

# **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** (NSC), and has completed single-arm clinical study for patients with a complete thoracic spinal cord injury. FDA has accepted the preclinical version of the NSC. 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 approximatively 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 contusion (49% of cases), or lacerations (21% cases). 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 x 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
<b>Methyprednisolone</b> is an anti-inflammatory steroid, it exists under different names. Medrol is sold with a doctor prescription.	<ul style="list-style-type: none"> <li>▪ If administered within 8 hours of injury, improves neurological outcome in motor and sensory</li> <li>▪ Reduces in vitro Astrocyte cell death</li> </ul>	<ul style="list-style-type: none"> <li>▪ Does not improve long-term neurological outcome</li> <li>▪ Increase complications, including infection, respiratory difficulties, GI hemorrhage and death</li> <li>▪ Risk of hyperglycemia</li> <li>▪ Seizures, rash, weight gain, mood changes, bleeding, pain</li> </ul>	(Fehlings et al.) (Zou et al.) (Wang et al.) (KAISER)
<b>Cerebrospinal Fluid (CSF) drainage</b> maintains perfusion pressure to decrease spinal cord blood flow.	<ul style="list-style-type: none"> <li>▪ Decrease intrathecal pressure and the amount of tissue damage</li> <li>▪ Better neurological outcomes</li> <li>▪ Improves bladder and bowel movements</li> </ul>	<ul style="list-style-type: none"> <li>▪ Neural injury</li> <li>▪ Increases risks of hematomas</li> <li>▪ Intracranial bleeds</li> <li>▪ Needs reimplantation of critical vessels</li> <li>▪ Infection</li> </ul>	(Epstein) (Martirosyan et al.)
<b>Body-weight support treadmill</b> is a device to help patient to regain “functional ambulation”.	<ul style="list-style-type: none"> <li>▪ Better quality of life, psychological well-being and decrease of depression</li> <li>▪ Restores motor function</li> </ul>	<ul style="list-style-type: none"> <li>▪ Special accommodation like house modifications might be required</li> <li>▪ Requires physical therapy assistance</li> </ul>	<a href="https://www.hocomat.com/us/solutions/lokomat/">https://www.hocomat.com/us/solutions/lokomat/</a>
<b>NeuroRegen™</b> is a collagen scaffold with mesenchymal stem cells transplantation in SCI patients.	<ul style="list-style-type: none"> <li>▪ Resists compression from surrounding tissues thus less scar tissue</li> <li>▪ Could be purified so lower risk of inflammatory response</li> <li>▪ Completely resorbed after healing</li> </ul>	<ul style="list-style-type: none"> <li>▪ Source from animals (bovine tendon)</li> <li>▪ Causes fever in patient (caused an FDA recall)</li> </ul>	Clinical trial NCT02352077 and research (Li et al.)
<b>Pharmicell Co</b> is developing an autologous mesenchymal stem cell therapy for patients with ASIA-B SCI.	<ul style="list-style-type: none"> <li>▪ Remyelination</li> <li>▪ Decreases apoptosis</li> <li>▪ Reduces glial &amp; trophic factors</li> <li>▪ Lowers immunosuppression</li> </ul>	<ul style="list-style-type: none"> <li>▪ Increase likelihood of tumor formation as cells migrate away from the site of transplantation.</li> <li>▪ Neuropathic pain</li> <li>▪ Autonomic dysreflexia</li> </ul>	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.).
- Aorta at the thoracic 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. Despite two clinical trials, with encouraging results, including motor and sensory rehabilitation for 8 patients, NeuroRegen™ scaffolds have never been commercialized. From (Qu et al.) currently (as of 2020), there are no approved treatments 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.).



■

## D – Solution Description

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



- **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 without with stem cells promotes survival and axonal growth and locomotor recovery (Teng et al.). Animals or patients treated with OPC1 have exhibited improved motor performances (Manley 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 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. Surgical procedures of NSC show 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 prevent cystic cavation, 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 to molecular weight (MW) however a high molecular polymer weight might be linked to a slower decreases in the loss of properties due to its hydrolysis (Speight). The neural-scaffold is made of bioabsorbable polyglycolic polymer (PLGA-PLL; FDA approved polymers;), which resorbed completely over 4-8 weeks 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 or CCL2) is a chemoattractant molecule which plays an important neuroprotective and anti-apoptosis role in SCI (Tang et al.). The NSC promotes interaction between neural stem cells such as OPC1 cells (Guest et al.). The OPCs within the scaffold by secreting these factors; amplify the scaffold positive neural effect; promoting neural repair, axonal growth and glial differentiation (Priest et al.).
- **hAlu:** is a genetic marker to assess the biodistribution of transplanted cells and gives an efficacy measurement of the product. Using hAlu markers, 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 gives 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:** 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. Toxicology assessment of OPC1 have been performed concluding that these cells do not induce changes in hematology, coagulation, urinalysis or clinical observations in animal models or patients (Priest et al.).



## E – Verification and Validation

### Verification

### Validation

## E – Verification and Validation

There is often a lot of information you can include in this section. It needs to be structured into a logical analysis showing the verification and validation success, in *technical* detail, as a take home "This really works" message to the reader.

How do these studies map to specific, quantitative, design criteria from the solution description?

### Verification

[Use subheadings for each part]

Verification is typically a bench or animal study, where you are assessing the quantitative feature/specification of the device itself - thickness, bioactive proteins, strengths, biocompatibility, etc. Not typically clinical trials, those are validation.

Use the text to describe at least one key verification study. Explain how the reported data demonstrates the *most* important aspect for proof of concept. Show how the data connects to the design inputs.

Please focus on at least one quantitative verification and provide details on the method, outcome, and connection to design requirements. It helps to include at least one specific quantitative example from the papers and connect that example to the intended design parameter for that metric.

### Validation

Describe the methods and outcomes of at least one validation study. Connect the methods and outcomes to the needs of the intended population described earlier in the project.



If the company/lab have not published clinical trial results, then focus on the specific parallels, methods, and outcome from the available studies to the eventual human population.

**Wrapping up:** A concluding summary of the verification function and the validation scope (relating the validation to the patient population in the Background section) would be helpful. This section is almost the end of the paper so really try to give the reader a take home "it works" message.

## Conclusions

[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

- NSCIC: National spinal cord injury statistical center: [Facts and Figures 2020](#)
- lifeexpectancy.org
- SpinalCord.com: [4 Things You need to. Know about SCI Medicaid Coverage](#)
- Kaiser: reference: [Drug Encyclopedia Entry on Medrol](#)
- Oejo, Antonio. and Ricardo Correa. "Methylprednisolone." *StatPearls*, StatPearls Publishing, 22 May 2022.
- 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>.
- **MABP**: <https://www.healthline.com/health/mean-arterial-pressure>
- **CRP**: <https://my.clevelandclinic.org/health/diagnostics/23056-c-reactive-protein-crp-test>
- **ISNCSCI**: <https://www.isncscialgorithm.com/>
- Biopsy score: <https://news.cancerconnect.com/treatment-care/understanding-your-biopsy-results-and-pathology-report>
- Skelly, Christy L., et al. "Adverse Events." *StatPearls*, StatPearls Publishing, 9 August 2022.
- 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
- 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.



- 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

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>.

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>.

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](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>.
- 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>.
- 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>.
- 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>.
- Li, Xing, et al. "Transplantation of HUC-MSCs Seeded Collagen Scaffolds Reduces Scar Formation and Promotes Functional Recovery in Canines with Chronic Spinal Cord Injury." *Scientific Reports*, vol. 7, no. 1, Apr. 2017, p. 43559. *DOI.org (Crossref)*, <https://doi.org/10.1038/srep43559>.
- 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>.

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>.

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>.



- 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>.
- Tang, S. K., et al. "Redirection of Doublecortin-Positive Cell Migration by over-Expression of the Chemokines MCP-1, MIP-1 $\alpha$  and GRO- $\alpha$  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>.
- 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>.

