

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
Methylprednisolone 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, improves 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.)
NeuroRegen™ is a collagen scaffold with mesenchymal stem cells transplantation in 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 (caused an FDA recall) 	Clinical trial NCT02352077 and research (Li 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 ▪ Restores motor function 	<ul style="list-style-type: none"> ▪ Special accommodation like house modifications might be required ▪ Requires physical therapy assistance 	https://www.hocoma.com/us/solutions/lokomat/
Pharmicell Co is developing 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"> ▪ Increase 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 second 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.).
- 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.

- 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.).
- 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
Mean Arterial Blood Pressure (MABP) Spinal Cord Blood Flow (SCBF) = MABP/vascular resistance	mmHg	[70, 100]	[MABP] (Martirosyan et al.)
C-reactive protein test (CRP) Check for inflammation due to infection	mg/L	[2.86, 3.36]	(Kwiecien et al.)
Biological factors (clusterin, apoE, MCP-1) Measure factors which stimulate axonal growth, neural repair, and myelination (glial differentiation)	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.)
Neurological Level of Injury Scores International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) scores to assess sensorimotor impairment.	A natural number	Two ranges: [0-100] and [0-224],	[ISNCSCI]
Adverse Event (AE) Total number to monitor the safety of the product	- A number	>=0	(Christy L. Skelly et al.)

- **MABP:** SCI can be viewed as a two-step trauma. The primary injury results from impact, compression to the spinal cord. The second injury is cellular and biochemical. First concern of the surgeon is to relieve any pressure from the surrounding bone by removing fractures or dislocated vertebrae. 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.). MABP immediately spikes and then falls and severe trauma decreases SBF because vascular resistance and MABP increase (Martirosyan et al.).
- **CRP:** SCI causes hemorrhage, ischemia, severe inflammation, and cellular necrosis. After SCI, pro-inflammatory cytokines such as interleukins 1beta (IL1-beta), 6 (IL-6) as well as necrosis factor alpha (TNF-alpha), interferon gamma (IFN-gamma), CC, CXC, and CX3C chemokines; levels are elevated (Kwiecien et al.). IL1-beta, IL-6, and TNF are reported to induce synthesis by the liver of C-reactive protein (CRP) (Sheldon, J et al). In addition, hsCRP (high-sensitivity CRP) levels are higher for people with chronic SCI (chronic SCI: SCI complications longer than 1 year) with a mean CRP of 3.36 +/- 2.86 mg/L putting these people in high risk of CVD (American Heart Association) (Gibson, A E et al).
(is the scaffold be rejected)
- **Biological factors:** Cluterin (CLU) promotes cell aggregation, and it has hypothesized that astrocytes and neurons in response to traumatic lesion up-regulate CLU to preserve cell proximity. CLU also acts as a chaperone protein to bind toxin or damaged molecules in the ECM (Klimaschewski et al.). 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 chemokine which recruits monocyte/macrophages to the sites of inflammation. MCP-1 is a chemoattractant molecule which plays an important neuroprotective and anti-apoptosis role in SCI (Tang et al.).
- **ISNCSCI:** is an examination to score on the ASIA grade the motor and sensory impairment and severity of SCI based on low level raw scores. Raw scores are divided into motor [0,100] and sensor scales [0,224] (ISNCSCI):
Motor scale is divided to subscale of upper extremity [0,50] and lower extremity [0,50], upper and lower of Right [0, 25] and left [0, 25]). Each upper and lower extremity is divided into 5 motor nerve function values in [0, 5].
Sensor scale is divided into light touch [0-112] and pin prick [0,112]. Light touch and pin pricks are further subdivided. The scores need to be measured at different time points to evaluate the trend of the recovery. A recent study proposed to compute a single score between two time points (Grassner et al.)
- **AE:** Safety assessment should be established through the monitoring of the patient for a minimum of a year on a specific schedule. A list of adverse events is established with the medical staff. These events are graded on a severity scale of 1 to 5 (1=mild, 5: death) and recorded and counted (Christy L. Skelly et al.).



Table should include 4-6 thoughtful and critical design criteria. Criteria should also align with the requirements and constraints of the clinical problem. Criteria should include specific descriptions, scientific details, quantitative/functional criteria, and references for how the solution meets the criteria. Table should be filled out completely.

[paragraph text]

Summarize the process of selecting the design criteria and the associated metrics (based on the clinical need/problem statement). It's important to include references to support the choice of these design criteria. Try to be specific to the CTE criteria we're studying in the course and the identified problem statement and not address medical treatments in general.

Describe *how* the solution/specific CTE product works. Provide details on how the solution functions (mode of action).

Describe how the design of solution matches up with the design criteria. Explain the correlation between the function/design of the solution and the selected design criteria.

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.

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