

Cell and Tissue Engineering – Course Project

Neural-Spinal Scaffold A Spinal Cord Injury Regeneration Platform And OPC1, Oligodendrocyte Progenitor Cell Therapy

Yves Greatti

A – Topic

Spinal cord injury (SCI) is a devastating trauma in the life of a patient and has severe costs on our society. Today there are about 285,000 people in the U.S living with SCI, and approximately 17,000 new acute SCI cases diagnosed each year (NSCIC). Mortality rates in the first years after the injury, have fallen by some 50%, however beyond this period, there have not been significant improvements (lifeexpectancy.org). Older people have half of the life expectancy of younger people and people in their twenties have a life-expectancy of about 30 years or 15 years (NSCIC). People sustaining a SCI have permanent and profound injury complications occurring in multiple with functional loss or disability, and potential neurologic disorders.

InVivo Therapeutics develops the **Neural-Spinal scaffold** (NSS), and has completed single-arm clinical study for patients with a complete thoracic spinal cord injury. FDA has accepted the preclinical version of the NSS. The company has started a two-arm clinical study looking for 20% or greater improvement in the treatment group on the ASIA Impairment Scale (AIS) grade. The device has entered the market in 2014.

OPC1, Lineage Therapeutics oligodendrocyte progenitor cell (OPC) therapy, has received a regenerative medicine advanced therapy (RMAT) and orphan drug designations from the FDA. OPC1 has been tested in two clinical trials. Among the patients enrolled in the later trial, 96% reported improved in motor functions with 32% at two or more levels

In February 2021 Lineage Therapeutics announced that they entered an agreement with Neurgain PDI for commercialization of OPC1.

Problem statement

As of today, there is no effective treatments for SCI that can regenerate the spinal cord after injury. There is a need for tissue-engineered construct for promoting axonal regeneration. Remyelination is an important mechanism for SCI recovery. Oligodendrocytes derived from OPCs produce the myelin sheath, remyelinate CNS lesions and promote neurotrophic factors, increasing neuronal survival in SCI.



B – Background

Problem Description

Traumatic spinal cord injury (SCI) is a debilitating neurological condition with severe socioeconomic impact on the health care system. Since 2015, in the U.S., about 30% of persons with SCI are re-hospitalized for disease of the skin, or respiratory, digestive circulatory, and musculoskeletal diseases (NSCIC). There are approximately 54 new cases of SCI per one million people (17,730 new cases) (Jain et al.). The injured individuals are predominantly male. The age distribution is bimodal with a first peak involving young adults and a second peak for adults over the age of 60. Injuries in this last group, usually result from falls and these patients have worst outcomes than younger patients. More than 90% of SCI cases are traumatic such as traffic accidents, violence, sports or falls (NSCIC). Incomplete tetraplegia is the most frequent neurological outcome (NSCIC).

SCIs are mostly contusions (49%), or lacerations (21%). Compression shows no breach or disruption in the surface anatomy, and presents areas of hemorrhage and necrosis. In contrast, laceration results in clear-cut of the spinal cord, the lesions are dominated with collagenous connective tissue. In massive compression, the cord is pulpified to a varying degree with extensive fibrous scarring (Norenberg et al.).

The initial primary injury causes neuronal death (axons and oligodendrocytes), increase in the level of pro-inflammatory cytokines, recruit of inflammatory cells; such as macrophages, neutrophils and lymphocytes in the spinal cord; demyelination, ischemia and hypoxia. This process persists for weeks and initiates a second wave of apoptosis in neurons and oligodendrocytes. In the late phase (weeks to months/years), the injured tissue is isolated from the environment by reactive astrocytes through the formation of a mesenchymal scar. This phase is also characterized by developments of cysts, syrinx, and Schwannosis (Norenberg et al.) (Desai et al.).

Neuro-Spinal scaffold targets patients who have suffered a thoracic AIS A traumatic spinal cord injury at neurological level of injury of T2-T12. The neural-spinal graft is composed of two biocompatible and



bioresorbable polymers which together form an adhesive matrix that can deliver the cells near the injury site for enhancing axon guidance in the spinal cord. This matrix is able to provide neurotrophic factors, and other cues to improve cell survival and potential pro-generative drugs. The scaffold is surgically implanted into the gap in the spinal cord at the site of injury, and is resorbed over several weeks.

In the first clinical trial, conducted by Lineage, OPC1, oligodendrocytes progenitor cells, were injected to individuals with a neurological level of injury between T3 and T11 and with AIS-A. After 10-year follow-up the trial no serious adverse events (SAEs) were reported. In a second trial, escalating doses were administered to 33 participants. No SAEs reported were related to OPC1, 22 participants attained a one-motor-level improvement and 7 attained a two-motor-level improvement on one side of the body.

Motivation

According to Coherent Market Insight, the spinal cord injury therapeutic market is estimated to be valued at USD 6.7 million in 2021 and is expected to have a compound annual growth rate (CAGR) of 5.1% to reach USD 9.6 million in 2028. North America represents the largest market with 42.1%.

Compared to a neurological “incomplete” injury (AIS-B, C or D), AIS-A has the least potential improvement, and the lowest lifetime survival (Dukes et al.). In term of costs, Medicaid is the only national program covering services that SCI survivors require (SpinalCord.com). Mean annual cost of hospitalization are the highest among persons with AIS-A, AIS-B, or AIS-C injuries; with a daily cost of \$2,601 (2015 US\$) (Dukes et al.). Recently a research project received \$17 Millions USD from the Canadian government to study SCI. Over a year, the combined products (Neural-spinal scaffold and OPC1) can be sold at \$24,000 ($12 \times 2,000$) and with 708 units sold, the project will be even, with a \$7,200 cost saving per unit ($2,600 - 2,000 = 600 \times 12$) or 5.1 million ($7,200 \times 708$) total saving for Medicaid. This estimation does not include aftercare costs (however with these products, patients reported some improvement of their motor functions within a year).



C – Solution Landscape

Description	Advantage	Disadvantage or GAP	Reference
Methyprednisolone is an anti-inflammatory steroid, it exists under different names. Medrol is sold with a doctor prescription.	<ul style="list-style-type: none"> ▪ If administered within 8 hours of injury, may improve neurological outcome in motor and sensory ▪ Reduces in vitro Astrocyte cell death 	<ul style="list-style-type: none"> ▪ Does not improve long-term neurological outcome ▪ Increase complications, including infection, respiratory difficulties, GI hemorrhage and death ▪ Risk of hyperglycemia ▪ Seizures, rash, weight gain, mood changes, bleeding, pain 	(Fehlings et al.) (Zou et al.) (Wang et al.) (KAISER)
Cerebrospinal Fluid (CSF) drainage maintains perfusion pressure to decrease spinal cord blood flow.	<ul style="list-style-type: none"> ▪ Decrease intrathecal pressure and the amount of tissue damage ▪ Better neurological outcomes ▪ Improves bladder and bowel movements 	<ul style="list-style-type: none"> ▪ Neural injury ▪ Increases risks of hematomas ▪ Intracranial bleeds ▪ Needs reimplantation of critical vessels ▪ Infection 	(Epstein) (Martirosyan et al.)
Body-weight support treadmill is a device to help patient to regain “functional ambulation”.	<ul style="list-style-type: none"> ▪ Better quality of life, psychological well-being and decrease of depression ▪ May restore motor function 	<ul style="list-style-type: none"> ▪ Special accommodation like house modifications might be required ▪ Requires physical therapy assistance 	https://www.hocomat.com/us/solutions/lokomat/
NeuroRegen™ is a collagen scaffold with mesenchymal stem cells transplantation for SCI patients.	<ul style="list-style-type: none"> ▪ Resists compression from surrounding tissues thus less scar tissue ▪ Could be purified so lower risk of inflammatory response ▪ Completely resorbed after healing 	<ul style="list-style-type: none"> ▪ Source from animals (bovine tendon) ▪ Causes fever in patient (FDA recalled this product) 	Clinical trials: NCT02688049, NCT02352077 and research paper (Chen et al.)
Pharmicell Co has developed an autologous mesenchymal stem cell therapy for patients with ASIA-B SCI.	<ul style="list-style-type: none"> ▪ Remyelination ▪ Decreases apoptosis ▪ Reduces glial & trophic factors ▪ Lowers immunosuppression 	<ul style="list-style-type: none"> ▪ Increases likelihood of tumor formation as cells migrate away from the site of transplantation. ▪ Neuropathic pain ▪ Autonomic dysreflexia 	Phase II/III; NCT01676441

- Methylprednisolone sodium succinate (MPSS) is a controversial drug used for many years to prevent the loss of spinal cord neurofilaments characterizing the secondary injury in SCI, to facilitate neuronal conduction, to improve vascular perfusion, and to prevent accumulation of calcium deposits (Lee and Jeong). MPSS binds to glucocorticoid receptors, blocks proinflammatory genes, promotes expression of anti-inflammatory genes, and inhibits synthesis of cytokines (Antonio, O et al.). Despite a variety of studies showing its limited neurologic impact and potential for serious adverse events (Lee and Jeong); patients want to use it and recently the American Association of Neurological Surgeons suggested a 24-hour infusion of high-dose MPSS within 8 hours of an SCI (Fehlings et al.).
- Thoracic spinal nerve is cross-clamped during SCI surgery. For this specific surgery; risks of ischemia resulting in paraplegia are increased due to the distal localization of blood supply. In addition, hypertension induced by aortic cross-clamping results in an increase of cerebrospinal fluid pressure (CSFP), lowering spinal cord perfusion pressure (SCPP) and diminishing blood supply to the spinal cord. In addition, veins collapse when CSFP within spinal cord tissue becomes higher than venous pressure. Drainage of the CSF (CSFD) reduces CSFP, improving SCPP (Martirosyan et al.). Reviews of CSF drainage outcomes have reached contradictory conclusions showing that in one hand; in animal models or patients; incidence of paraplegia decreased from 50% to 8% or even 90% (Martirosyan et al.) and the opposite: for example, a study reviewed the data of 12 hospitals between 2000 and 2013 where CSFD was performed without postoperative motor benefits (Yoshitani et al.).
- The levels of injuries to thoracic spinal cord nerves (T3-T11) can result in paraplegia. Patients with limited mobility, can use special equipment, like a parawalker or body weight support on a treadmill (BWSTT). Locomotor training can enhance recovery of walking and individuals with severe SCI can still benefit from it on improving cardiovascular, respiratory, and bowel function; yet quantitative



results of its benefits still need to be established (Dobkin et al.).

- Collagen is abundant in the central nervous system, and connective tissue. Implanted collagen hydrogels could promote the migrations of neurons, the growth and regeneration of nerve axons, and the inhibition of hypertrophy of glial cell (gliosis). Collagen is difficult to harvest and requires expensive thorough purification protocols to suppress the immune response. Two clinical trials were completed, covering motor and sensory rehabilitation. The later one was a non-controlled phase 1, and had limited outcomes. Currently (as of 2020) (Qu et al.), there is no FDA approved scaffold for restoring mobility and sensation after SCI.
- A variety of stem cells of different types have been investigated for SCI (Schwann cells, mesenchymal stromal cells, neural progenitor cells, OPCs). While the use of stem cells may be promising, most preclinical studies have shown only modest improvements in functional recovery. To date despite its promises, there is not one stem cell therapy approved by the FDA for SCI (Badner et al.). After a single-arm clinical trial with unpublished results, Pharmicell Co does not exist anymore.

So far, there is not an FDA approved therapy to intervene directly in the spinal cord following SCI and repair it.



D – Solution Description

Need / Criteria	Unit of Measure	Ideal Value / Range	Reference
Mean Arterial Blood Pressure (MABP) Clinical feasibility of scaffold implantation	mmHg	[70, 100]	[MABP] (Martirosyan et al.)
Tissue sparing and new tissue formation Regrowth or new neurite formation is critical in SCI repair	mm ² or mm ³	None or less than a legally commercialized similar construct	(Thomas and Moon)
Biodegradability Scaffold should undergo degradation in a timely manner to avoid causing infection.	Molecular weight (MW)	None or less than a legally commercialized similar construct	(Reddy et al.)
Biological factors (clusterin, apoE, MCP-1) Measure factors which stimulate axonal growth, neural repair, and myelination (glial differentiation)	<ul style="list-style-type: none"> Clusterin, apoE: mg/L MCP-1: pg/mL 	<ul style="list-style-type: none"> clusterin: [1.87-1.94] apoE: [35-49] MCP-1: [69.5-175.2] 	(Wąsik et al.) (Kaneva et al.) (Valković et al.)
Human Alu Distribution of the stem cells within the body	pg human DNA	None or less than a legally commercialized similar construct	(Rivera et al.)
Tumorigenicity Assessment for teratomas or ectopic tissues formation within or outside the CNS.	- number	[2,4]	(Biopsy score)
Basso Beattie and Bresnahan (BBB) score This score is used to assess motor functions and recovery in rats. International Standards for Neurological Classification of Spinal Cord Injury (ISNCSC) includes different scores for patients.	- number	[0, 21]	(Wong et al.)

- **MABP and Intraspinal Pressure:** In the thoracic vascular region, proper spinal cord blood flow (SBCF) supply is critical to avoid ischemia. However aortic cross-clamping prompts an increase in CFSP and a decrease in spinal cord perfusion pressure (SCPP) reducing blood supply to the spinal cord (Robertazzi et al.). Studies have also shown that immediate neurological deficits are the result of minimal SCBF (Crawford et al.). Severe trauma decreases SBF because vascular resistance and MABP increase (Martirosyan et al.). The neural-spinal scaffold (NSC) consisting in PLGA and poly-L-lysine “mini-tubes”; is inserted within the compressed spinal cord parenchyma. It creates an isolating interface protecting the spared tissue. By absorbing the compression energy into the biocompatible material of the mini-tube, it diffuses the site of pressure down the surface of the mini-tube, away from the initial compressed site. Scaffold implantation could also result in an increase of intraspinal pressure. However past surgical procedures using NSCs, showed that pressure is rapidly reduced and back to normal after implantation (Guest et al.).
- **Tissue sparing and new tissue formation:** SCI damages grey matter that undergoes necrosis leading to non-neural scar and white matter loss. The neural-spinal scaffold prevents cystic cavitation, leads to new tissue containing Schwann cells, axons and white matter formation (Guest et al.). Similarly, OPC1s promote motor behavioral recovery including reduced cavitation and increased myelination (Priest et al.).
- **Biodegradability:** the mechanical characteristics of the polymers used in the scaffold differ depending their molecular weights. Biodegradability is not directly linked to molecular weight (MW) however a high molecular polymer weight might be correlated to a slower decrease in the loss of properties due to its hydrolysis (Speight). The neural-scaffold consists in an inner and outer scaffolds made from a blend of PLGA (75%, MW \approx 40,000), and a copolymer (25%, PLGA block MW \approx 30,000, polylysine block \approx MW 2,000); FDA approved; which resorb completely over 30-60 days by simple hydrolysis to water and excreted via the kidney (Guest et al.).



- **Biological factors:** Cluterin (CLU) promotes cell aggregation, and it has hypothesized that astrocytes and neurons in response to traumatic lesions up-regulate CLU to preserve cell proximity. Apolipoprotein E (apoE) is a plasma lipoprotein with an important role in lipid and cholesterol metabolism, and deficiency of apoE increases inflammation and oxidative stress; reducing functional recovery after SCI (Cheng et al.). Monocyte chemoattractant protein-1 (MCP-1) is a chemoattractant molecule which plays an important neuroprotective and anti-apoptosis role in SCI (Tang et al.). The NSC microgrooves can have different diameters (0.5 μ m and 4 μ m) and depths; and may be seeded with human neuronal stem cells such as OPC1s (Guest et al.). By generating these biological factors, the OPC1s within the scaffold; amplify the scaffold positive neural effect and promote neural repair, axonal growth and glial differentiation (Priest et al.).
- **hAlu (human Alu):** is a genetic marker to assess the biodistribution of transplanted cells and gives an efficacy measurement of the product. Using hAlu markers in animal models injected with OPC1s, we know the distribution of the cells at the targeted site; their levels within the site as well for the rest of the body of the host; which then provide us an indication of the toxicity of the therapy. At low doses, OPC1 cells are limited to the spinal cord and lower brainstem, while remaining minimal or absent from the CSF or blood (Manley et al.).
- **Tumorigenicity (and Toxicity):** there are concerns that transplantation of differentiated pluripotent stem cells (PSC) can lead to tumor formation in the patient at the transplantation site. But also transplanted cells can survive and may form tumors at distal sites. In animal models, necropsy, histological examination of spinal cord and brain tissues were conducted to identify any potential teratoma or ectopic tissue formation related to OPC1. On patients, clinical assessment of OPC1s were also performed concluding that these cells do not induce changes in hematology, coagulation, urinalysis, and does not cause physiological instability or neurological pain in animal models or patients (Priest et al.).



- **BBB:** is used to assess motor function from complete paralysis to normal use in rodents. The score is mapped to 3 categories: Early Stage (0-7: little or no hindlimb movement), Intermediate Stage (8-13: intervals of uncoordinated stepping), and Late Stage (14-21: forelimb and hindlimb coordination). The neural-spinal scaffold promotes survival, axonal growth and locomotor recovery (Teng et al.) . In addition, animals or patients treated with OPC1s, have exhibited improved motor performances (Manley et al.).

E – Verification and Validation

Verification

Functional Recovery Following Traumatic Spinal Cord Injury Mediated by a Unique Polymer Scaffold Seeded with Neural Stem Cells.

In this study by (Teng et al.), a cut of 4mm at the T9-T10 level was performed in a population of rodents. 4 groups of rats were created: (1) scaffold + neural stem cells (NSCs), (2) scaffold alone, (3) NSCs in the SCI, and (4) lesion-control. One day postinjury (p.i.) and then weekly thereafter, behavioral assessment of the rats was performed using the open-field BBB scale. At 70 days p.i., 69% of scaffold plus cells group, 54% of scaffold alone, compared to only 17% of cells-alone, and 33% of lesion-control groups attained a score of at least 10 (threshold of significant walking behavior). The scaffold plus cells group showed more normal sensory responses: at 70 days p.i., 50% of the animals regained a normal pain withdrawal reflex on the lesioned side (only 15% for the cells-alone and lesion-control).

Internal Decompression of the Acutely Contused Spinal Cord

In this other experiment performed by Guest et al., two groups of animals were used: rodents and minipigs. They all went through an internal timed decompression procedure (ID) consisting in opening the pia of the spinal cord to allow the insertion of the NS scaffold. During the implantation, monitored intraspinal pressure, initially peaked when the scaffold was inserted; but swung back to the normal expected range after dural closure. ID + scaffold reported a decrease in cavity volume (86%) and an



increase of preserved tissue width (44%) relative to the untreated animal group. Compared to the control group, scaffold implanted animals had an increase of 0.6 mm³ in white matter width and 2mm³ remodeled volume tissue. This PLGA scaffold degraded over 4-8 weeks. H&H staining, one week after implantation, revealed that few cells have entered the scaffold. At 2 weeks, the scaffold was extensively infiltrated. By week 3 and onward, the scaffold volume was reduced further and further. And by week 12, the scaffold was mostly replaced by new tissue with foreign body giant cells. By comparison, 12 weeks after, for an SCI only, the injury was filled with an empty cyst with macrophages along thin septations. The newly formed tissues were analyzed by immunofluorescent labeling for laminin-1 and detected regenerating axons entering laminin-rich newly formed tissue. GFAP staining also indicated reactive astrocyte penetrating into scaffold tissue. After scaffold degradation, myelin P0 protein staining, showed Schwann cell extensively remyelinating these tissues (axial sections).

Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitor Cells

For this research, (Manley et al.) injected OPC1s (2.4×10^5 cells per rat) directly into the spinal cord, close to the injury site of rats subjected to an SCI at level C5. Assessment of the locomotor performance was measured using the TreadScan system; prior and at 1,2- and 4-months post injury. Compared to animals treated with Hank's balanced salt solution, OPC1 animals exhibited the greatest score improvements closely matching the uninjured animals. And OPC1 treatment resulted in a significant reduction to no parenchymal cavitation at the injury site, and treated animals exhibited myelinated axons. H&E staining and quantification of hALU by PCR showed that OPC1 cells were located in the spinal cord within and around the injury site (2 days, 3-, 6-, and 9-months post treatment); no OPC1s migration occurred outside of the CNS parenchyma. Histological examination of the spinal cord, did not reveal any teratoma, or tumor. No toxicities were reported with OPC1 treatment including no impacts on morbidity or mortality. In vitro, proteins secreted by OPC1s involved in axonal growth (clusterin), neural repair (MCP-1), and suppression of apoptosis (apoE, TIMP1 or 2) were detected by Luminex assay at high levels (see supplementary



Table 2 in (Priest et al.)). In addition, a variety of transcription factors involved in neurogenesis; Olig1, PDGFR α , Nestin, NG2; were highly expressed (>70% marker positive).

Validation

- InVivo Therapeutics has completed its first clinical trial in 2015, and since then has an on-going second clinical trial (INSPIRE 2.0). In INSPIRE 2.0, 19 patients with nonpenetrating SCI with a visible contusion on MRI, AIS A scale, neurological level of injury at T2-T12 underwent NSS implantation. These patients were monitored for adverse and adverse device events (AEs and ADEs), bowel and bladder functions and they had follow-up MRIs to assess for presence or not of cyst formation. 7 of 16 had an improvement exceeding historical benchmarks (AIS grade A to B or C at 6 month). 4 patients (25%) had an improvement in motor score of 1 to 18 point by 24 months. Bowel and bladder functions were improved in all 6 responders. And finally no ADEs were reported (Kim et al.).
- Lineage Therapeutic has completed 2 clinical trials. In the most recent (Phase 1/2a dose escalation trial), 25 patients with C4-7 AIS grade A or B, received different doses of OPC1 (2×10^6 , 1×10^7 or 2×10^7). At -1-year follow-up, 21/22 (96%) and 7/22 (32%), recovered 2 or more levels of neurological function on at least one side of their body. The only AEs reported such as urinary tract infections, muscle spasms, or neuropathic pain are commonly reported SCI complications, none of SAEs were related to OPC1 (Fessler et al.).

Conclusions

SCI is a tragic and traumatic major event in the life of a person impacting emotionally and financially, not only the patient, and her close circle but also our society. The pathophysiology of SCI is complex, multifactorial, and multiphasic and has been a major challenge for the medical and scientific communities including cell-and-tissue engineers. The NSS has shown to reduce the intraspinal pressure, containing neurological damages during the acute phase and



in chronic phase, preventing cystic cavitation, and by promoting axonal growth restoring circuit connectivity across the lesion. And OPC1s have the ability to release many potential beneficial factors at the damaged site critical for neuronal repair. Although, the results obtained in motor functional and sensory recovery during the clinical trials using NSS and OPC1 were impressive, the failure of various previous repair strategies can give cause for cautious optimism about using intraspinal polymer scaffolds or stem cell-based as SCI therapies. Many questions remain open starting with the efficacy of these two products combined in one. The adjustments of the mechanical features of the scaffold like pore shape, distribution, porosity, to affect the rate of the OPC1 penetration, their differentiation, will be required to increase the formation of new tissues and accelerate SCI recovery. How much more research needs to happen before SCI is cured; is difficult to forecast but NSS and OPC1s seem to have lay down the foundations on which a cure eventually will be found. It will be less a miracle than the undeterred determination of researchers coming from different scientific disciplines to discover it; and among them; CTE has a major role to play.

[Only submitted in the final report]

Provide a short closing paragraph which summarized the key-take-away messages from your analysis and ties the whole project together. Link back to the problem statement.

References

- Badner, Anna, et al. "Spinal Cord Injuries: How Could Cell Therapy Help?" *Expert Opinion on Biological Therapy*, vol. 17, no. 5, May 2017, pp. 529–41. DOI.org (Crossref), <https://doi.org/10.1080/14712598.2017.1308481>.
- Biopsy score: <https://news.cancerconnect.com/treatment-care/understanding-your-biopsy-results-and-pathology-report>
- Chen, Wugui, et al. "NeuroRegen Scaffolds Combined with Autologous Bone Marrow Mononuclear Cells for the Repair of Acute Complete Spinal Cord Injury: A 3-Year Clinical



- Study." *Cell Transplantation*, vol. 29, Jan. 2020, p. 096368972095063. *DOI.org (Crossref)*, <https://doi.org/10.1177/0963689720950637>.
- Cheng, Xiaoxin, et al. "Apolipoprotein E as a Novel Therapeutic Neuroprotection Target after Traumatic Spinal Cord Injury." *Experimental Neurology*, vol. 299, Jan. 2018, pp. 97–108. *DOI.org (Crossref)*, <https://doi.org/10.1016/j.expneurol.2017.10.014>.
 - Crawford ES, Crawford JL, Safi HJ, Coselli JS: Redo operations for recurrent aneurysmal disease of the ascending aorta and transverse aortic arch. *Ann Thorac Surg* 40:439–455, 1985
 - **CRP:** <https://my.clevelandclinic.org/health/diagnostics/23056-c-reactive-protein-crp-test>
 - Desai, Jyaysi, et al. "Molecular Pathophysiology of Gout." *Trends in Molecular Medicine*, vol. 23, no. 8, Aug. 2017, pp. 756–68. *DOI.org (Crossref)*, <https://doi.org/10.1016/j.molmed.2017.06.005>.
 - Dobkin, B., et al. "Weight-Supported Treadmill vs over-Ground Training for Walking after Acute Incomplete SCI." *Neurology*, vol. 66, no. 4, Feb. 2006, pp. 484–93. *PubMed Central*, <https://doi.org/10.1212/01.wnl.0000202600.72018.39>.
 - Dukes, Ellen M., et al. "Relationship of American Spinal Injury Association Impairment Scale Grade to Post-Injury Hospitalization and Costs in Thoracic Spinal Cord Injury." *Neurosurgery*, vol. 83, no. 3, Sept. 2018, pp. 445–51. *PubMed Central*, <https://doi.org/10.1093/neuros/nyx425>.
 - Epstein, Nancy E. "Cerebrospinal Fluid Drains Reduce Risk of Spinal Cord Injury for Thoracic/Thoracoabdominal Aneurysm Surgery: A Review." *Surgical Neurology International*, vol. 9, Feb. 2018, p. 48. *PubMed Central*, https://doi.org/10.4103/sni.sni_433_17.
 - Fehlings, Michael G., et al. "A Clinical Practice Guideline for the Management of Patients With Acute Spinal Cord Injury: Recommendations on the Use of Methylprednisolone Sodium Succinate." *Global Spine Journal*, vol. 7, no. 3 Suppl, Sept. 2017, pp. 203S–211S. *PubMed Central*, <https://doi.org/10.1177/2192568217703085>.
 - Fessler, Richard G., et al. "A Phase 1/2a Dose-Escalation Study of Oligodendrocyte Progenitor Cells in Individuals with Subacute Cervical Spinal Cord Injury." *Journal of Neurosurgery: Spine*, July 2022, pp. 1–9. *DOI.org (Crossref)*, <https://doi.org/10.3171/2022.5.SPINE22167>.
 - Gibson, A E et al. "C-Reactive protein in adults with chronic spinal cord injury: increased chronic inflammation in tetraplegia vs paraplegia." *Spinal cord* vol. 46,9 (2008): 616-21. doi:10.1038/sc.2008.32
 - Guest, James D., et al. "Internal Decompression of the Acutely Contused Spinal Cord: Differential Effects of Irrigation Only versus Biodegradable Scaffold Implantation." *Biomaterials*, vol. 185, Dec. 2018, pp. 284–300. *DOI.org (Crossref)*, <https://doi.org/10.1016/j.biomaterials.2018.09.025>.
 - **ISNCSCI:** <https://www.isncscialgorithm.com/>
 - Jain, Nitin B., et al. "Traumatic Spinal Cord Injury in the United States, 1993–2012." *JAMA*, vol. 313, no. 22, June 2015, pp. 2236–43. *PubMed Central*, <https://doi.org/10.1001/jama.2015.6250>.
 - Kaneva, Anastasiya M., et al. "Plasma Levels of Apolipoprotein-E in Residents of the European North of Russia." *Lipids in Health and Disease*, vol. 12, no. 1, Dec. 2013, p. 43. *DOI.org (Crossref)*, <https://doi.org/10.1186/1476-511X-12-43>.



- Kaiser: reference: [Drug Encyclopedia Entry on Medrol](#)
- Kim, Kee D., et al. "Acute Implantation of a Bioresorbable Polymer Scaffold in Patients With Complete Thoracic Spinal Cord Injury: 24-Month Follow-up From the INSPIRE Study." *Neurosurgery*, vol. 90, no. 6, June 2022, pp. 668–75. *PubMed Central*, <https://doi.org/10.1227/neu.0000000000001932>.
- Lee, Byung-Jou, and Je Hoon Jeong. "Review: Steroid Use in Patients With Acute Spinal Cord Injury and Guideline Update." *Korean Journal of Neurotrauma*, vol. 18, no. 1, 2022, p. 22. *DOI.org (Crossref)*, <https://doi.org/10.13004/kjnt.2022.18.e21>.
- lifeexpectancy.org
- **MABP:** <https://www.healthline.com/health/mean-arterial-pressure>
- Manley, Nathan C., et al. "Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitor Cells: Preclinical Efficacy and Safety in Cervical Spinal Cord Injury." *Stem Cells Translational Medicine*, vol. 6, no. 10, Oct. 2017, pp. 1917–29. *DOI.org (Crossref)*, <https://doi.org/10.1002/sctm.17-0065>.
- Martirosyan, Nikolay L., et al. "Blood Supply and Vascular Reactivity of the Spinal Cord under Normal and Pathological Conditions: A Review." *Journal of Neurosurgery: Spine*, vol. 15, no. 3, Sept. 2011, pp. 238–51. *DOI.org (Crossref)*, <https://doi.org/10.3171/2011.4.SPINE10543>.
- **NSCIC:** National spinal cord injury statistical center: [Facts and Figures 2020](#)
- Norenberg, Michael D., et al. "The Pathology of Human Spinal Cord Injury: Defining the Problems." *Journal of Neurotrauma*, vol. 21, no. 4, Apr. 2004, pp. 429–40. *DOI.org (Crossref)*, <https://doi.org/10.1089/089771504323004575>.
- Priest, Catherine A., et al. "Preclinical Safety of Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitors Supporting Clinical Trials in Spinal Cord Injury." *Regenerative Medicine*, vol. 10, no. 8, Nov. 2015, pp. 939–58. *DOI.org (Crossref)*, <https://doi.org/10.2217/rme.15.57>.
- Ocejó, Antonio. and Ricardo Correa. "Methylprednisolone." *StatPearls*, StatPearls Publishing, 22 May 2022.
- Priest, Catherine A., et al. "Preclinical Safety of Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitors Supporting Clinical Trials in Spinal Cord Injury." *Regenerative Medicine*, vol. 10, no. 8, Nov. 2015, pp. 939–58. *DOI.org (Crossref)*, <https://doi.org/10.2217/rme.15.57>.
- Qu, Wenrui, et al. "Polymer-Based Scaffold Strategies for Spinal Cord Repair and Regeneration." *Frontiers in Bioengineering and Biotechnology*, vol. 8, Oct. 2020, p. 590549. *PubMed Central*, <https://doi.org/10.3389/fbioe.2020.590549>.
- Reddy, M. Sai Bhargava, et al. "A Comparative Review of Natural and Synthetic Biopolymer Composite Scaffolds." *Polymers*, vol. 13, no. 7, Mar. 2021, p. 1105. *DOI.org (Crossref)*, <https://doi.org/10.3390/polym13071105>.
- Rivera, Teresa, et al. "Human-Induced Pluripotent Stem Cell Culture Methods Under CGMP Conditions." *Current Protocols in Stem Cell Biology*, vol. 54, no. 1, Sept. 2020, p. e117. *PubMed Central*, <https://doi.org/10.1002/cpsc.117>.
- Robertazzi RR, Cunningham JN Jr: Intraoperative adjuncts of spinal cord protection. *Semin Thorac Cardiovasc Surg* 10: 29–34, 1998
- Sheldon, J et al. "C-reactive protein and its cytokine mediators in intensive-care patients." *Clinical chemistry* vol. 39,1 (1993): 147-50.



- Skelly, Christy L., et al. "Adverse Events." *StatPearls*, StatPearls Publishing, 9 August 2022.
- Speight, James G. "Monomers, Polymers, and Plastics." *Handbook of Industrial Hydrocarbon Processes*, Elsevier, 2020, pp. 597–649. *DOI.org (Crossref)*, <https://doi.org/10.1016/B978-0-12-809923-0.00014-X>.
- SpinalCord.com: [4 Things You need to. Know about SCI Medicaid Coverage](#)
- Tang, S. K., et al. "Redirection of Doublecortin-Positive Cell Migration by over-Expression of the Chemokines MCP-1, MIP-1 α and GRO- α in the Adult Rat Brain." *Neuroscience*, vol. 260, Feb. 2014, pp. 240–48. *DOI.org (Crossref)*, <https://doi.org/10.1016/j.neuroscience.2013.12.022>.
- Teng, Yang D., et al. "Functional Recovery Following Traumatic Spinal Cord Injury Mediated by a Unique Polymer Scaffold Seeded with Neural Stem Cells." *Proceedings of the National Academy of Sciences*, vol. 99, no. 5, Mar. 2002, pp. 3024–29. *DOI.org (Crossref)*, <https://doi.org/10.1073/pnas.052678899>.
- The Effects and Potential Mechanisms of Locomotor Training on Improvements of Functional Recovery after Spinal Cord Injury | Elsevier Enhanced Reader. <https://doi.org/10.1016/bs.irn.2019.08.003>.
- Thomas, Katharine E., and Lawrence D. F. Moon. "Will Stem Cell Therapies Be Safe and Effective for Treating Spinal Cord Injuries?" *British Medical Bulletin*, vol. 98, 2011, pp. 127–42. *PubMed Central*, <https://doi.org/10.1093/bmb/ldr013>.
- Valković, Toni, et al. "Plasma Levels of Monocyte Chemotactic Protein-1 Are Associated with Clinical Features and Angiogenesis in Patients with Multiple Myeloma." *BioMed Research International*, vol. 2016, 2016, pp. 1–7. *DOI.org (Crossref)*, <https://doi.org/10.1155/2016/7870590>.
- Wang, Timothy Y., et al. "Management of Acute Traumatic Spinal Cord Injury: A Review of the Literature." *Frontiers in Surgery*, vol. 8, Dec. 2021, p. 698736. *PubMed Central*, <https://doi.org/10.3389/fsurg.2021.698736>.
- Wąsik, Norbert, et al. "Clusterin, a New Cerebrospinal Fluid Biomarker in Severe Subarachnoid Hemorrhage: A Pilot Study." *World Neurosurgery*, vol. 107, Nov. 2017, pp. 424–28. *DOI.org (Crossref)*, <https://doi.org/10.1016/j.wneu.2017.08.006>.
- Wong, Jamie K., et al. "A Straight Alley Version of the BBB Locomotor Scale." *Experimental Neurology*, vol. 217, no. 2, June 2009, pp. 417–20. *DOI.org (Crossref)*, <https://doi.org/10.1016/j.expneurol.2009.03.037>.
- Yoshitani, Kenji, et al. "Cerebrospinal Fluid Drainage to Prevent Postoperative Spinal Cord Injury in Thoracic Aortic Repair." *Journal of Anesthesia*, vol. 35, no. 1, Feb. 2021, pp. 43–50. *DOI.org (Crossref)*, <https://doi.org/10.1007/s00540-020-02857-w>.
- Zou, Hong-jun, et al. "Methylprednisolone Induces Neuro-Protective Effects via the Inhibition of A1 Astrocyte Activation in Traumatic Spinal Cord Injury Mouse Models." *Frontiers in Neuroscience*, vol. 15, 2021. *Frontiers*, <https://www.frontiersin.org/articles/10.3389/fnins.2021.628917>.

