potential expedited review down the line.

- **Jan 2023 – CONNECT-SCI Trial Launch:** The trial (officially NCT05965700) starts recruitment in the U.S. (sites include Shirley Ryan AbilityLab in Chicago) and Canada (Vancouver). It aims for 40 patients (20 chronic, 20 subacute). Inclusion: C4–C7 injuries, AIS B-D, 18–75 years [207] [163]. Chronic cohort: 1–10 years post-injury; Subacute: 1–3 months post. The study uses advanced outcome measures like DTI MRI and TMS-evoked MEPs to quantify connectivity.

- **Feb 2025 – First Subacute Patient Dosed:** NervGen announces dosing of first participant in the subacute cohort [199]. By this time, the chronic cohort had fully enrolled (20 participants), with last patient likely enrolled in late 2024.

- **June 2, 2025 – Positive Topline Data (Chronic Cohort):** NervGen releases topline results from the chronic cohort [167] [208]. Key findings: statistically significant improvement in MEP amplitude to a hand muscle (the first such demonstration in an SCI trial) [167]. They also report a strong trend in GRASSP hand function, and state that the drug "demonstrated a significant scientific advance" [179]. These results are concurrently presented on June 3 at the ASIA (American Spinal Injury Association) 2025 meeting in Arizona [209] [210], where Dr. Perez shares details with the SCI research community. The news is met with optimism – a noted SCI researcher not involved in the study calls it "unprecedented pharmacologic improvement in chronic SCI" in press coverage.

- **July 2025 – Company Leadership & Nasdaq Prep:** Following the positive results, NervGen's board appoints a new interim CEO (Dr. Adam Rogers) to drive strategic growth [211]. The company leverages momentum to raise funds for next trials, announcing a US$10M private placement in Nov 2025 [212]. They prepare for a Nasdaq listing to access more capital (the stock uplists in Nov 2025).

- **August–Nov 2025 – Data Deep Dive and Publicity:** On Aug 26, 2025, NervGen's Q2 report provides more color: NVG-291 improved *corticospinal connectivity* and participants reported functional gains in both upper and lower body [171] [194]. In late 2025, the company shares "expanded data" from chronic patients: by 12-month follow-up, benefits persisted and even broadened [181] [185]. This expanded data is announced Nov 24, 2025 [213] [214], just ahead of NervGen's Nasdaq debut and investor R&D day. For instance, they highlight that NVG-291 patients had significantly better bladder control – a huge win for patient quality of life [181]. These findings likely come from exit interviews and additional analyses performed after all chronic patients completed a 1-year post-study interview.

- **Late 2025 – MS Trial Initiation:** NervGen also moves NVG-291 into a small trial for Multiple Sclerosis patients (given its remyelination promise). In Q4 2025, they dose the first MS patient in an exploratory Phase 1b (to assess safety/tolerability in MS and look for any signs of improved

remyelination via evoked potentials). This demonstrates the broad interest in the drug across indications, though SCI remains priority.

- **2026 – Ongoing Subacute Cohort & Phase 2 Planning:** Through 2026, the CONNECT-SCI subacute cohort completes enrollment and follow-ups (expected final data late 2026). If positive trends appear (even if not as dramatic due to spontaneous recovery noise), it still bodes well. NervGen uses 2026 to design a larger Phase 2 or 3 trial. Likely they decide to focus on **cervical chronic/incomplete** for a pivotal trial, as that's where they have clear evidence. They might aim for a global trial (US, Canada, Europe, maybe Australia) with a few hundred patients to satisfy regulators. By end of 2026, I anticipate an announcement of the next trial design (perhaps a seamless Phase 2/3 with adaptive design to expedite progress). They'll also likely seek **Breakthrough Therapy designation** from FDA after seeing the durability of effect and patient-reported outcomes. The regulatory dialogues in 2025 indicated FDA is open to various routes for approval given the need [215] [216].

- **2027–2028 – Pivotal Trial Launch:** Provided funding (the Nasdaq listing should help raise $ for a big trial), a Phase 2b/3 trial could launch in 2027. For example, a trial with ~100-150 subjects per arm, possibly including both AIS B/C cervical injuries and maybe separate stratification for thoracic or more severe injuries to gather broader label data. They might consider combining NVG-291 with intensive rehab or stimulation in a subset to see if further gains can be achieved (though the Phase 1b/2a didn't mandate extra rehab beyond standard care, which is notable – improvements came *without* any special training regimen, indicating the drug's intrinsic effect). This larger trial would run through 2028–29.

- **2030 – Potential Approval Timeline:** If all goes smoothly, NVG-291 could achieve enough evidence to file for regulatory approval around 2029–2030, initially for treating chronic cervical SCI patients to improve motor function. Given Fast Track and possibly Breakthrough status, FDA might allow an accelerated approval if the pivotal trial confirms significant functional improvements, as there are zero existing treatments. It's not impossible that with extremely compelling Phase 2a data and urgent need, some form of early access could be considered, but more likely they'll complete a confirmatory trial. So a realistic timeline for market availability, if everything is positive, is early 2030s.

(Timeline summary sources: Jerry Silver research timeline [S7], NervGen press releases [S4][S8], ClinicalTrials.gov [S2], NeurologyLive interview with Dr. Mikol [S9]).

Mechanism of Action Explained (Plain and Technical)

Plain English Mechanism: When you get a spinal cord injury, a lot of scar tissue forms in the spinal cord. That scar tissue is full of molecules (called **CSPGs**, for short) that act like a "no entry" sign for nerve fibers – they stop nerves from regrowing and reconnecting. Normally, after development, these molecules are there to stabilize connections, but after injury they become barriers. NVG-291 is a drug that essentially **lifts those barriers**. It allows nerve cells to ignore the "stop signs" from the scar and try to regrow or make new connections. It does this by targeting a specific receptor on the nerve cells called **PTP sigma (PTPσ)**. Think of PTPσ as the lock that keeps nerves from growing when it binds to scar molecules – NVG-291 picks that lock.

In more concrete terms: NVG-291 is a small protein (peptide) that, once injected, travels to the spinal cord and attaches to PTPσ receptors on neurons and support cells. PTPσ normally, when it grabs onto

scar molecules, sends an internal signal that freezes the nerve's growth. NVG-291 binds to PTPσ in such a way that it prevents this freeze signal. So the nerve cell becomes more willing to sprout new axons or extend existing ones, even in the presence of scar. At the same time, other repair processes that were blocked can resume – for example, *myelin-making cells* (which wrap nerve fibers to help signals conduct) can remyelinate axons that lost their myelin, because CSPGs also inhibit those cells and NVG-291 relieves that inhibition [190] [153].

Key Pathway – PTPσ and CSPGs: Technically, PTPσ (Protein Tyrosine Phosphatase sigma) is a receptor that spans the neuron's membrane. Outside the cell, it has domains that bind to molecules like chondroitin sulfate (the business end of CSPGs). Inside the cell, it has an enzyme domain that, when active, alters phosphorylation of substrates to convey "stop growth" signals. The part of PTPσ called the "wedge" domain normally fits into the catalytic site to regulate its activity. NVG-291 was derived from that wedge region – so it acts like a decoy wedge. It enters the neuron and binds PTPσ in a way that *keeps it in an inactive conformation*, even if CSPGs outside are attached [159]. The result is PTPσ can't properly transmit the inhibitory signal. This mechanism was elegantly shown in Silver's lab: they observed that neurons with PTPσ genetically removed could grow past CSPGs [160], and adding the wedge peptide reproduced that effect chemically.

Downstream Effects: By blocking PTPσ, NVG-291 triggers a cascade of beneficial events: - **Axon Regeneration/Sprouting:** Neurons whose axons were cut or blocked by scar can extend processes. In experiments, the peptide allowed *serotonergic axons* from the brainstem to regrow far into the spinal cord beyond the lesion, something they never do with an intact scar [153]. Also, surviving axons can sprout collateral branches to circumvent lesions, forging new pathways. - **Plasticity/Synaptic Reconnection:** NVG-291 essentially re-opens a growth state in neurons (a bit like making them act as if they were younger and more plastic). So circuits can reorganize. For example, if one pathway was destroyed, nearby intact pathways might sprout and connect to denervated areas, restoring function via a different route. - **Remyelination:** Oligodendrocytes (and Schwann cells in PNS) often fail to remyelinate axons in an inhibitory environment. CSPGs inhibit oligodendrocyte precursor cells. Removing that inhibition fosters remyelination – evidence: NVG-291 is being tested in multiple sclerosis because it enhanced remyelination of nerve fibers in MS models [217] [218]. In SCI, demyelination around the lesion contributes to loss of function; NVG-291 likely helps re-insulate axons, improving conduction (which could partly explain the increased MEP amplitude). - **No Growth vs. Aberrant Growth trade-off:** A concern with promoting plasticity is potentially causing pain or spasticity by forming abnormal connections. Interestingly, NVG-291 doesn't appear to cause such side effects; in fact it reduced hyper-excitability (spastic reflexes) [186]. Why? Possibly because it also affects interneurons and inhibitory circuits to rebalance networks. PTPσ is on many cell types, so modulating it might also normalize some pathological circuits (like overly excited reflex loops due to injury).

Specifics of NVG-291's Composition: NVG-291 is a *peptide* roughly 39 amino acids long. It includes a sequence from the PTPσ wedge region and a cell-penetrating peptide (the TAT sequence from HIV, which is commonly used to shuttle peptides into cells). The TAT lets NVG-291 cross cell membranes to reach PTPσ inside neurons. The peptide is positively charged, helping it traverse the negatively charged extracellular matrix as well. It's administered subcutaneously (under the skin) once daily. Subcutaneous injection leads to slow release into circulation. The peptide likely crosses the blood-brain/spinal cord barrier partially (TAT helps peptides cross barriers). In preclinical models, daily dosing for several weeks was needed; similarly, in humans, they chose a 12-week course daily. The idea is to maintain a pro-growth environment throughout the period that new connections can form and consolidate.

Route and Pharmacokinetics: Sub-Q injection is relatively easy (patients or caregivers could do it at home if it becomes routine therapy). NervGen reported that NVG-291's half-life in humans was reasonable to allow once-a-day dosing (likely a few hours half-life, but effects last longer due to

downstream changes). It doesn't accumulate indefinitely; by 24 hours, a dose is mostly gone, hence daily injection. There's no need for infusion or hospital visits after training in injection technique.

Why Incomplete Injuries in trial? Mechanistically, NVG-291 can potentially help even complete injuries by promoting any latent circuits or rerouting, but the company started with motor-incomplete injuries in trials to maximize chance of detecting changes. In incomplete injuries, there are still some intact fibers that can be strengthened (leading to bigger amplitude signals, etc.). In complete injuries (AIS A), if absolutely no fibers cross the lesion, NVG-291 would have to stimulate long-distance regeneration from scratch. In animals, it did cause some new growth across gaps, but in humans gaps are larger. Likely NVG-291 would need adjunct strategies (like a graft or stimulation) to help actual reconnection in anatomically complete lesions. But incomplete injuries have dormant pathways that NVG-291 can awaken and enhance. That's exactly what the large MEP amplitude increase suggests – previously weak connections became much stronger under NVG-291, enough to drive muscle responses significantly [219].

Jerry Silver's Anecdote: Dr. Silver often uses a helpful analogy: after injury, the nervous system is like a city with broken bridges (axon cut) and traffic jams (inhibition). NVG-291 doesn't magically rebuild the whole bridge, but it lowers the toll gates that were closed. So, if there's even a tiny footbridge, it can be developed into a functional crossing. In chronic SCI, often there are some axons that never fully connected or were dormant; NVG-291 can let those flourish. It basically *creates an environment more like during development*, when axons were free to grow and find targets, albeit we're doing it in an adult nervous system.

Mechanism Supported by Biomarkers: They are looking at biomarkers like neurofilament (a marker of axonal damage) in blood – a decrease might indicate reduced ongoing injury or improved stability of axons. In MS, for example, a drop in neurofilament on NVG-291 would hint that remyelination is protecting axons from degenerate. In SCI context, not sure if they measured NF-L. But importantly, they measured *startle MEPs* which are a proxy for reticulospinal tract activity – those being reduced means NVG-291 selectively allowed purposeful motor pathways to dominate over reflex pathways [186]. This mechanistic effect – reducing spastic reflex signal – aligns with the idea that NVG-291 fosters *appropriate* plasticity rather than chaotic sprouting.

Other Receptors: PTPσ has family members (like LAR) also involved in inhibition. NVG-291 specifically targets PTPσ; it may also have some cross-effect on the LAR receptor (some data suggests the wedge peptide might also inhibit LAR's phosphatase a bit – not necessarily a bad thing as LAR too binds CSPGs). It does not directly interact with the Nogo receptor pathway, another inhibitor route – but interestingly, PTPσ and Nogo receptors converge on similar downstream signals (like Rho/ROCK pathway controlling cytoskeleton). So NVG-291 partially addresses a shared pathway of inhibition from multiple sources (CSPGs and myelin inhibitors).

Duration of Effect: The trial showed that improvements persisted even 9 months after stopping dosing [220]. This implies that NVG-291 induced lasting structural changes (once axons regrow or are remyelinated and synapses form, those can remain after drug is gone, as long as they're used). It's akin to giving a growth push, and then the circuits take hold. That is promising – it might mean a treatment course could be finite (e.g. 3-6 months of therapy, rather than a lifetime drug). Many SCI therapies, like electrical stimulators, require ongoing use; NVG-291 might be more like a regenerative jump-start with enduring benefits.

Analogy: If we liken the spinal cord to a highway system: - After injury, some highways are destroyed and roadblocks (scar) are everywhere. - NVG-291 doesn't rebuild the highway by itself, but it *removes the roadblocks and sets up detour signs*. - Neurons (drivers) then find new routes – maybe side streets

(alternative pathways) – to get signals around the damaged area. - Over time, those detours get paved and improved (with use, the connections strengthen), effectively restoring traffic flow (neural signals). - Also, maintenance crews (myelinating cells) can finally reach and repair the exposed wires (demyelinated axons), making transmission faster and more reliable. - The outcome: Information can travel more freely between brain and below injury segments, improving voluntary control and sensation.

This mechanism is why NVG-291 is often described as enabling the nervous system to heal itself. It's not introducing new cells or external hardware; it's unlocking latent capabilities for repair.

In summary, NVG-291's mechanism is *targeted regeneration enabler*. It doesn't force specific movements; it broadly reduces inhibitory factors so the body can rewire where it naturally needs to. Combined with physical activity and therapy, that rewiring can translate into regained function, as evidenced by patients reporting new abilities they practiced (e.g. using their hands more). It's a novel and elegant approach because it addresses a fundamental biological barrier rather than trying to overcome it with brute force.

(Sources: NeurologyLive Q&A [S9] bullet points on mechanism, Nature 2015 study [S11], Silver's mechanistic figures [S11], NervGen mechanism briefs [S9]).

Intervention Details (Drug, Dosing, Treatment Window, Translation)

The Drug – NVG-291: NVG-291 is a synthetic **peptide (small protein)**. It's not a pill – the digestive system would break it down – so it's given by injection. Each dose is formulated in a sterile solution for subcutaneous (under-skin) injection, much like insulin. The dosage used in CONNECT-SCI was determined in Phase 1; although exact values are not public, likely in the low milligram range per day. The drug is stable under refrigeration and can be self-administered with a sub-Q syringe (like an insulin pen possibly in future).

Dosing Regimen: In the trial, dosing is **once daily for 12 weeks** [221] [166]. Preclinical studies in rats used daily injections for about 4–7 weeks and saw maximal effects. They chose 12 weeks (~3 months) in humans to give ample time for neural changes to manifest and consolidate. It's possible future protocols might use longer dosing (maybe 6 months) or repeated courses, but starting with 3 months was cautious to assess safety and see an effect. Patients in the trial come for regular visits: baseline assessments, then dosing period (they likely learned to inject at home after initial supervision; the trial likely had them come weekly or biweekly for check-ups and outcomes at 6wk, 12wk, then follow-ups at 16wk and beyond).

Route and Administration Logistics: *Subcutaneous injection* was chosen for convenience and to avoid high peaks in bloodstream that IV might cause. Sub-Q often results in slow absorption over hours, which can maintain more steady levels. Also, patients could do sub-Q at home rather than needing IV infusions at a hospital. In Phase 1, they probably tested both sub-Q and maybe IV; sub-Q proved sufficient. The injection is likely done in abdomen or thigh. Because it's daily, injection site rotation is needed to avoid irritation.

Treatment Window Rationale (Chronic vs Subacute): - *Chronic (1+ year post-injury):* Historically considered too late for interventions beyond rehab, but NVG-291's animal data suggested even at

chronic stages it can spark new growth. They targeted chronic cohort to prove even long-standing injuries can respond (as that's a holy grail in SCI). And indeed they did see improvements even 10 years post-injury individuals (the average chronic cohort was ~3.5 years post) [222] [222]. The drug doesn't rely on acute regenerative processes; it induces them anew. - *Subacute (3 weeks to 3 months post):* This period is after the acute phase (which is chaotic with inflammation and natural recovery) but early enough that the body hasn't fully stabilized. Some spontaneous recovery happens in subacute incomplete injuries – a challenge in trials is distinguishing drug effect from spontaneous. But idea is NVG-291 could amplify the recovery seen in subacute, leading to better outcomes than natural history. Also, some pathways might die off in chronic if unused; intervening in subacute could preserve or re-route connections before they're lost. So subacute might actually be an ideal therapeutic window to maximize outcome (less time for muscles to atrophy or for maladaptive changes to cement).

No Therapy given in Acute (<2 weeks): They purposely did not test in the immediate acute phase (like days after injury) in this trial. That's because acute SCI has a huge inflammatory cascade and often other interventions (like surgery, steroids, etc.) going on. Testing a new drug in that window can be confounded and risky (and acute trials are logistically tough – need enrollment within hours of injury). The team likely will consider an acute trial in the future if subacute and chronic results remain positive, as acute use might further reduce initial damage or scarring. But starting with subacute/chronic was safer and let them isolate drug effects beyond spontaneous early recovery window.

Combination with Rehabilitation: Notably, CONNECT-SCI did not mandate any special intensive rehab beyond standard of care. Participants presumably continued their normal rehab routines if any (some chronic might have been years out of rehab). The improvements occurred largely due to the drug. However, for practical treatment, one would pair NVG-291 with activity-based therapy to harness the increased plasticity. For example, if a patient is on NVG-291 and practicing hand exercises, the new connections forming will be functionally useful. In the trial, even without a mandated extra training program, patients naturally used regained abilities in daily life (like those who felt stronger likely tried to use hands more). In a clinical setting, one would likely integrate a targeted physio program during the dosing period to maximize outcomes (like how rehab and epidural stim are combined).

Translational Steps and Model Comparability: The move from rodent to human for NVG-291 had promising alignment: rodents regained bladder function (which requires reconnection of certain descending pathways or sprouting of reflex circuits). In humans, one of the expanded findings was improved bladder control [181], which is striking and suggests similar circuit effects. The corticospinal tract is much more important in primates for voluntary movement than in rodents (rodents rely more on brainstem pathways). So seeing corticospinal improvement (MEPs) in humans is a direct translation of what they hoped, even though rodents didn't measure MEPs per se. Instead, rodents had improved locomotor scores and EMG activity. The translatability is strong because PTPσ and CSPGs are common biological factors across species.

Other Potential Uses (PTPσ Pathway beyond SCI): - *Multiple Sclerosis:* In MS, demyelination leads to lost function even if axons survive. CSPGs build up in chronic MS lesions too, inhibiting remyelination. NVG-291 in animal MS models improved remyelination and functional recovery (NervGen cited preclinical results to justify their MS trial). So mechanism: allow oligodendrocytes to remyelinate axons free of CSPG blockade. - *Alzheimer's Disease:* PTPσ is involved in binding chondroitin-rich perineuronal nets that regulate synaptic plasticity. In Alzheimer's, enhancing plasticity might help cognitive function by bypassing damaged synapses. They have some preclinical evidence (hence pipeline interest) but it's early and less direct than trauma contexts. - *Peripheral Nerve Injury:* PNS can regenerate somewhat, but often incomplete especially in long gaps. NVG-291 in a severe peripheral nerve injury model (sciatic nerve gap) improved regrowth and functional outcomes [223] [224]. Could be used to boost nerve repair after accidents or surgeries. - *Traumatic Brain Injury & Stroke:* Similar logic: glial scar in brain injuries and

stroke cavities inhibit plasticity. A PTPσ blocker could aid stroke rehab by promoting sprouting of spared fibers to rewire lost connections.

Intellectual Property & Manufacturing: NervGen has patents on the composition of matter of NVG-291 (granted in various regions – one press release noted a U.S. patent issuance for PTPσ-targeting peptides) [225] [226]. They also have patents for uses in various injuries (one mentioned heart attack – because CSPGs play a role in cardiac scar too, interestingly NervGen got a patent for treating heart injury with such peptides [227] [228]). Manufacture is synthetic (solid-phase peptide synthesis) which is a well-known process; scale-up is costly but feasible. Peptides of this size are routinely made for other drugs (like TIDES). They will have to ensure purity and no immunogenic sequences – so far no immunogenicity issues reported (likely because it's human-sequence-based and relatively short term dosing).

Comparison to Other Approaches: NVG-291's approach is unique among current SCI therapies: - Not a cell transplant (no surgery needed). - Not a device (like epidural stim). - A systemic drug that acts on the central nervous system's environment, akin to some previous attempts like *Cethrin* (a Rho pathway inhibitor delivered locally in acute SCI – which had mixed results). But NVG-291 is systemic and chronic-phase oriented, making it more versatile. - Anti-Nogo antibodies (e.g. Novartis's ATI355) also aimed to promote growth by blocking myelin inhibitors, but large trials in acute SCI did not show clear functional benefit. PTPσ pathway might be a more central "master switch" affecting multiple inhibitors, possibly explaining NVG-291's better success. - Chondroitinase enzyme (breaks down CSPGs) is a gold-standard in animal SCI research – it has restored function in many rodent studies. NVG-291 is somewhat mimicking chondroitinase's effect (both target CSPG inhibition), but NVG-291, being a drug, is easier to deliver than an enzyme or gene therapy and may have fewer side effects (chondroitinase could in theory degrade some needed extracellular matrix, whereas blocking PTPσ might be more targeted). - So NVG-291 is basically a pharmacological approach to do what many have tried via gene or cell methods – enhance regeneration. If it continues to succeed, it could potentially be combined with those other therapies for synergistic effects (e.g., giving NVG-291 to a patient who got a cell transplant or who is using epidural stimulation, to maximize their improvements).

Invasiveness and Scalability: NVG-291 is **minimally invasive** – just injections, no surgery. This is a huge plus for scalability: it can in principle be administered at any hospital or even at home, reaching SCI patients globally if approved. Contrast that with cell therapy that requires neurosurgery and specialized lab processing per patient (like the OEC trial). NVG-291 production would be centralized and distributed as vials, which is far more scalable. The simpler administration also means it could be given to a large proportion of patients, including those who might not tolerate major surgeries.

Patient Experience: Participants in the chronic cohort described being on the drug for 3 months and noticing gradual changes – e.g., one might have felt stronger grip after some weeks and started practicing self-care tasks more. It's not an immediate effect like a stimulant; it's more like physical improvements that accumulate as the nervous system adapts. Because it's not a stimulant or something affecting neurotransmitters directly, there's no cognitive high or sedation – participants likely didn't "feel" the drug in a subjective way (except injection sting). The effects are measured in what they can do.

Monitoring During Treatment: They likely monitored participants regularly with neurological exams, but the big measurements were baseline and end-of-treatment (16 weeks after start). Many probably underwent TMS sessions to evoke MEPs at baseline, 6wk, 12wk, 16wk. They also did MRIs at baseline and week16 to see any changes in spinal cord structure or connectivity (though none reported yet, maybe still analyzing). Also blood draws for biomarkers.

In sum, the intervention is relatively **straightforward and patient-friendly** as far as experimental treatments go – a daily shot for 3 months. If it becomes a product, one can imagine a regimen like: an SCI patient (chronic incomplete) gets evaluated, if suitable, they receive NVG-291 daily for 3 months along with rehab, then stop and see stable gains. Possibly the course could be repeated after another 3-6 months if more gains could be coaxed, or if plateau, maybe no further dosing needed. This remains to be seen in future studies.

Trial Details (CONNECT-SCI Protocol) and Results Deep Dive

Trial Design Recap: CONNECT-SCI is a Phase 1b/2a trial (essentially an early Phase 2 proof-of-concept) with two parallel arms – chronic and subacute – both *randomized, placebo-controlled, double-blind*. Each arm aimed for n=20 (though initially they said 20 per cohort, some sources imply 20 total with both cohorts combined; however, given separate mentions of 20 in chronic, it seems 20 each). The randomization in chronic cohort was 1:1 (10 NVG-291 : 10 placebo) [196]; in subacute I believe they considered possibly 2:1 to get more drug exposure but likely also 1:1 for statistical clarity (some sources say 2 cohorts of 20 and results will be analyzed separately but possibly also combined later) [229].

Eligibility: - Level C4-C7 (so lower cervical to upper – likely to focus on upper limb outcomes, and because MEPs are easier to measure for hand muscles which are C8/T1 – some might have C8 segment involvement if injury at C7). - AIS B, C, or D (meaning no motor below but some sensory, or some motor but weak, or stronger but not normal) [163]. - Chronic cohort = injury ≥1 year (up to 10 yrs; mean 3.5 yrs reported) [222]. Subacute = injury 3 weeks to 3 months (some sources say 20-90 days). - Ages 18-75, both sexes (once female restriction lifted). - Exclusions: any condition that could confound endpoints (e.g. severe spasticity requiring anti-spastic meds changed recently, etc.), or inability to undergo MRIs or TMS, etc. They also likely excluded people with complete injuries or significant brain injury etc.

Endpoints & Assessments: - *Primary (co-primary)*: 1. Change in amplitude of **motor evoked potentials (MEPs)** in FDI (First Dorsal Interosseous) muscle of hand [167]. 2. Change in MEP amplitude in **Tibialis Anterior** muscle of leg [174]. (These were measured via transcranial magnetic stimulation of the motor cortex and EMG recording in those muscles. FDI is innervated by C8/T1 via ulnar nerve; Tib Ant is L4/L5 via peroneal nerve. By choosing one upper, one lower limb muscle, they covered cervical and lumbosacral segments.) - They assessed these at baseline and week 12 (end of dosing), possibly also intermediate. - **Baseline differences**: They would have made sure participants had MEPs present at baseline (since AIS B might have none). They probably included only those with at least a minimal MEP to have something to improve (maybe AIS B with zones of partial preservation could still have some MEPs, or they might have mostly AIS C/D). - The chronic cohort results: FDI MEP amplitude in NVG-291 group increased ~3-fold vs ~1.1-fold in placebo (the press phrased "normalized MEP amplitude increased 3-fold in treated, with p=0.0155") [173]. Tib Ant: no significant difference (likely slight increase but not enough vs placebo). - A tripling of MEP amplitude is huge; clinically, that could correspond to going from trace muscle contraction to a robust contraction. It implies more corticospinal fibers are conducting or existing ones conduct better (maybe remyelinated or synaptic strength improved). FDI MEP presence in chronic incomplete means there were some surviving fibers; NVG-291 amplified those signals dramatically. - *Secondary:* - **GRASSP (Graded Redefined Assessment of Strength, Sensibility and Prehension)** – specifically they reported on the quantitative prehension subscore (GRASSP has components like strength, sensation, and prehension for each hand). They saw +3.7 improvement vs +0.4 placebo [176]. This was not $p<0.05$ but an obvious numeric trend. To contextualize, GRASSP scores range, e.g., 0-20 or so for some subscales; a ~3-pt change in hand function is considered clinically meaningful if it's in strength or ability (like going from needing tenodesis grip to having some finger flexion). - **SCIM (Spinal Cord Independence Measure)** or similar ADL measures likely recorded,

possibly in exit interviews (the improvements in bladder and self-care tasks likely would reflect in SCIM scores in areas of self-care and respiration/sphincter control). They haven't disclosed SCIM, but the narrative accounts suggest NVG group might have improved in SCIM more than placebo by follow-up (maybe not at 16w, but by 12m when those functions manifested). - **10-Meter Walk Test** or gait speed for those who could walk at baseline (some AIS D participants might have walking ability). They noted no clear difference on "other clinical measures" in topline [177], which likely include walking speed and the Nine-Hole Peg Test (9-HPT) for hand dexterity, or pinch strength. It's possible small sample and variability masked changes there. For instance, the CEO in interviews mentioned "No clear separation on other measures based on initial topline, additional analyses forthcoming" [177]. - **Spasticity**: They probably measured via Ashworth scale or frequency of spasms. They didn't detail in PR, but the qualitative data indicated spasticity was reduced (a participant quote about less stiffness, plus the objective startle MEP test). - **SSEPs (somatosensory evoked potentials)**: Possibly measured, but more relevant in complete injuries. Not mentioned, so maybe not a focus. - **MRI DTI (Diffusion Tensor Imaging):** They intended to evaluate descending connectivity in trial description [230]. Possibly measuring fractional anisotropy (FA) of white matter tracts above vs below lesion. If NVG-291 causes sprouting or remyelination, FA might increase across the injury. But analyzing DTI in SCI is complex. No mention yet; maybe results pending or not enough resolution in small sample. - **Biomarkers:** Could include things like *NfL (neurofilament light)* in blood or CSF (reduced levels might indicate less axon stress). Not reported, likely sample too small or not done due to cost. - **Reticulospinal excitability (Startle MEP):** They did mention "statistically significant reduction of hyperactive reticulospinal signaling via startle MEP in upper and lower limbs" [186]. That suggests they did a "StartReact" paradigm: giving a loud auditory stimulus triggers involuntary startle reflex, which in SCI is often exaggerated below lesion (due to loss of inhibitory control). NVG-291 reduced that MEP amplitude, meaning regained inhibition or balanced network. This is a cool sophisticated measure to show NVG-291 isn't just boosting everything indiscriminately; it actually normalized reflexes by presumably regrowing inhibitory interneuron circuits or reinstating cortical control. - **Quality of Life/Independence:** Formal measures (like SF-36 or WHOQOL) might have been included. The press mostly conveyed through patient quotes in exit interviews that independence improved (e.g. "I can now take care of myself"). Possibly measured via SCIM or Spinal Cord Ability Rater, etc. We'll see on full publication.

Chronic Cohort Outcomes Summarized: - Safe/tolerable. - MEP in hand: +300% (p~0.016). - MEP in leg: non-sig change. - Hand function GRASSP: treated group ~+3.7 points vs placebo ~+0.4 (p maybe ~0.1). - No difference in 10m walk or 9-hole peg (likely due to small numbers who could perform test; or NVG ones improved but so did placebo if AIS D). - No change in AIS grade for anyone (likely, since no mention; maybe a couple AIS C might have become AIS D with improved motor scores). - But exit interviews at 1 year after treatment revealed: - X% of treated reported improvements in ADLs vs Y% of placebo. Press quotes suggest almost all treated noted something major regained, placebo minimal. - Specifically, regained voluntary bladder voiding or substantial increase in time between catheterizations in some treated vs none in placebo (implied by "substantial improvements in bladder control compared to placebo" [181]). - Less spasticity in treated vs no change/worse in placebo. - Possibly some treated regained sexual function or blood pressure stability (not mentioned in press, but those are often tied to autonomic improvements). - Quotes: - Treated: "I can now brush my teeth/hair, cut food, do art projects, open soda can, twist a door knob" [184] – implying fine motor improvement. - Another might have said "I can now get myself into bed from wheelchair, and stand a bit better" (we don't have that quote but wouldn't be surprising if lower limb). - Placebo recipients likely didn't report such changes beyond perhaps standard progression or small rehab gains.

Subacute Cohort (still blinded as of Jan 2026): - They will measure similar outcomes, but baseline in subacute might show more improvement in placebo naturally (spontaneous). - If NVG-291 group improves significantly more or faster, that's success. Given chronic results, one expects subacute also to do well, though difference might be a bit less dramatic relative to control because control in subacute

does improve too. - One nuance: they are dosing subacute at 20-90 days – which overlaps with natural recovery period up to ~6 months. They may measure at 6 months out to see final outcomes vs baseline. That data might show NVG-291 group reaches higher functional plateau than placebo group. - If subacute results are positive, NVG-291 might then be indicated both for chronic patients to regain lost function and for early use in new injuries to maximize recovery (like a neurorecovery booster given as soon as patient stable after injury).

Functional Impact in Real Terms: - A 3x MEP increase might correlate to going from flicker of finger movement to actual useful grasp strength. Possibly some NVG-291 patients went from not being able to pinch to being able to pinch moderately. - 3.7 GRASSP prehension increase is meaningful: e.g. going from needing tenodesis grasp (wrist extension trick) to maybe being able to flex fingers a bit or hold a small object. - Bladder improvement likely means going from full-time catheterization to possibly being able to initiate voiding occasionally (some might have dropped frequency of catheter, or regained sensation of fullness which itself is huge to avoid accidents). - Spasticity reduction can ease caregiving (less spasms means easier dressing, less pain, better sleep). - These are the kinds of improvements patients rank extremely high. Even if they didn't suddenly walk, regaining upper body function and bladder control outranks walking in many surveys of tetraplegics for quality of life impact.

Statistical/Clinical Significance: - The trial wasn't large enough to measure things like SCIM with statistical significance, but likely clinically meaningful differences occurred. E.g., a SCIM increase of, say, 5-10 points in treatment vs 0-2 in placebo would indicate more independence (SCIM covers self-care, respiration, sphincter, mobility). - The significance achieved on MEP is strong because small sample and still got $p<0.02$, meaning effect size is large. That's encouraging for Phase 3 powering. - The fact multiple outcomes (MEP, GRASSP, interviews) all favored NVG group gives consistency (though not all reached significance due to N). - Safety significance: injection site reactions obviously less severe than any effect of regained function – an easy trade-off.

Cross-check vs other attempts: - ReNetX's *CSPG decoy* (AXER-204) completed a Phase 2 in chronic cervical AIS B-D in 2021; it did not meet endpoints (tested effects of an anti-Nogo receptor fusion protein in chronic, outcome measure was upper extremity motor score – no significant difference). So NVG-291 achieving success where that failed suggests maybe PTPσ blockade is more effective or trial design was better (MEP is more sensitive than motor score possibly). - Mentioning that because it highlights the novelty that NVG-291 is first to show a positive RCT in chronic SCI. The NeurologyLive piece even said it's the first to show improved motor recovery via increased MEP amplitude [179]. - It sets a precedent and raises hope that pharmacological neurorehabilitation for chronic SCI is plausible.

Trial Extension or Open-Label: They haven't announced but I wonder if after 16 weeks, they allowed placebo patients to get drug in an open-label extension (typical in Phase 2 when effect seen, for ethical reasons, and to gather more safety). Perhaps after all outcome measures at 16 weeks, they offered placebo group NVG-291 for 12 weeks too. If they did, those individuals' improvements might also be tracked (which would further confirm efficacy if they then improve after switching). If not done, likely because they want to keep things clean for subacute analysis or plan to do such cross-over in Phase 2.

All signs suggest NVG-291 is a *genuine disease-modifying therapy* for SCI, not just symptomatic. It addresses the underlying block to regeneration. The trial's results appear to validate decades of basic research that this approach can work in humans.

Safety, Risks, and Side Effects

Known Safety Profile (so far): NVG-291 has been well-tolerated in both healthy volunteers and SCI patients up to 12 weeks of dosing. No serious or irreversible adverse events attributed to the drug have been reported [178]. The most common side effects are: - **Injection site reactions:** mild redness, swelling, or pain at the injection site. In Phase 1 and Phase 1b, many subjects got some injection site erythema or small hematomas (like what one might get from daily insulin shots). These were typically mild (Grade 1) and resolved without intervention [178]. - **Transient sensory effects:** In Phase 1, a few participants reported transient numbness or tingling sensations at higher doses. This was likely related to the drug's effect on neurons (perhaps a temporary peripheral nerve effect since PTPσ also expressed in sensory neurons). However, these were not severe and did not last. In SCI patients, it's not noted if any new tingling occurred – possibly hard to differentiate from existing paresthesia. But importantly, no increase in neuropathic pain was seen. - **Systemic effects:** No significant changes in blood pressure, heart rate, or lab values (liver enzymes, kidney function, blood counts) were seen versus placebo. NVG-291 doesn't target organ receptors, so it's expected to be fairly specific to nervous tissue responses. The Phase 1 did include thorough lab panels – presumably all came back normal aside from maybe some minor changes within normal variation.

Serious Adverse Events (SAEs): In the CONNECT trial, no drug-related SAEs occurred. There were some SAEs reported in press but all were deemed unrelated (e.g., one might have had a UTI requiring hospitalization – common in SCI – but it occurred equally in placebo or prior to dosing). No one had a severe allergic reaction or anything requiring stopping the drug. The partial FDA hold in 2020 was due to preclinical findings (effects on menstrual cycle in rats) – so let's address that: - In preclinical toxicology, female rodents at high doses of the peptide had prolonged estrus cycles (a sign of possible hormone or ovarian effect). The mechanism is unclear (PTPσ expressed in reproductive tissues? Or an off-target effect?). As a precaution, FDA had NervGen start Phase 1 only in male and post-menopausal female volunteers [192] [231]. After additional animal studies, they found no histological damage to reproductive organs and the effect might have been species-specific or dose-specific. The FDA then allowed including premenopausal women. In the multiple dose Phase 1, they did include premenopausal women at the intended therapeutic dose and found no meaningful effect on their menstrual cycles or hormones reported. So that risk was largely put to rest (though continued monitoring in Phase 2 will likely include checking female hormonal cycles to be sure). But at this point, the reproductive risk seems low, especially given the dosing is finite (3 months, not chronic long-term). - Still, in the trial they likely advised women of childbearing potential to use contraception, etc., as a precaution (standard for experimental drug).

Long-Term Safety Unknowns: - **Tumorigenicity:** Always a question when promoting cell growth – could it potentially promote tumor growth? PTPσ is present on some tumor cells (like certain cancers). However, NVG-291 is given temporarily and doesn't permanently alter cells. No increase in tumors in animal chronic studies was noted. It's something to watch in the long term, but short trials have not indicated any red flags (like no out-of-proportion cancers in Phase 1 or 1b, albeit small N). Preclinical rodent studies did not see any increase in spinal cord scarring or aberrant growths beyond intended axon growth. - **Immune response to peptide:** The drug is a peptide partly based on human protein sequence. It could potentially be antigenic if the body sees it as foreign. Phase 1 likely measured anti-drug antibodies; no mention suggests none significant. Possibly, because of the TAT segment (from HIV), there might be some antibodies generated, but short dosing period might avoid any neutralization issues. If one were to have repeated courses, it's something to watch if antibodies develop that clear the drug faster or cause reactions. No allergic reactions have been reported though. - **Effect on neural plasticity beyond intended timeframe:** The improvements persisted post treatment which is good, but we should consider: does turning on plasticity have any downsides? For example, in theory, too much plasticity could cause pain or spasticity if aberrant circuits form. But ironically,

NVG-291 *reduced* pain/spasticity symptoms in results. Possibly because it allows proper circuits to re-form that modulate these issues. There was a mention that in animal models of chronic pain, PTPσ also plays a role – and blocking it might actually reduce chronic pain (some evidence suggests CSPGs contribute to chronic pain states). So currently, it seems more likely to help than harm in that domain. - **Autonomic Effects:** Did any treated patients have episodes of autonomic dysreflexia or hypotension? Possibly they monitored, and given less spasticity and improved bladder function, one might guess fewer dysreflexia episodes, not more (some AD is triggered by bladder overfilling – if regained control, that trigger lessens). They didn't report any adverse autonomic crises, which they would have if it occurred. - **Concurrent Medications:** Many SCI patients are on drugs (antispasticity drugs like baclofen, pain meds, etc.). The trial presumably allowed stable regimens. No interactions have been flagged. NVG-291's mechanism is very localized to neural tissue; it doesn't use cytochrome metabolism heavily (peptides are broken down by proteases), so drug interactions minimal.

Patient Risk-Benefit: For someone with chronic SCI, the potential benefits (return of function) far outweigh a bit of injection site annoyance. That's likely why participants were enthusiastic – a few injection bumps is trivial compared to, say, what OEC trial participants undergo (nasal biopsy, major back surgery, etc.). NVG-291's safety profile relative to other interventions is extremely benign. For example, some experimental treatments like high-dose anabolic steroids or nerve growth factors had serious side effects (blood clots, pain). NVG-291's targeted approach didn't have those systemic issues. Also no cognitive or mood side effects noted (the drug doesn't cross into brain widely to affect cognition except maybe in an injury area). Patients didn't report headaches or fatigue or such – none mentioned at least.

One possible risk to consider: If used in acute phase (not done yet in humans, but eventually might try), turning on growth too early in an environment of acute inflammation could theoretically cause misrouting or increased excitotoxicity. But in subacute (a few weeks out) the environment is likely ready. They purposely avoided hyperacute usage likely to let initial stabilization occur (plus patients in first 2 weeks often medically unstable). When they do attempt acute (maybe future trial, e.g. start at day 4 post-injury), they'll have to ensure it doesn't exacerbate acute damage. Preclinical acute models might have been done – likely safe as long as start after hemorrhage subsides.

Reproductive and Use in Women: After the hold was lifted, they likely had some women in the chronic cohort. The press doesn't specify breakdown, but likely at least a few were female. If any effect on menstruation occurred, they'd have noted, but none reported. That's reassuring. Still, it's prudent not to give this drug during pregnancy – how it might affect a developing fetus is unknown (PTPσ plays a role in neural development, theoretically blocking it at that stage could cause issues). So pregnant women were excluded and will be in the near future. But that's standard; not a big concern for the main SCI population early on (if approved, it'll come with guidelines for contraception during therapy, etc., like many drugs do).

In summary, the risk profile is low: Minor injection site issues, and potential immune or reproductive concerns that so far haven't manifested significantly. The known side effects are manageable with simple measures (e.g., rotate injection sites, apply cold compress for injection site). There's no known serious organ toxicity or neurological worsening due to NVG-291. Actually, it seems to either not affect or improve most neurological symptoms.

Risks of Not Taking It (for perspective): Chronic SCI without such treatment means likely no further recovery, possible gradual decline (muscle atrophy, etc.). So many would be willing to accept far more risk for some hope of improvement. But fortunately, NVG-291 doesn't ask them to accept much risk at all.

Class-related concerns: NVG-291 inaugurates a new class of "matrix modulators." There's no track record of similar drugs in humans to compare. So regulators will keep an eye on any unanticipated consequences as more patients take it. For example, if dozens of patients are treated, rarely something weird could appear (like if someone had a subclinical malignancy, does NVG-291 accelerate it? No evidence, but they'll watch). Given we have an understanding of PTPσ's role (mostly local to injuries and certain cell guidance), it's less likely to cause distant systemic issues.

Conclusion on safety: The data so far indicate NVG-291 is **safe and very tolerable** for SCI patients, which is critically important – it means it can realistically be deployed widely if efficacious. The main caution going forward will be continuing to monitor long-term outcomes and ensuring combining it with other therapies (like if patients are on anti-spasticity meds, etc.) doesn't have unforeseen effects. But the risk/benefit analysis at this point is strongly favorable for NVG-291.

Intellectual Property, Manufacturing, and Scalability

Intellectual Property (IP): NervGen Pharma holds a robust patent portfolio around NVG-291 and related peptides. Key IP includes: - **Composition of Matter Patent for NVG-291:** Granted in major markets (e.g., US Patent announced Nov 2021) covering the peptide's sequence and structure [225] [226]. This prevents any generic or competitor from making the same peptide. Typically, such patents last 20 years from filing; given initial filings likely around 2018, protection would extend into ~2038, possibly beyond with extensions (especially if they get orphan drug exclusivity for SCI which could add years). - **Use Patents:** Patents covering use of PTPσ inhibitors for treating various conditions – e.g., SCI, peripheral nerve injury, heart attack (NervGen press said a patent was allowed for heart disease use of ISP which they consider broadening beyond neuro) [227] [228], and likely MS, stroke, etc. These ensure that even if a competitor tried a different PTPσ blocker, they might infringe on method-of-use for nerve repair. - **Delivery/Combination Patents:** Possibly patents around combination of NVG-291 with other therapies or specific formulations (like sustained release forms). Not sure if any filed yet, but could be future strategy. - The IP originated from Case Western Reserve University (Jerry Silver's institution) and the University of Toronto (co-inventors like Dr. Karimi-Abdolrezaee). NervGen presumably has an exclusive worldwide license. They've been actively growing patent estate – e.g. adding the cardio patent suggests they think beyond SCI.

Manufacturing & Scalability: - NVG-291 is a synthetic peptide produced by solid-phase peptide synthesis (SPPS). The sequence (with a TAT cell-penetrating domain and the wedge sequence) is on the order of 30-40 amino acids. Peptides of this length can be made at scale using modern synthesizers and then purified by HPLC. - The cost of goods for peptides is higher than small molecules but with scale it comes down. For reference, other therapeutic peptides (like Glatiramer acetate in MS – which is actually a random polymer of AAs – or certain hormone analogs) are produced in multi-kilogram scale. NVG-291 likely would be dosed in maybe tens of mg per injection (just guessing: If in rats they used e.g. 10 mg/kg, in humans perhaps 0.3 mg/kg ~ 20 mg for a 70kg person daily?). That's 20 mg/day for 90 days ~ 1.8 g per patient per course. For 1000 patients, need ~1.8 kg of peptide. That's doable with contract manufacturing (CROs like Bachem or PolyPeptide have capacity for multi-kilogram peptides). - They'd produce it under cGMP conditions. The Phase 1/2 material likely came from a specialized peptide manufacturer partner. NervGen might continue using a CMO (Contract Manufacturing Org) rather than building their own plant, at least until high volume needed. - Purity and characterization: They must ensure each batch is pure (with any variants or truncations removed). Peptides can sometimes aggregate; formulation likely includes a buffer to keep it stable (maybe an acetate buffered saline). - Storage: Typically peptides are lyophilized (freeze-dried) and reconstituted before injection. Not sure if NVG-291 is stable in solution – might come in vials you add sterile water to. Or possibly in pre-filled

syringes if stable enough. But likely a lyophilized product to maximize shelf life (maybe stable 2+ years at 2-8°C). - **Scalability:** The good thing about synthetic manufacturing is it's linear scalable – just bigger batches. There's no need for personalized production (unlike cell therapies). So if demand goes up, one can invest in bigger synthesis columns or parallelize production. It's expensive but straightforward. Already, given they plan Phase 3, they'll be negotiating manufacturing for larger quantities. - In terms of cost: Peptides can be pricey, but in context of SCI treatments, any new therapy would have premium pricing due to small population and high value. However, because it's not an ultra-complex biologic (like a gene therapy which costs $1M), but a peptide, one could hope it's relatively affordable (maybe on par with MS drugs or similar). If they succeed and produce at scale, cost per 3-month course might be in tens of thousands of USD. Insurers might cover given lack of alternatives and life-changing nature. Also, NVG-291 might qualify for orphan drug (though SCI population ~300k in US, borderline orphan but likely qualifies) giving some incentives and exclusivity. - **Quality control:** They have to monitor that each batch of NVG-291 is identical (as peptides can have different folding; but NVG-291 likely doesn't require folding, it's not a complex protein with tertiary structure – it's somewhat disordered peptide, plus TAT which is inherently unstructured). So main QC is sequence verification and purity. The release specs would include peptide content, impurity profile, absence of endotoxins, etc.

Practical Scalability: NVG-291 has a huge advantage: it's an off-the-shelf product that can be shipped and used anywhere with minimal infrastructure. A patient in rural areas could theoretically self-inject daily at home after an initial training. They'd need periodic check-ups, but not daily hospital visits. Compare that to something like epidural stimulation which requires surgical implantation and long follow-ups – NVG-291 is far more scalable globally if it works. - This means if approved, distribution can follow normal pharma channels (pharmacies, specialty distributors). Cold-chain shipping (like how insulin is shipped) might be needed if it's not stable room temp. But cold chain is standard for many drugs now.

Company and Funding: - NervGen is a small biotech (~20-30 staff). It has raised funds through venture capital, grants (they got a DoD grant for some preclinical work in 2020), and now through equity markets (TSX-V in Canada, and recently Nasdaq listing in Nov 2025 gave them exposure to US investors). - If Phase 2 trial is large, they might partner with a big pharma for co-development or at least for international territories. A large pharma might be interested given first-in-class potential. The company has signaled interest in partnering especially for MS or AD indications (which are bigger markets). For SCI, they might carry forward themselves given orphan nature (and they have Fast Track). - They've also initiated an **Expanded Access Policy** in late 2025 [232] [233], meaning in some cases patients not in trial might request compassionate use. That suggests they believe safety is good and want to allow critical cases to potentially get drug early.

Likely First Approvals & Real-World Use: - If all goes well, NVG-291 could be approved for "treatment of chronic spinal cord injury in patients with residual motor function (AIS B-D), to improve motor and sensory function." Possibly initial label might specify cervical injuries (since trial was that). Off-label, doctors could try for thoracic incomplete as well. Then maybe expanded label for subacute use once data confirmed. - Real-world, it might be used in rehab centers: e.g., a patient 6 months post injury at a rehab hospital might be put on NVG-291 for 3 months while doing therapy. Or a patient 5 years post with plateau could be re-admitted to a rehab program with NVG-291 on board to try to get new gains.

Competing or Complementary IP: - No one else has a PTPσ blocking peptide in clinic. There was some academic work on small molecules blocking LAR/PTPσ, but not near clinical stage. - ReNetX's approach was a decoy receptor for Nogo and other myelin inhibitors (they had IP on that, but their trial missed endpoints; not sure if they'll pivot or if their tech still alive). - If NervGen's tech stands alone, they'll have quite a monopoly in regeneration drugs for some time. They might license it out for combination (e.g., combining NVG-291 with cell therapy might require cross-licensing if another company has cell IP – but

more likely NervGen could collaborate and share). - NervGen also licensed from Case Western some IP for using it in MS and AD (Case had patents on cognitive enhancement via CSPG modulation). - Patent life into late 2030s means if it launches ~2030, they'd have at least ~8+ years market exclusivity (maybe more with orphan exclusivity and possible pediatric extension if tested in adolescents). - This is important for investors as it means they can recoup R&D with premium pricing before generics. Also, by that time, perhaps a next-generation variant or new formulation could extend IP further.

Manufacturing at scale (ease or complexity): - One note: TAT peptides can sometimes stick to containers due to basic residues, so formulation might need surfactants to prevent loss on vial walls. But those are formulation science details presumably solved in development. - If demand soared to tens of thousands of patients, they'd likely outsource to a big peptide manufacturer (there are facilities that can produce multi-kg peptides routinely, e.g. for diabetes GLP-1 analogs which are peptides mass-produced). - Or if acquired by a larger pharma, that pharma might integrate production into their biologics manufacturing pipeline.

Logistics of patient usage if approved: - Because it's injection, initial training by a nurse is needed, but many SCI patients or their caregivers are used to injections (some do Lovenox blood thinner shots after injury, etc.). So not a big hurdle. - There's no special equipment needed beyond syringes. Possibly an autoinjector could be developed for ease (like an EpiPen style device for daily use – though daily EpiPen is overkill, more likely something like insulin pens). - The company might eventually create a pen with multi-dose cartridge to minimize needle sticks (some peptides are delivered by insulin pen technology nowadays). - The injection doesn't need to be intravenous, so patients don't need help finding veins (which can be tough in SCI patients due to muscle atrophy), sub-Q can be done in belly or thigh even by themselves if hand function allows. Some tetraplegics might need a caregiver to inject, but they likely already have caregivers for other tasks, so that's manageable.

Overall, NVG-291 is highly scalable from both manufacturing and deployment perspectives – which is exciting, because a therapy that can reach a lot of patients is how you have broad impact.

Controversies, Skepticism, and Field Perspective

Initial Skepticism: The idea of regenerating the spinal cord pharmacologically had been met with skepticism due to past failures. For years, researchers tried things like growth factors, anti-Nogo antibodies, etc., without clear success in humans. So when NervGen emerged, some in the field took a "wait and see" stance. Key skeptical points were: - *"No drug has ever improved chronic SCI – why will this be different?"* The answer came in 2025: because it targets a central pathway (PTPσ) and indeed showed results, addressing that skepticism directly. - *Preclinical over-promising:* Some noted that Jerry Silver's rat results were dramatic, but replications by others or translation often disappoint. There was also a specific scientific debate: after Silver's Nature 2015, another group (Li et al. 2015 in J. Neurosci) published a paper failing to replicate benefits of a similar peptide (they used a modified ISP called sISP in mice and reported no functional benefit [234]). Silver rebutted that the conditions were different. This raised some controversy about how robust the animal findings were. But the success in humans now gives Silver's approach a strong vindication. - *Mechanism completeness:* Some skeptics thought "just blocking CSPGs might not be enough because there are multiple inhibitors (myelin proteins like Nogo, MAG, etc.) and neuron-intrinsic limitations." NVG-291's results suggest that overcoming CSPGs (and possibly some overlapping pathways) might indeed be enough to yield functional gains, at least in incomplete injuries. It doesn't address everything (e.g., if neurons died, new ones aren't created by NVG-291), but it seems enough survive to matter. - *Small sample, hype risk:* There is some caution that the current results, while great, are from 10 treated patients. Some in the community (and investors)

could over-interpret it as a "cure." The proper messaging (and indeed Dr. Mikol's interviews) is measured: it's a step forward, not full restoration. If hyped as "patients regained use of arms", one must clarify they improved, not necessarily full function. The NeurologyLive interview, for instance, tempered it: calling it a significant advance but noting heterogeneity of SCI means results vary [235] [236]. - *Field acceptance:* The SCI research community tends to be careful given many disappointments. After this trial, however, I suspect many scientists are becoming believers. It's telling that an editorial piece on a neurology site basically cheered the result and called it a big step. Still, some may reserve full judgment until Phase 3 confirms it in larger numbers. The "cautious optimism" approach is likely prevalent: they are excited but want to see the next trial replicate these findings.

Competing Approaches & Potential Skepticism: - **Cell therapies (like OEC transplants, NSC transplants)**: Some might question if NVG-291 is needed if, say, cell therapies progress. However, many view them as complementary. Actually, Dr. Silver's initial vision was that combining a strategy like NVG-291 with cell grafts and rehab might yield the best outcomes (multi-modal). There's no head-to-head competition yet. A patient or doctor could consider both: "should I get a cell transplant or do NVG-291?" They operate differently (one provides bridge, the other loosens environment). Possibly in the future they'll be combined. - Some regenerative medicine purists might favor cell approaches and want more proof a drug can do enough on its own. - **Epidural stimulation**: Now a somewhat established technology enabling stand/step with device assistance. Some might say: why not just use an epidural stim implant, which already helped dozens of patients achieve some standing/stepping? The difference: stim requires the device on to produce movement; turn it off, movement is gone. It doesn't restore the actual neural pathway for voluntary control in absence of stimulation (though it has led to some plasticity as well, but mainly it's an ongoing neuromodulation). NVG-291 aims for actual biological repair, leading to regained volitional control by the brain. They aren't mutually exclusive; maybe future rehab will use both (stim to actively train muscles and NVG-291 to regrow circuits – could be synergistic). - So far, NVG-291's improvement is measured in things like hand dexterity; epidural stim mainly tackled locomotion and trunk control (because they place stim in lumbar cord). NVG-291 shines in cervical injuries (hand function regained), where stimulation is trickier (cervical stimulation research is ongoing but not as advanced as lumbar). - **Chondroitinase gene therapy**: There's a group pushing a gene therapy to produce chondroitinase enzyme in spinal cord (research in UK primates by Verhaagen & colleagues funded by Wings for Life). If that enters trials, it could be a competitor. But gene therapy has its own complexities (delivery via viruses, irreversible expression etc.). NVG-291 by contrast is a tunable therapy (start/stop at will). Some proponents of chondroitinase might want to compare which is better – but realistically, if NVG-291 can achieve much the same effect without gene therapy's risk, it might preempt that approach. - **Jerry Silver's role & hype**: Dr. Silver is an esteemed researcher and he's on NervGen's scientific advisory board. He's passionate and sometimes his excitement can be misinterpreted as hype. But he's also a realist in understanding this is part of the solution. I recall at conferences he advocated that combinatorial treatments will likely be needed for complete injuries (like adding peripheral nerve grafts plus the peptide, etc.). The field might debate whether NVG-291 alone will help complete (AIS A) injuries. Right now, evidence is only in incomplete (AIS B-D). Some skeptics might point that out: "This is great for incomplete injuries (which already had some capacity), but what about people who are fully paralyzed with no sensory function?" That remains to be tested – possibly a next step is to try NVG-291 plus something (like intense locomotor training or bridging scaffold) in AIS A patients. It might not restore walking, but maybe it could convert an AIS A to AIS B or C (e.g., give some sensation or a bit of motor below injury). That would still be a big deal for those patients (even going from A to B – having sensation – improves daily life significantly). - **Market/Investor context:** From investor perspective, there's always speculation. The stock soared on June 2025 news, likely. Then, investors will want to see if big pharma partners or if the data is strong enough for an accelerated path. If something negative came in subacute cohort or any safety surprise, skepticism would return. The management seems confident with data, raising funds to push to pivotal.

Peer Perspective: After the ASIA 2025 presentation, likely peers in SCI research were buzzing. Some might be skeptical until published in a journal (they'll want to see full data and stats). But those who saw the data were quoted as "encouraged". It's somewhat analogous to when epidural stim first had people standing – at first, caution, then acceptance as more replications occurred.

Regulatory Skepticism: The FDA always retains some skepticism until larger trials. Fast Track is nice but does not mean they are convinced – it just means they acknowledge serious need and promising mechanism. For actual approval, they'll need a robust Phase 3 outcome, likely a co-primary endpoint that is a functional measure (like improvement in SCIM or upper extremity motor score) that is clinically meaningful. MEP is great scientifically, but regulators prefer functional endpoints for approval. They might accept an objective biomarker like MEP if strongly correlated to function, but likely the Phase 3 will have a functional outcome (e.g. improvement in GRASSP or SCIM or AIS grade conversion) as primary, with MEP as supportive evidence. Achieving statistical significance in those functional measures in larger sample is next big hurdle. I suspect with more numbers, GRASSP or SCIM differences would indeed become significant.

Comparing NVG-291 to OEC trial (from Deliverable 1): They target similar outcome (improve function), but OEC is invasive and still unproven, whereas NVG-291 now has proven concept non-invasively. If NVG-291 continues to shine, some might question whether cell transplants are needed except possibly for complete injuries where bridging a gap physically might be needed. It could reorder priorities in SCI research: more focus on combining enabling environment (like NVG-291) with intense rehab, vs. high-risk surgeries. Some controversies may arise if certain groups heavily invested in cell therapies feel overshadowed or vice versa. Ideally, the field will see them as complementary (in fact, an OEC scaffold + NVG-291 could be an interesting combined approach for complete injuries: OECs provide physical guide, NVG-291 removes inhibition, maybe synergy).

Wrap-up on controversies: For now, NVG-291 has positively surprised many skeptics. It transformed "controversial – will it work?" into "first evidence it does." The main controversies going forward will revolve around how broadly it works (complete vs incomplete, acute vs chronic, etc.), how to integrate it with other treatments, and ensuring that the results are reproducible and not a fluke of small sample. There is cautious optimism but still a responsibility to confirm in a larger trial, given the history of one-phase wonders that didn't hold up (though none in SCI had such clear positive signs as this, to my knowledge).

Most in the SCI community (patients, clinicians) are likely more hopeful than skeptical now. Anecdotally, patient forums are excited by the news. They'll want access ASAP. That could create some pressure on regulators or on expanded access. Already, NervGen's expanded access policy suggests they anticipate requests from desperate patients. They have to manage that ethically (they likely will allow some cases outside trial if evidence is strong and patient can't join trial, etc., under compassionate use).

What to Watch Next (for NVG-291 and CONNECT-SCI program)

Looking ahead from January 2026, here are the key upcoming milestones and things I'll be monitoring for NervGen and NVG-291:

1. **Subacute Cohort Results – 2026:** The *CONNECT-SCI subacute cohort* data should read out likely by mid-to-late 2026. This will tell us if NVG-291 also significantly benefits patients treated soon after injury (20–90 days post). I'm watching for whether NVG-291-treated subacute patients show greater improvements in ASIA motor scores or independence compared to natural recovery. A

positive result (e.g., faster or greater neurological recovery than placebo) would expand the usage window and possibly position NVG-291 as a standard rehab addition for new injuries. Even if the benefit is more modest than in chronic (due to higher placebo improvement), any clear added improvement would be big news. NervGen might present subacute data at a scientific meeting in late 2026 (perhaps ASIA 2026 or SfN 2026) and/or via press release.

2. **Full Peer-Reviewed Publication of Chronic Cohort – 2026:** I anticipate a detailed paper will be published in a high-impact journal (perhaps *Lancet or Lancet Neurology, or NEJM* if they aim high) detailing the chronic cohort trial results [237]. This paper should include specifics on outcomes, responder analyses, MRI findings, etc. It will allow the scientific community to scrutinize and appreciate the data. I'll read carefully whether the improvements were uniform or if some patients responded more than others (e.g., did all treated patients improve hand function or was it, say, 7 of 10? The press implies broad improvement but a paper would clarify distribution). The publication will also likely detail any exploratory endpoints, like quality-of-life metrics or imaging. Seeing that in a peer-reviewed form will cement credibility and inform next trial designs. I expect this paper could come in the second half of 2026, given time for analysis and peer review.

3. **Phase 2b/3 Trial Launch – 2027:** Based on the chronic cohort success, NervGen will likely initiate a larger trial. I'll watch for announcements in 2027 of a **Phase 2b/3 trial** design. It might be called "CONNECT-2" or similar. Key things:

4. Will it be **global** (multiple countries)? Quite possibly, to enroll enough patients, and to pave way for global approvals.
5. **Endpoints:** I suspect they might choose a functional primary endpoint such as improvement in upper extremity motor score or SCIM (spinal cord independence measure) after, say, 6 months of treatment. They will likely still include MEPs and other objective measures as secondary but regulators will want a clinically meaningful function measure.
6. **Sample size:** Could be 100–200 patients (maybe 50-100 per group) depending on effect size estimates.
7. **Duration:** They might extend dosing beyond 12 weeks if safe, to see if longer dosing yields even more gains or to align with rehab programs. Possibly a 6-month dosing period with evaluations at 6 and 9 months. Or they may stick to 3 months dosing and follow for 6-12 months total to measure retention of gains.
8. The design might stratify by injury severity or level (like separate analysis for AIS B vs C; or they might limit to AIS C/D for a clearer outcome because AIS B might not have any baseline motor to measure improvements except going to C).

9. I'll watch if they include any AIS A (complete) – they might not in this pivotal trial, focusing on where they have evidence (incomplete). Treating complete injuries might be a subsequent exploration or require combining with another therapy.

10. **Regulatory Milestones:** With Fast Track in hand, I'll look for **Breakthrough Therapy Designation** from the FDA. Breakthrough requires preliminary clinical evidence of substantial improvement on clinically significant endpoints. The chronic cohort results might qualify, especially given improvements in hand function and independence. If subacute data also positive, by late 2026 they could apply for and receive Breakthrough status. That would speed development further, offering more FDA guidance on trial design etc. Also, maybe **Orphan Drug** status if it qualifies (SCI maybe not "rare" enough by some definitions, but for chronic incomplete perhaps yes; regardless, the market size is not huge).

11. Also look for **EMA (Europe) interaction**: They might seek PRIority Medicines (PRIME) status in Europe akin to Breakthrough. If big Europe trial planned, that's likely.

12. **Expanded Access Cases:** Now that the expanded access policy exists, I'll be watching if any reports come out of individual patients outside the trial receiving NVG-291. Perhaps a high-profile case (maybe an athlete or known figure with SCI) could request compassionate use. If such a case happens and they share their experience (even anecdotal improvements), that will draw attention. NervGen might release some aggregated info if multiple EAP patients do well (keeping in mind they must handle that carefully since not a controlled setting).

13. However, they must also preserve drug supply for trials. So expanded use might be limited until manufacturing scales up.

14. **Multiple Sclerosis Trial Data – 2026/2027:** NervGen's MS trial (a Phase 1b in people with MS, presumably testing safety and perhaps MRI myelin markers or walking tests) is likely to report results by 2027. If NVG-291 shows signs of remyelination or functional improvement in MS (e.g., improved nerve conduction or walking speed), that broadens its potential. I'll watch that. A positive MS signal could attract a partnership with a bigger pharma (the MS market is large, and big players might want NVG-291 for MS).

15. But importantly, MS results will also bolster the SCI story by showing the drug's mechanism helps CNS repair across conditions.

16. **Stroke or Other Indications Starting Trials:** Possibly by 2027, we might see initial trials of NVG-291 in stroke rehab or traumatic brain injury. If academic partners or DoD push for it, an exploratory trial in stroke patients (maybe subacute stroke to improve limb recovery) could start. I'll monitor clinical trial registries for any listing of NVG-291 in new indications.

17. For example, a small trial in aging patients with incomplete spinal cord compression (cervical myelopathy) or something might appear – as a way to test plasticity in another scenario.

18. **Scientific Conferences & Presentations:** Key meetings like the **American Spinal Injury Association (ASIA)** annual meeting (mid-year) and the **Society for Neuroscience (SfN)** meeting (fall each year) are where updates might appear. For instance, I expect:

19. ASIA 2026: Possibly subacute cohort data presentation.
20. SfN 2026: Combined analysis or mechanistic deep dive (like correlating tract changes with outcomes).
21. ISCoS (International Spinal Cord Society) 2026 or 2027: maybe interim Phase 3 updates or additional analysis of chronic group year-long follow-up (like how durable and whether any late improvements occurred).

22. If Phase 3 starts in 2027, they might share design and baseline characteristics at a conference, which can be telling (like including more severe injuries or not).

23. **Real-World Integration (if early access granted):** If by 2028 Phase 3 is positive, sometimes health authorities might allow early access programs before formal approval. The spinal cord injury specialized centers might gear up for delivering NVG-291 as part of rehab. I'd watch if leading rehab hospitals (e.g., Shepherd Center, Craig Hospital, etc.) start training staff or devising protocols to incorporate NVG-291 when available. Possibly even participating in Phase 3 as sites (some of those likely will).

24. Notably, these centers might start prepping patient selection criteria, scheduling for injections etc. It's subtle to observe, but one can gauge interest through research collaborations.

25. **Partnerships or Acquisition:** On the business front, as NVG-291 proves itself, a larger pharmaceutical company might seek to partner or buy NervGen to bring this to market. If, say, by end of 2026 the subacute results also shine, I'd not be surprised if a major neurology pharma (like Biogen, Novartis, etc.) partners up or even acquires NervGen. So I'll watch press releases or industry rumors about deals.

    - This matters because a big partner can inject resources to accelerate trials and regulatory filings globally. It could mean an earlier approval or broader trial program (like including pediatric SCI or etc).
    - If no partnership, NervGen might still go alone but will need to raise significant funds for Phase 3. So I'll also watch their financial health (since failing to fund Phase 3 could delay things – but given the promising data, raising money might be easier now).

In summary, the next few years will be about *confirming and expanding NVG-291's success*, moving from demonstration to full-scale evidence for approval. The milestones above will mark progress from a small trial success to a widely available therapy if all goes well. Each positive step (subacute confirmed, Phase 3 launched, etc.) will increase confidence that NVG-291 is on track to become a landmark treatment in neurorehabilitation.

Deliverable 3: Comparison Matrix – Griffith OEC Nerve Bridge vs. NervGen NVG-291

Aspect	**Griffith OEC "Nerve Bridge" Trial** (Autologous Olfactory Cell Transplant + Rehab)	**NervGen NVG-291** ("PTPσ Peptide" Drug + Standard Rehab)
Mechanism Target	*Cell-facilitated regeneration:* Fills injury cavity with patient's own **OECs** (olfactory ensheathing cells) forming a 3D "bridge" to support axon growth. OECs modulate the local environment (secrete growth factors, phagocytose debris) and provide physical channels for regenerating axons [10] [11]. Also requires intensive **activity-based rehabilitation** to drive nerve integration [19].	*Molecular inhibition release:* Systemic drug that blocks **PTPσ receptors**, thereby neutralizing the inhibitory signals from **CSPGs** in glial scar [160] [159]. Essentially a **"scar dissolver"** at the signaling level – it frees neurons to regrow or sprout new connections and promotes remyelination [153]. Rehabilitation is beneficial but not specialized (standard physio); the drug works on neural plasticity broadly.

Aspect	**Griffith OEC "Nerve Bridge" Trial** (Autologous Olfactory Cell Transplant + Rehab)	**NervGen NVG-291** ("PTPσ Peptide" Drug + Standard Rehab)
Invasiveness	**Highly invasive:** Requires two surgeries – (1) nasal endoscopic biopsy to harvest cells, (2) major spinal surgery (laminectomy) to implant cell-laden scaffold into cord [13]. Surgical risks (infection, CSF leak, cord manipulation) are present. Hospital stay and lengthy recovery needed for surgery, plus a ~1 year commitment to near-daily intensive rehab [14] [85].	**Minimally invasive:** No surgery. NVG-291 is given via **daily subcutaneous injections** (like insulin shots) for a finite period (e.g. 3 months) [221]. Can be done outpatient or at home. Low physical burden: just injection site care. Rehab is whatever standard therapy the patient can do; no special invasive procedures.
Scalability	**Limited scalability:** Each patient's therapy is personalized – cells must be harvested and cultured for weeks (autologous process). Requires a GMP cell lab and surgical team; throughput is low (only a few patients can be processed at a time). Logistics of intensive rehab (5 days/week for 8+ months) also limit reach to those near specialized rehab centers [6] [63]. Exporting this globally would need significant infrastructure (cell facilities, trained neurosurgeons, rehab centers).	**High scalability:** NVG-291 is an "off-the-shelf" therapeutic. The drug can be mass-manufactured and distributed widely (like any pharmaceutical). Administration is simple – injections that patients or local clinicians can do. No need for specialized surgical units or cell labs. It could, in theory, be prescribed by neurologists and administered at home, enabling reach to thousands of patients worldwide. The main scaling factor is drug production and training rehab providers to incorporate it, which is far easier than scaling surgeries.
Evidence Maturity	**Early-phase (evidence still emerging):** The approach is currently in **Phase I/IIa**. Preclinical rationale is strong (OECs helped animals in some studies) [43], and prior human OEC transplants showed safety but mixed efficacy. The ongoing trial has **no published outcomes yet** beyond "commenced and recruiting" [30]. So efficacy in humans remains unproven as of Jan 2026 (first results expected ~2027). Evidence thus far: anecdotal successes (e.g. prior case in Poland) but also cautionary tales (nasal cell grafts causing mucosal tumors in some patients a decade later). The current RCT will provide the first high-quality data.	**Mid-phase (promising human efficacy shown):** NVG-291 is in **Phase 1b/2a** and has *already demonstrated significant efficacy signals in humans*. In a 20-patient chronic SCI RCT (Phase 1b), it met a primary endpoint (300% increase in motor evoked potential amplitude vs placebo, $p<0.02$) [173] and showed durable functional improvements (e.g. better hand function, bladder control) [176] [181]. Safety proven in Phase 1 (healthy volunteers) and Phase 1b (no serious adverse effects) [178]. Next up are larger Phase 2/3 trials. So, evidence maturity is higher – we have tangible human data backing its mechanism. Not yet approved, but on a clear path with Fast Track status.

Aspect	**Griffith OEC "Nerve Bridge" Trial** (Autologous Olfactory Cell Transplant + Rehab)	**NervGen NVG-291** ("PTPσ Peptide" Drug + Standard Rehab)
Likely First Beneficiaries	**Chronic, motor-complete SCI patients (AIS A/B) at mid-thoracic to low-cervical levels** who have no other restorative options. The trial specifically targets thoracic and C5–C8 injuries that are ≥4 months post and motor-complete or near-complete [103]. These individuals currently cannot regain function through rehab alone; the OEC bridge is aimed at giving them some return (sensory, autonomic, or even motor) where there was none. So the first to benefit, if successful, would be those with long-term paralysis and minimal voluntary movement – e.g., paraplegics and quadriplegics who are 1–10 years post-injury with stable lesions. Particularly, **people with no distal motor function** stand to gain the most (even small improvements would be life-changing). Also, those who can commit to the intensive rehab – typically relatively younger, motivated patients with good support systems – will be prime candidates.	**Chronic, motor-incomplete SCI patients (AIS B, C, D)**, especially **cervical injuries**. NVG-291's trial has focused on those with some preserved pathways that can be strengthened [163]. So likely first beneficiaries are individuals with incomplete tetraplegia who maybe have some arm movement but poor hand function – NVG-291 could significantly improve hand/finger control (as seen in trial) [176]. Also, incomplete paraplegics who can perhaps stand or take a few steps but not independently – NVG-291 might enhance their motor signals and lead to greater mobility. Essentially, **those with residual connections ("sparks") – the drug fans those sparks into functional fire**. In the future, subacute patients (new injuries in early rehab) will also benefit early – giving NVG-291 during rehab could maximize recovery before chronic scarring sets in. One can envision it being standard for, say, a 25-year-old with a C6 incomplete injury starting 1 month post-trauma to help them regain much more function than they otherwise would.

Aspect	**Griffith OEC "Nerve Bridge" Trial** (Autologous Olfactory Cell Transplant + Rehab)	**NervGen NVG-291** ("PTPσ Peptide" Drug + Standard Rehab)
Main Risks	- **Surgical/Medical risks:** Nasal biopsy can cause bleeding or loss of smell. Spinal surgery risk of infection, **worsening neurological deficit** if something goes wrong (though carefully planned to avoid further damage) [13] . There's a risk of neuropathic pain or spasticity increase if regenerating axons miswire (though intensive rehab aims to guide proper reconnection) – past OEC transplants haven't widely reported pain as an issue, but it's monitored. - **Cell therapy risks:** Possibility of transplanted cells forming abnormal tissue. In prior cases, nasal cell grafts formed benign tumors in a few patients a decade later. The current trial mitigates that by using purified OECs (less likely to form cysts than whole mucosa). Still, long-term vigilance is needed (yearly MRIs to ensure no growth). - **Rehab burden:** 5 days/week of strenuous therapy can lead to overuse injuries, fatigue, or financial/logistic strain. Participants may face increased pain or risk of fractures if not careful during training. The trial monitors health closely and built in rest weeks [63] [238] . - **Resource risk:** Because it's complex, there's a risk patients invest a lot (time, hopes) and see minimal improvement (if it underperforms). That psychological toll is considered too.	- **Side effects:** NVG-291's trial showed mostly mild injection site reactions (redness, small bruises) [178] . No severe systemic effects seen. A theoretical risk was interference with menstrual cycle (from animal data), but no issues observed in human dosing [192] . It's prudent that women avoid pregnancy during treatment (unknown effects on fetus). - **Unknown long-term effects:** The drug transiently enhances plasticity – thus far it *reduced* spasticity and pain rather than worsened them [186] , which is good. But ongoing monitoring is needed to ensure no late complications like aberrant nerve sprouting causing pain (none seen up to 12 months in trial). - **Immunogenicity:** As a peptide, repeated courses could potentially trigger anti-drug antibodies (which might reduce effectiveness or cause reactions). So far, in a 3-month course, no such issues reported; it likely flew under the immune radar due to its human-based sequence. - **Off-target effects:** PTPσ is expressed outside the CNS (in some immune cells, etc.), but blocking it for 12 weeks caused no overt immune problems or organ toxicity in humans. Preclinical safety was reassuring. - **Overall risk level:** Quite low – no patients had to discontinue the drug and no serious adverse events were attributed to it [178] . Compared to many CNS drugs, NVG-291 has a benign profile (no sedation, no mood effects, no organ damage signals). The main "risk" is that it might not help everyone; but for those it does, the side effect burden is minor relative to gains.

Aspect	**Griffith OEC "Nerve Bridge" Trial** (Autologous Olfactory Cell Transplant + Rehab)	**NervGen NVG-291** ("PTPσ Peptide" Drug + Standard Rehab)
Invasiveness vs. Benefit Trade-off	Because OEC transplant is invasive and demanding, it's being offered (experimentally) first to those with the **most severe paralysis** for whom potential benefits justify high risks. These patients (AIS A or B) currently have zero motor function; even a small return – say regaining some sensation or one muscle level of movement – can justify undergoing risky surgery. Thus, the high invasiveness aligns with attempting to treat the most profoundly affected, who have no other options. For an AIS C or D who already has some function, the risk/effort of this intensive approach might not be justified unless it clearly outperforms less invasive methods (to be determined). In short: high risk, aimed at high-reward (restoring some function in those who'd otherwise never regain it).	NVG-291 is low-risk and easy to administer, making the risk-benefit calculus very favorable even for those with moderate injuries. Because side effects are minimal, even patients with partial function (AIS C/D) who stand to gain improvements in quality of life can justify taking the drug. There's little downside to trying it – if it works, great improvement; if not, they haven't lost ground (just a few injection site bumps). As a result, NVG-291 can be applied across a broader range of patients, including those with incomplete injuries who might balk at surgical interventions but would readily take a safe drug to potentially boost their recovery. If future data suggest benefit in AIS A as well (perhaps in combination with other therapies), its non-invasiveness would make it an attractive first-line attempt even there, because it doesn't burn any bridges (pun intended) – it could be given before or alongside other treatments with minimal interference.

Aspect	**Griffith OEC "Nerve Bridge" Trial** (Autologous Olfactory Cell Transplant + Rehab)	**NervGen NVG-291** ("PTPσ Peptide" Drug + Standard Rehab)
Time to Next Major Readout	- **Interim trial data:** Possibly late 2026 the OEC trial may report interim safety or early observations (if any patients show notable improvement, might be hinted at in conference talks). But primary outcomes likely won't be revealed until trial completion ~2027–28. - **Trial completion:** Final results from the 30-patient RCT expected ~2028 [33] . That will be the big decisive readout on efficacy. - **If positive:** They would then plan a larger Phase 2/3, which could take several more years (2030+ for widespread availability). However, early safety successes might allow them to expand slightly sooner (e.g., treating second cohort or high cervical patients under protocol amendments). Realistically, no clinical "breakthrough" announcement of functional recovery (beyond anecdotes) is expected until at least 2027 when controlled data are analyzed. - **Key watchpoints:** Look for conference reports (e.g. 2027 ISCoS) for hints of outcomes, and whether the trial proceeds to a Phase II with more patients (which would signal early positive signals). Also watch if any participants' stories leak (e.g., a participant saying they regained X) – though with blinding, that's unlikely until study end.	- **2026:** The CONNECT-SCI *subacute cohort* results are expected perhaps by late 2026. This will be the next major data readout (following the chronic cohort's 2025 topline). If subacute results show enhanced recovery versus placebo, it cements NVG-291's utility across injury stages. - **2027:** Likely initiation of a pivotal Phase 3 trial. The design and start of that trial (and possibly interim analyses built in) will be milestones. If an interim analysis is planned, we could get signals by 2028. - **2028–29:** Phase 3 primary endpoint readout could occur if trial enrollment goes swiftly by 2027. Given Fast Track/Breakthrough, NervGen might file for approval in 2029 if Phase 3 is positive. - **In the meantime:** Look for a full publication of the Phase 1b chronic results in 2026 (which will further validate and peer-review the findings) [157] . Also potential partnership announcements (a large pharma might join for Phase 3 – which itself is a form of validation). - **Regulatory interactions:** Possibly Breakthrough Therapy designation in 2026, and discussions of an **accelerated approval** pathway if data remain strong (especially since MEP improvement is a biomarker that correlates with function – regulators may accept it). So NVG-291's trajectory is rapid – within ~5 years of first-in-human, it could reach the market if all goes well, meaning by around 2030, chronic SCI patients might access it via prescription. Each year from now on likely holds some major development (e.g., 2025 chronic data, 2026 subacute data, 2027 Phase 3 start, 2028/29 pivotal data).

(Sources: [S4] U2FP analysis of OEC trial design vs drug, [S2] ANZCTR registry, [S9] NeurologyLive interview, [S8] NervGen press releases, trial outcomes as summarized above.)

Deliverable 4: Video Kit – Topic 1 (Griffith OEC Nerve Bridge Trial)

Outline for a 15-minute YouTube Video:

- **0:00 – 0:30 — Hook** (see hook options below)
- **0:30 – 2:00 — Introduction & Context:** Present the problem: chronic spinal cord injury and the historical belief that it's permanent. Introduce that now a team in Australia is attempting a *"world-first" human trial using nasal cells to repair the spinal cord* [30] . Briefly mention who is behind it (Griffith University, Perry Cross Foundation) and why it's generating hope [58] .
- **2:00 – 4:30 — The Science of the 3D Nerve Bridge:** Explain in simple terms what olfactory ensheathing cells (OECs) are and why scientists think they can help (they support nerve growth in the nose) [15] . Use a graphic to show how they take cells from the patient's nose and grow them into a tiny nerve bridge the size of a worm [9] . Explain how this bridge is implanted into the spinal cord injury site as a living scaffold [13] . Emphasize it's *the patient's own cells*, so no rejection [62] .
- **4:30 – 6:30 — Inside the Clinical Trial Design:** Outline the trial's basics – 30 patients, randomized to two groups (cell transplant+rehab vs rehab only) [239] [102] . Show a timeline graphic: screening, 3 months of rehab prep, surgery, then 8 more months of rehab [14] [85] . Mention inclusion criteria (thoracic or low-cervical injuries, AIS A/B/C, at least 4 months post-injury) [103] . Perhaps include a simplified table of what they'll measure (safety, MRI changes, motor/sensory tests, quality of life) [8] [122] . Convey that it's Phase 1/2, mainly checking safety and if it's feasible to do such an intense protocol [95] .
- **6:30 – 8:30 — The Rehabilitation Regimen:** Explain why **rehab is so crucial** in this trial – "activity is needed to help new connections form" [64] . Show what a day in the rehab might look like: maybe footage or illustration of a participant doing treadmill training, FES cycling, upper limb exercises, etc., 5 days a week [63] . Mention that control group does the same rehab, minus the transplant, so we can see if the cells truly make a difference [90] . Could mention one of the trial's unique aspects: the heavy involvement of the SCI community in designing it (consumer panel guiding what outcomes to target) [27] – adds human touch.
- **8:30 – 10:00 — What We Know So Far & Early Progress:** Be transparent that as of now (Jan 2026), no results are out yet – they're *recruiting* and doing the procedures [30] [7] . But share what the lead researchers are hoping for: e.g., Prof. St John said "even regaining some bladder or finger movement can hugely improve life" [142] . If available, mention that the first surgeries have taken place (commenced Aug 2025 [30]) and that all went safely so far (no official data, but presumably safety is fine to continue). Perhaps include a short quote from Perry Cross about hope (he said it's a "long-awaited breakthrough" and that even the possibility of improved independence and dignity is incredible [240] [241]). This adds optimism while acknowledging it's early.
- **10:00 – 11:30 — Potential Outcomes & Challenges:** Lay out the best-case, worst-case scenarios plainly. Best-case: The trial shows it's safe and that those who got the OEC transplant regain significantly more function (for example, maybe a few levels of motor improvement or improved sensation) [65] . It could then move to a larger trial and eventually become a treatment in hospitals. Worst-case: It might show no difference beyond rehab (so maybe the cells didn't help), or safety issues (like increased pain or an adverse event) could arise – though everything possible was done to minimize risk. Remind viewers this is an experiment and not a guaranteed cure (tamp down any "miracle cure" hype) [38] .
- **11:30 – 13:00 — Reality Check (Expectations vs. Hype):** Title this section "Reality Check" on screen. Emphasize that the researchers themselves are cautious – they talk about *"aiming low but hoping high"* [35] . Explain that media headlines claiming "cure" are premature [38] . Set expectation that maybe a subset of participants will improve certain functions, but it's unlikely anyone will go from complete paralysis to walking from this alone. Remind that it's one step of

many. Use the U2FP quote: "Promising? Yes. On the verge of cure? No, that's hype." [38] to encapsulate it.

- **13:00 – 14:00 — Who Might Benefit First & Future Steps:** Summarize that if it works, initial beneficiaries will likely be people with chronic mid-level SCI who currently have no movement – they might be the first to gain something back. Looking beyond, if safety is confirmed, they might try it in higher-level injuries or combine it with other therapies (imagine doing this transplant plus a drug or stim). Mention that the team is already planning how to improve it further (St John quote that they see this trial as "first step" and are planning improvements not tested yet) [154] . So even if results are modest, they have ideas: maybe more cells, or repeat transplants, etc., could amplify it later.
- **14:00 – 15:00 — Conclusion & Next Milestones:** Wrap up by expressing cautious optimism. "This trial represents decades of work coming to fruition – for the first time, people with chronic paralysis are getting a transplant aimed at repairing the cord." [30] The next milestones: fully enrolling all 30 patients (target by ~2026) and then analyzing results by 2028. Encourage viewers to stay tuned for updates – we'll know in a couple years if history is made or if we need to adjust course. End on a hopeful note: regardless of outcome, this trial is teaching us valuable lessons and pushing the boundaries of what's possible, turning what was once science fiction into a scientific trial [58] .

Hook Ideas (3 versions, ~30 seconds each):

1. **Emotional Hook (Human story):** *"19-year-old Sarah was told she'd never walk or even feel below her chest again after a spinal cord injury. Now, she's volunteering for a bold experiment – doctors took cells from her nose, grew them into a tiny nerve bridge, and implanted it into her spine. Why? To try to reconnect the broken pathways and give her back what she lost. It sounds like science fiction, but it's happening right now in a world-first trial. Could this actually bring feeling or movement back to people years after paralysis? Let's explore the hope, the science, and the realities behind this groundbreaking spinal cord repair attempt."*

2. **Clinical Hook (Scientific intrigue):** *"What if the key to repairing a severed spinal cord lies… in your nose? Australian scientists are now extracting olfactory cells – the ones that help you smell – and using them to bridge gaps in injured spinal cords* [9] *. In this video, we go inside the first-ever human trial of this technique: from how a 'living nerve bridge' is engineered* [10] *, to the marathon rehab patients undergo, to what outcome measures will prove if it works* [8] *. If successful, this could fundamentally change spinal injury treatment. Let's examine the procedure and the early progress of this landmark trial."*

3. **Skeptical-but-hopeful Hook:** *"We've all seen the sensational headlines: 'Paralysis cure on the horizon!' – Most of the time, they don't pan out* [38] *. But there's a serious scientific effort underway that might* finally *move the needle. It involves nasal cells, a 3D-printed scaffold of sorts, and an intense year of therapy. Sound crazy? It might be crazy enough to work. Today we'll cut through the hype and look at exactly what this spinal cord injury trial is doing, what 'success' would actually mean (hint: it's not people jumping out of wheelchairs overnight), and why experts are excited yet cautious* [38] [35] *. If you're skeptical about 'cures', so are we – but you'll want to hear about this pragmatic approach to healing the spine."*

On-screen Graphic Suggestions:

1. **Timeline/Process Graphic:** A simple flowchart of the trial timeline – e.g., "Rehab Phase 1 (12 weeks) → Surgery: OEC transplant → Rehab Phase 2 (32 weeks) → Final assessments" with icons

for each stage (dumbbell icon for rehab, syringe or cell icon for surgery, clipboard for assessments). This helps viewers visualize the patient journey [14] [85].

2. **OEC Extraction and Culturing Diagram:** An infographic showing a nose with a small tissue biopsy taken, then an arrow to a petri dish with cells expanding, then arrow to a 3D scaffold ("nerve bridge") about 1 cm long [9], then arrow to a spinal cord cross-section showing the bridge placed in the lesion. Labels: "1. Nasal cell harvest, 2. Cell culture (OECs), 3. 3D nerve bridge formation, 4. Surgical implantation." [10] [13]

3. **Spinal Cord Injury Illustration:** Before-and-after concept drawing – left side: an injured spinal cord with a gap (maybe scar and no continuity), right side: after OEC bridge placed (show bridging tissue and maybe some green regrowing axons crossing). Annotate possible outcomes like "increased connectivity" or "axons regrowing" on the after side [10] [13].

4. **MRI/Tractography Concept:** A sample DTI tractography image (not actual data, but concept) showing nerve tracts in a spinal cord pre and post – highlight that one of the trial goals is to see if new tracts appear on MRI [8]. Perhaps with question marks "Will we see new connections on MRI?" – to illustrate one of the trial's primary endpoints is structural.

5. **Outcome Measures List:** A bulleted list on screen of the key outcomes they're measuring: "Safety – any adverse events?; Feasibility – can 30 patients complete this intense protocol?; MRI changes – evidence of tissue repair; Motor & sensory function – ASIA scores, strength tests; Autonomic function – bladder/bowel; Quality of life – independence, psychological well-being." Each with a small icon. This gives audience concrete things to look for in eventual results [8] [122].

6. **Intensive Rehab Footage/graphic:** Show e.g. a silhouette of a person in a harness doing treadmill training (to represent locomotor training), another doing seated balance training, etc. Possibly a montage of what "5 days/week for 8 months" might entail [63]. Caption: "Intensive Activity-Based Rehab: up to 3 hours per day, 5 days/week" [63]. This emphasizes the importance of physical training in the trial.

7. **Cell vs. Control Group Illustration:** Two stick-figure patients, one labeled "Transplant + Rehab" with an icon of a bridge in the cord, the other "Rehab Only." Under each, question marks like "Any improvement?" and we plan to compare. This emphasizes the trial's controlled nature (which is unique compared to past open-label attempts) [90].

8. **Past Attempts & New Twist Graphic:** Perhaps a mini timeline: "2001: First OEC transplant (Portugal) – safe, minor gains"; "2014: Famous case (Poland) – some walking with aid" (with a silhouette of man with walker); "2025: Griffith Trial – randomized, rigorous test of OEC scaffold + long rehab." Show these to give historical context. Then a highlight that previous efforts lacked control groups and had issues like tumors (maybe show an x-ray or MRI of a cyst with arrow, labeled "10 yrs later: nasal tissue graft resulted in benign tumor" to caution what went wrong). Then emphasize "New trial addresses past issues: uses purified cells only, includes control group, extensive rehab for full potential [64]."

9. **Quote/Text Overlay:** A powerful quote on screen (in tasteful typography) from Perry Cross or Prof. St John. For example: *"For someone like me, who knows all too well the permanence of spinal cord injury, this trial offers not just the possibility of improved function, but a renewed sense of*

independence and dignity." – Perry Cross [242] [37]. This can play during a transitional moment to underscore the human impact.

10. **Realistic Outcomes vs. Cure Chart:** Perhaps a simple chart or infographic contrasting "What improvement might look like" vs "What it's not." E.g., left column with green checkmarks: "Improved hand grip, better bladder control, some sensation return, ability to do one more daily task independently" – right column with red X's: "Instant walking, full cure of paralysis, no rehab needed." Summarize that success is measured in degrees of improvement, not all-or-nothing. This helps manage audience expectations in an easy-to-digest way.

Expected Viewer Comments & Suggested Replies:

1. **Viewer:** *"I've seen so many 'breakthrough' SCI cures fail in the past. Why should we believe this is different?"*
   Reply: *You're right to be skeptical – the SCI field has had false dawns. What's different here is that this trial is controlled and science-driven. They're not declaring a cure; they're carefully measuring if this works better than rehab alone [90]. Also, past attempts often injected cells haphazardly; here it's a structured bridge plus heavy rehab support [14]. We won't know if it works until data's in (around 2028), and the researchers themselves are cautious [35]. In short, they're doing the rigorous testing that was often lacking before. So cautious optimism is warranted, not hype – and if it doesn't work, they'll know and we'll learn from it.*

2. **Viewer:** *"When will we know the results? I or my loved one would sign up in a heartbeat if it works."*
   Reply: *The trial is underway and will likely finish by ~2028 [33]. Recruitment is happening now (they have criteria, e.g. the injury needs to be at certain levels and chronic [103]). If it succeeds and a larger trial confirms it, maybe in the early 2030s it could become available as a treatment. It's a long road – science takes time to ensure safety and real effect. In the meantime, if your loved one fits the criteria, they might reach out to the trial team to see if they can enroll (if willing to travel to Australia). But keep in mind it's very demanding and experimental. We all hope it yields positive results, but until then, best stick with proven rehab and watch this space.*

3. **Viewer:** *"This sounds super invasive… taking cells from your nose and doing spine surgery. What if something goes wrong? Could it make the person worse?"*
   Reply: *The team has worked hard to minimize risks. The nose biopsy is small (some people might lose a bit of smell, but it's usually minor). The spinal surgery is done by experienced neurosurgeons; it does carry risks (infection, possible damage) but they are only doing this in stable patients and under strict monitoring [13]. There's also an ethics board watching safety. If at any point it seems harmful, the trial would be stopped [61]. So far, in earlier human cases, the procedure was generally safe (the main complication years later was some nasal cells overgrowing, which they address now by purifying the cells better). Of course, any surgery on the spine is serious – but these participants understand the risks and feel it's worth it for a chance at improvement. In short, yes it's invasive and there's risk, but it's being done very carefully to avoid making anyone worse.*

4. **Viewer:** *"How do the cells actually* know *what to do in the spine? Why would nose cells fix the spinal cord?"*
   Reply: *Great question! Olfactory ensheathing cells (OECs) are special – their job in the nose is to help new smell nerve fibers regrow from the nose into the brain throughout life [15]. So they naturally support nerve regeneration. When put in the spinal cord, they seem to create a friendly environment for nerves – they release growth factors, clean up debris, and guide cut axons to reconnect [10]. Think of them like gardeners tending a pathway for nerves to grow. In animal studies, OECs helped bridge spinal cord gaps and some nerves regrew through them. They also can form channels aligning with*

spinal cord tissue. They don't turn into nerve cells themselves; they act as support and guides. It's not guaranteed to work in humans, but that's the logic – they bring regeneration-friendly properties right to the injury site.

5. **Viewer:** *"Will this help someone who's been paralyzed for decades, or is it only for recent injuries?"*
   Reply: *This trial is focused on chronic injuries – people at least 4 months post-injury, even many years out* [102]*. So yes, it's trying to help even those long after the initial trauma. Past thinking was that chronic = too late, but new research suggests even chronic cords have dormant capacity if given the right kickstart. Now, older injuries do have challenges (muscles atrophy, etc.), so pairing the transplant with intense rehab is key to awaken those circuits* [64]*. If this works, it could benefit people who've been paralyzed a long time – perhaps with slightly less effect if it's been decades, but any return would be welcome. They didn't set an upper limit on years post-injury (the trial includes up to 10 years and maybe beyond on case by case)* [3]*. So it's definitely aimed at chronic cases. Early injuries might benefit too, but they're starting with chronic where spontaneous recovery is already done, so any improvement can be clearly attributed to the therapy.*

6. **Viewer:** *"What exactly counts as 'improvement'? Are they trying to make people walk again or smaller goals like blood pressure or feeling?"*
   Reply: *They consider a wide range of improvements a success – not just walking. In fact, most trial participants have injuries that would make walking tough even with some recovery (like mid-thoracic or lower cervical injuries)* [103]*. Improvement could be: regaining some sensation below the injury, or recovering some motor function like moving a finger or toe where they couldn't before* [65]*. It could also be autonomic improvements – e.g., better bladder control or blood pressure stability. The lead scientist mentioned examples: even bladder/bowel or hand function improvements can hugely improve quality of life* [142]*. They're measuring all these. A big dramatic outcome would be, say, an AIS A complete paraplegic becoming AIS C (meaning they gain some muscle control). But they're not necessarily expecting people to jump up and walk. It's more likely to be incremental gains – which for an individual can mean new independence in daily tasks or not needing as much caregiver help. They have questionnaires for overall health and independence too, so they'll know if people are more self-sufficient after. In summary, any restoration of function – sensory, motor, or autonomic – counts as improvement here.*

7. **Viewer:** *"If it works, can it fix higher injuries (like someone on a ventilator with a C2 injury)? Or is it only certain levels?"*
   Reply: *The current trial excludes the very high cervical injuries (C1-C4) primarily for safety – those folks rely on ventilators, and the surgery could be riskier for them* [105]*. Also, their injury site is near the brainstem, a delicate area. So initially it's not being tested in high quads. If it shows safety and benefit at lower levels, I imagine they might cautiously try it at higher levels in a future trial. In theory, if you transplanted OECs into a C2 injury, it could help that area too – but the stakes are even higher (breathing, etc.). So they'd need to approach that carefully. Possibly, a modified approach (like doing multiple small bridges or ensuring respiratory function is safeguarded) would be needed. Long-term, the hope is yes, it could apply broadly – but realistically the first adoption will be mid-cord injuries. For someone with a high injury on a vent, other interventions (like phrenic nerve pacing, diaphragmatic pacing) currently exist to help breathing. The OEC trial is tackling the middle ground first. So, not yet for the highest injuries, but maybe down the line.*

8. **Viewer:** *"Why do they need a control group? If someone regains function, isn't it obvious it worked?"*
   Reply: *Having a control group (rehab-only) is super important because believe it or not, sometimes people can improve slightly even years later with focused rehab or due to measuring variability* [90]*. Also, the placebo effect is real – just being in a trial and hopeful can influence how people report feelings or do in therapy. By comparing to a control group, they ensure any gains in the transplant*

group are truly beyond what intensive rehab alone could achieve [90]. This has never been done in an SCI cell therapy before – prior attempts were open-label and we couldn't tell if modest improvements were due to treatment or just chance or extra therapy. The control group makes the evidence much stronger and credible. If both groups improve similarly, then the cells didn't add much. If the cell group blows past the control group, then we have real proof. It also helps account for any biases – the participants know if they got surgery or not, but the outcome assessors are blinded, etc., to keep data objective [61]. So yeah, it might seem obvious if someone recovers, but scientifically and for regulatory approval, you need that controlled proof.

Deliverable 4: Video Kit – Topic 2 (NervGen NVG-291 / CONNECT-SCI Trial)

Outline for a ~15-minute YouTube Video:

- **0:00 – 0:30 — Hook** (choose from options below)
- **0:30 – 1:30 — Intro & Setup:** Begin by stating: "What if a *drug* could help heal a spinal cord injury even years later?" Introduce NVG-291 as a novel therapy that's making waves by showing first-ever drug-induced improvements in chronic SCI [179]. Provide quick context: NervGen's trial where patients improved signals and function with a peptide injection [173] [176].
- **1:30 – 3:30 — The Challenge of SCI Regeneration:** Briefly outline why spinal cords don't heal themselves: mention glial scar, inhibitory molecules (show an image of scar blocking axons). Set the stage that scientists have targeted these blockers for decades without success in humans – until now perhaps [169] [168].
- **3:30 – 6:00 — Mechanism of NVG-291 Explained:** Use analogies: glial scar = "chemical roadblocks" from CSPGs [202] [160]. PTPσ receptor = the "brake" on nerves that responds to those roadblocks [160]. NVG-291 = "brake release" peptide that tells nerves 'ignore the stop sign, you can grow' [159] [153]. Illustrate with a simple graphic: neuron with PTPσ receiving 'stop' signals, then NVG-291 wedge binding and disabling that signal, leading to axon growth continuing [153]. Also mention it can help re-wrap demyelinated nerves (remyelination) and promote plastic rewiring [218] [243]. Keep it accessible: "It basically re-opens the ability of neurons to form new connections in adulthood, something normally blocked after injury."
- **6:00 – 8:00 — Inside the CONNECT-SCI Trial:** Summarize NervGen's Phase 1b/2a trial design: two groups – chronic (1-10 yrs post injury) and subacute (1-3 months) [161] [162], all with cervical incomplete injuries (they had some movement) [163]. Mention it was placebo-controlled and double-blind (patients didn't know if they got drug, to keep data unbiased) [195]. Dosing: daily subcutaneous injection for 12 weeks [221].
- Show timeline: baseline assessments → daily shots for 3 mo → follow-up tests at 4 mo and beyond.
- Primary goal was to see if it improves motor signal conduction (via MEP tests) [167], plus checking safety.
- Secondary included functional tests (hand function, walking, etc.) [167] [125].
- **8:00 – 10:30 — Results Highlight (Chronic Cohort):** Present the key findings from the chronic cohort (mid-2025 data):
- **MEP Boost:** Treated patients had ~3x larger motor evoked potentials in their hands vs. baseline, significant over placebo [173]. Show a bar graph or similar: MEP amplitude baseline vs end for drug vs placebo (with drug's bar much taller). Explain: "This means the connection from brain to hand muscles got stronger, objectively, only in the drug group" [219].

- **Hand Function Gains:** Treated group's GRASSP prehension score went up ~3.7 points vs ~0.4 in placebo [176]. Represent via a simple chart or even list: e.g., "Grip strength/dexterity: Drug +3.7, Placebo +0.4." Not statistically "proven" due to small sample, but a strong trend.
- **Real-life improvements:** This is compelling – share one or two anonymized anecdotes from exit interviews: e.g., "Patients on NVG-291 reported new abilities like brushing their hair or opening cans – tasks they couldn't do before" [244]. Maybe show icons of those tasks highlighting regained independence (a hairbrush icon, etc.). Also mention bladder control improvements: "the drug group had notably better bladder control and less spasticity than placebo" [181] [185]. Perhaps illustrate with a simple before/after cartoon of a patient needing frequent cath vs improved control.
- Emphasize that these were chronic patients (average ~3.5 years post-injury) [222], so this wasn't spontaneous recovery – it was likely the drug effect.
- Safety note: "And all this came *without* serious side effects – no one had to stop the drug; the main side effect was mild injection site reactions" [178].
- **10:30 – 12:00 — What This Means:** Interpret the significance:
- This is *the first time a drug has significantly improved motor function in chronic SCI in a trial* [179]. That's a potential paradigm shift – previously, rehabilitation and electrical stimulation were the only avenues for improvement, now a pharmaceutical is showing it can actually help rewire the nervous system.
- Use an analogy: It's like for decades we've been trying to grow plants in toxic soil (scar), and now we've detoxified it so things can grow.
- Clarify scope: it helped those who had some residual connections (incomplete injuries). It's not proven yet in complete injuries (no signals at all), those likely need other strategies too (maybe combining this drug with a nerve graft or stimulation).
- But for the large population of incomplete SCI, this could augment their rehab outcomes significantly – e.g. turning a marginal hand movement into a functional grasp.
- **12:00 – 13:00 — Next Steps & Timeline:** Outline that:
- A trial for subacute patients (just months after injury) is ongoing (we expect results in 2026) [199]. If it shows that giving the drug early speeds up or enhances recovery, that's huge (could become standard in rehab hospitals soon after injury).
- A larger Phase 3 trial is being planned for more patients to confirm and extend these findings (maybe by 2027 start).
- If all goes well, NVG-291 could be FDA-approved around end of this decade. Note that FDA gave it Fast Track, recognizing its promise [197].
- Also mention they're exploring it in other conditions: e.g., multiple sclerosis (remyelination), which underlines how broad this mechanism might be.
- **13:00 – 14:30 — Reality Check & Combining Approaches:** Reinforce that:
- NVG-291 isn't a silver bullet that instantly cures paralysis. It seems to *enable* improvements – which likely still require physical training to realize fully. (In the trial, patients did standard rehab or daily activities – no special regimen, yet still improved – but optimal use might pair it with targeted therapy).
- It works best if there are surviving axons to strengthen. For complete severances, it might need help from other therapies (like perhaps bridging strategies or epidural stim).
- It's not an over-night effect either: it took weeks of dosing for changes to manifest, and then continued improvements emerged even after stopping (suggesting real neural changes) [220].
- But the fact that benefits persisted beyond treatment (some participants still had improved function at 12-month follow-up) [181] [188] indicates it's not just a temporary patch – it potentially spurred lasting rewiring.
- Combined approach: in future, one could imagine using NVG-291 alongside something like the OEC implant or electrical stimulation – one attacks chemical inhibition, another provides structural guidance or immediate functional assist, maybe synergy.

- **14:30 – 15:00 — Conclusion (Hope with Caution):** Summarize in an inspiring but measured tone: "For the first time, a drug is showing paralyzed people regaining abilities thought permanently lost [179]. It's an exciting breakthrough in the lab and clinic. There's still a journey ahead – larger trials to verify and to see who exactly benefits most. But NVG-291 represents a new front in treating SCI: not just compensating for damage, but actively repairing it by unlocking the nervous system's own healing capacity. We'll be following this closely as it progresses through trials – it could become part of the standard care in the coming years if results hold up. Science is turning what was once science fiction into reality piece by piece." Encourage subscribing or following for updates on subacute trial results, etc.

Hook Ideas (3 versions ~30s each):

1. **Emotional Hook:** *"For 10 years after his accident, John had no feeling or movement in his fingers. Then he volunteered for a trial – a simple daily injection – and months later, he could pinch and grasp again [184]. It wasn't magic; it was a new drug waking up nerves long thought dead. This is the true story of a medical first: a treatment giving people back functions they lost years ago."* (This hook is a dramatization combining anecdotes, focusing on regained hand function as an emotional entry.)

2. **Clinical/Intrigue Hook:** *"Can an injection help regenerate a damaged spinal cord? It sounds unbelievable, but a new drug, NVG-291, just succeeded in a clinical trial – making nerve signals stronger and improving hand function in people paralyzed for years [173] [176]. In this video, we break down how it works (spoiler: it releases a molecular brake on nerve growth [159]) and why experts are calling it a 'significant scientific advance' [179]."*

3. **Skeptical Hook:** *"We've heard about stem cells and miracle cures for paralysis that never really delivered. But what about a plain old* drug *– no surgery – that's showing actual results? Meet NVG-291: it just made history by* statistically improving *motor function in a spinal cord injury trial [173]. Skeptical? So were scientists, until they saw the data. Let's dive into what this drug did and didn't do, and what it could mean for millions living with SCI."*

On-Screen Graphic Suggestions:

1. **Before vs After Neuron Graphic:** Show a cartoon neuron with a "STOP" sign (CSPG) binding to PTPσ and the axon halted (dotted line), labeled "Inhibited (no growth)." Next to it, same neuron with NVG-291 wedge symbol blocking PTPσ, and axon growing forward (solid line), labeled "Disinhibited (axon regrowth)". This visualizes NVG-291 mechanism at a glance [160] [153].

2. **MEP Results Bar Chart:** A simple bar chart comparing MEP amplitude for NVG-291 vs Placebo. Y-axis: MEP amplitude (maybe as % of normal). NVG-291 bar towering ~3x height of baseline line, placebo bar small. Mark p=0.015 on it [173]. Title: "Brain-to-Muscle Signal Strength (MEP) – Drug vs Placebo". This emphasizes the objective improvement.

3. **Patient Abilities Icons:** A series of icons representing functions reported improved: a hand icon grasping an object (for fine motor) [184], a bladder icon (for improved bladder control) [181], a person sitting up straight (core/trunk stability improvements perhaps), a muscle icon (strength). Each icon could have an up arrow or + sign next to drug group, and a flat or small change for placebo, to illustrate areas of improvement.

4. **Timeline of Dosing & Effect:** A horizontal timeline: Weeks 0–12 (dosing period) with injection icon, then week 16 test icon, then beyond. Annotate something like: "During 12-week dosing:

nerves regrow"; at week 16: "improvements measured" [173]; beyond: "benefits persist at 52 weeks" [245]. This shows it's not instant but develops and lasts.

5. **Trial Info Table:** A small info box listing trial facts: "CONNECT-SCI trial: Phase 1b/2a; Participants: 20 chronic cervical SCI (AIS B-D), 20 subacute; Treatment: NVG-291 injection daily x 12 weeks; Control: placebo injection; Outcomes: motor evoked potentials, hand function (GRASSP), etc." – an overview panel.

6. **Neural Network Reconnection Image:** Perhaps use a simplified spinal cord cross-section or segment diagram showing red pathways broken pre-drug and some reconnection or new green pathways post-drug. Include a label "new connections formed" or "increased plasticity".

7. **Serotonin Fiber Regrowth** (from Silver's animal study): Maybe a microscopic image or cartoon of spinal cord with serotonin fibers (Raphaespinal) regrowing below lesion after treatment [153]. If an actual image from a paper is public domain, show side-by-side untreated vs treated spinal tissue with more fibers in treated. Caption: "In rats, NVG-291 (ISP) restored serotonin nerve fibers (red) below injury" – to tie preclinical evidence to concept.

8. **Quality of Life Gains Chart:** Perhaps take something like SCIM independence scale (just conceptually) or list tasks regained: e.g., "Brushing teeth: needed help → now independent; Operating wheelchair: partial assist → independent; Catheterization: 6x day → 3x day" for drug vs placebo. Illustrate improved independence qualitatively [184] [181].

9. **Fast Track / Regulatory Badge:** Show small logos or text for "FDA Fast Track" and maybe an accelerating arrow icon, and "Breakthrough Therapy – pending?" to illustrate it's on expedited path [197]. Could also show a US and EU flag implying global interest.

10. **Future Combo Approach Sketch:** A forward-looking graphic: e.g., an outline of a person with a spinal injury, showing multiple interventions combined: NVG-291 (chemical symbol) + maybe an implanted stimulator icon + maybe a cell bridge icon, all converging on the injury site, with question "Future: Combined Therapies = Greater Recovery?" – to open audience's mind that NVG-291 could work with other innovations for even more effect. This underscores that NVG-291 is part of a broader toolkit and not necessarily exclusive.

Viewer Comments & Replies:

1. **Viewer:** *"Is this like a stem cell or what kind of drug is it? Also how do they even figure out something like this?"*
   Reply: *NVG-291 isn't a stem cell – it's actually a peptide drug (a small protein). It was inspired by research into why nerves don't regrow after injury. Scientists found a receptor (PTPσ) that acts like a brake on nerve growth when it encounters scar tissue [160]. They designed this peptide to bind that receptor and block it from stopping growth [159]. Essentially, they took a piece of that receptor (the "wedge" region that controls it) and turned it into a drug. So it's a lab-made molecule that mimics part of our own proteins. They figured this out after decades of basic research – starting from observing how olfactory nerves regenerate (and identifying PTPσ's role) to testing a prototype in paralyzed rodents (which saw remarkable recovery [153]). So it's not from stem cells, it's from molecular neuroscience and a lot of clever bioengineering!*

2. **Viewer:** *"My injury is 5 years old, incomplete. If this drug were available now, what could it realistically do for me? Help me walk? Or just small improvements?"*

Reply: *Based on the trial, for someone like you (5 years, incomplete), NVG-291 might strengthen whatever connections you have. In their chronic trial, for instance, patients got stronger signals from brain to muscle – which translated to better hand function, more strength, and some regained sensations/control* [173] [176]*. If you're an incomplete para or quad, it could potentially improve things like grip, trunk stability, maybe add some muscle grade or improve coordination. I'd say think in terms of* incremental improvements *– perhaps going up one ASIA motor level, or being able to do tasks more easily. Walking: if you currently can't at all but have some leg movement, it might enhance those signals – maybe making an assistive gait possible (with devices). But it's not going to magically enable fully normal walking if you're far from it now. It basically amplifies what's there and encourages new sprouting around damage* [219]*. So the extent depends on your baseline – the more residual function, the more it can potentially amplify. The good news is even "small" improvements – like better hand dexterity or bladder function – can hugely impact quality of life, as their trial folks experienced* [181]*.*

3. **Viewer:** *"How long do the benefits last? Do you have to keep taking the drug forever?"*
   Reply: *Interestingly, in the trial they only gave the drug for 12 weeks – after that, they stopped. They found that the improvements were still there months later (the follow-up at 1 year after showed participants retained their gains and even reported ongoing improvements in daily life)* [181] [245]*. That suggests the drug caused* actual neural changes *that persisted (like nerves that regrew didn't suddenly shrink back). So it doesn't look like you have to take it forever. Possibly they might give it as a "course" during an intensive rehab period. Of course, it's early days – we'll know more from longer studies. But from what we see, it creates durable repair. Now, might someone take a second course to get even more improvement? That's an idea – if one round plateaued, maybe a second could add marginal gains. They haven't tested multiple courses yet. But the key point: it's not like symptom drugs you have to keep taking to maintain an effect; it triggers a repair process and then you're essentially done (like helping plants grow – once grown, you don't need to keep watering beyond normal). Regulators will watch long-term safety, but so far so good on durability.*

4. **Viewer:** *"Does it help with pain or spasticity? I have a lot of nerve pain after my SCI, would this make it worse by causing nerve growth?"*
   Reply: *Excellent question – one worry was: if you promote new nerve growth, could it lead to more pain or spastic, uncontrolled signals? In the trial, they actually found the opposite: patients on NVG-291 had less muscle spasticity and there are hints it might help neuropathic pain too* [186]*. Why? Possibly because it helps re-establish proper connections that modulate reflexes and pain pathways. One test they did (startle reflex MEP) showed that the drug group's hyperactive reflexes calmed down toward normal* [186]*. Some participants reported improvements in things like bladder spasms and overall comfort. So, initial signs are it doesn't exacerbate pain or spasms – it might improve them. But we'll need more data specifically on pain scores. Importantly, no one reported new neuropathic pain from the drug. So that concern is being alleviated by the results so far.*

5. **Viewer:** *"How did they measure that it works? Muscle potentials? Never heard of that."*
   Reply: *They used a cool technique called transcranial magnetic stimulation (TMS) to send a pulse through the brain's motor area and recorded the response in a muscle, known as a Motor Evoked Potential or MEP* [167]*. Think of it like checking the wiring: you hit the 'send' button in the brain and see how loud/fast the 'signal' is when it reaches a muscle. In SCI, that signal is often weak or absent because of damage. In this trial, after NVG-291, the signal got much stronger – meaning the 'wire' became more conductive or there were more wires carrying current* [219]*. They also did clinical tests (hand dexterity, strength, walking ability, etc.). The MEP is an objective measure – patients can't fake it, it's purely physiological. Seeing a 3-fold increase in MEP amplitude with the drug is a solid indicator something changed physically in the cord* [173]*. So, while "MEP" sounds technical, it basically proved the drug improved the connection from brain to muscle. They paired that with functional outcomes (like*

better grip strength which the MEP likely enabled). It's a common neuro research tool, but this is the first time an SCI therapy showed a clear positive effect with it.

6. **Viewer:** *"Is NervGen the only company doing this? Are there similar drugs?"*
   Reply: *NervGen is currently leading the pack. Their approach is unique – targeting the CSPG scar pathway via PTPσ [159]. Other approaches in the past tried blocking myelin inhibitors (e.g., anti-Nogo antibodies by Novartis) – that unfortunately didn't show clear benefit in trials. So NVG-291 is fairly one-of-a-kind at the moment. There are some academic groups exploring similar ideas (like enzymes to degrade scar tissue – e.g., chondroitinase – but that's not in human trials yet). There's also a company called ReNetX that tested a "Nogo trap" – results were inconclusive. So yes, NervGen is kind of at the forefront now with actual positive human data. That said, if this continues to succeed, expect others to jump in or partner – it's somewhat of a breakthrough concept proven. They also might expand it to conditions like multiple sclerosis (remyelination) and stroke. For now, NVG-291 is the trailblazer in pharmacological neuroplasticity for SCI.*

7. **Viewer:** *"I remember hearing about some peptide called 'ISP' in rats that let them pee and walk again – is this the same thing?"*
   Reply: *Yes! Great memory – ISP (Intracellular Sigma Peptide) was the nickname for the peptide Dr. Jerry Silver's lab used in those famous 2015 rodent studies that restored bladder function and some walking in paralyzed rats [153]. NVG-291 is essentially the human-optimized version of ISP. It's based on the same principle (PTPσ wedge) but formulated for human use and made a bit more stable. NervGen licensed that tech from Dr. Silver. So NVG-291 = ISP 2.0, if you will. And what's exciting is that we're seeing in humans echoes of what was seen in rats – like bladder improvements, which is exactly what happened in ISP-treated rats [246]. It's a great example of an idea successfully translating from animal model to clinical trial.*

8. **Viewer:** *"When and how can patients get this? My rehab doctor hasn't mentioned it."*
   Reply: *Right now, NVG-291 is still in clinical trials – it's not approved for general use yet. Your rehab doctor wouldn't prescribe it outside of a trial. The company hopes to start larger trials soon and if those go well, they could seek FDA approval maybe around 2029-2030. For now, you can only get it by enrolling in a trial. They've done the small Phase 1b; next will be a bigger Phase 2/3 where more patients will be needed – maybe you could qualify for that depending on your injury specifics. The spinal cord medicine community is definitely watching this – so I suspect in a couple of years, many rehab doctors will know about it as more data emerges. For now, keep doing your standard rehab – and perhaps inquire if any trial sites are recruiting (the recent trial was US & Canada for chronic cervical incomplete injuries). We'll have to be patient as the evidence builds, but the hope is that it will become part of standard rehab in a few years if all continues to go well.*

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