Cell and Tissue Engineering – Course Project

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

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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

Nn 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 x 12) or 5.1 million (7,200 x 708) total saving for Medicaid. This estimation does not include aftercare costs (however, patients reported improvement of their motor functions within a year which costs less than a lifetime immobilization with no progress).

C – Solution Landscape

Description	Advantage	Disadvantage or GAP	Reference
Title (you can come up with a short descriptor if the technology doesn't have a name) 1-2 sentences describing the Solution	-Bulleted list	- Bulleted list	Include patent number, bibliography style reference or company website.
Title (you can come up with a short descriptor if the technology doesn't have a name) 1-2 sentences describing the Solution	-Bulleted list	- Bulleted list	Include patent number, bibliography style reference or company website.
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<u>Example</u> **Meso Biomatrix Scaffold** Kensey Nash is developing a porcine mesothelaial matrix for soft tissue repair including nerve conduits.	- naturally-derived matrix facilitates cell infiltration and growth factor retention - easy to handle surgically (short hydration time durable, deformable)	- matrix material is derived from another animal (pig)	http://www.kenseynash.com

[table]

Table with 5 distinct solutions.

[text]

Summary of descriptions, advantages, disadvantages, references. A well-written paragraph summarizing and referencing the content in the table

Include a careful consideration of the advantages and disadvantages of each solution. Review the logical argument of the text to provide contrast between the solutions and a gap analysis/description.

Provide a thoughtful summary and analysis of the differences in the available solutions.

Use the text section to do more than just *repeat* the information in the table in the summary paragraph – use the text section to describe trends and gaps in the table to set up a natural conclusion of how your selected product is able to address those gaps. It may be helpful to organize the section into smaller paragraphs for each specific gap you have identified.

D – Solution Description

Need / Criteria	Unit of Measure	Ideal Value / Range	Reference
Title 1-2 sentences describing the criteria	-	-	Include bibliography style reference
Title 1-2 sentences describing the criteria	-	-	Include bibliography style reference
Title 1-2 sentences describing the criteria	-	-	Include bibliography style reference
Title 1-2 sentences describing the criteria	-	-	Include bibliography style reference
Example **Thrombogenicity** Indwelling vascular catheter should not cause thrombosis. This is a severe safety risk to the patient.	- mg of thrombus formation in animal study	- none or less than a legally marketed comparator device	Preclinical Device Thrombogenicity Assessments: Key Messages From the 2018 FDA, Industry, and Academia Forum, ASAIO Journal

[table]

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 <u>success</u>, 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
- 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.
- 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.
- 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.
- 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.