Problem Description

Traumatic spinal cord injury (SCI) is a debilitating neurological condition with severe socioeconomic impact on the health care system. Since 2015, about 30% of persons with SCI are re-hospitalized for disease of the skin, or respiratory, digestive circulatory, and musculoskeletal diseases[1]. There are approximatively 54 new cases of SCI per one million people (17,730 new cases)[2]. 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 (**Figure 1** below). Incomplete tetraplegia is the most frequent neurological outcome (**Figure 2** below). The estimated lifetime costs average 1 to 5 million per individual[3].

Figure 1: Cause

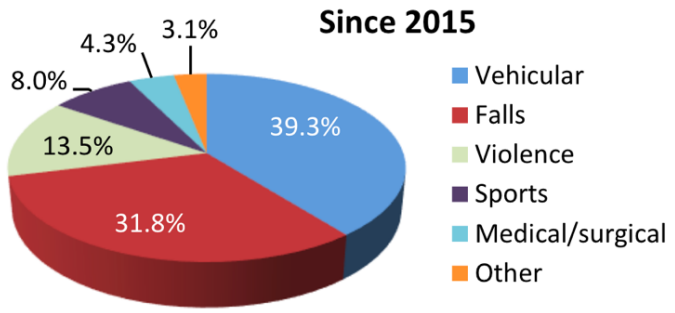
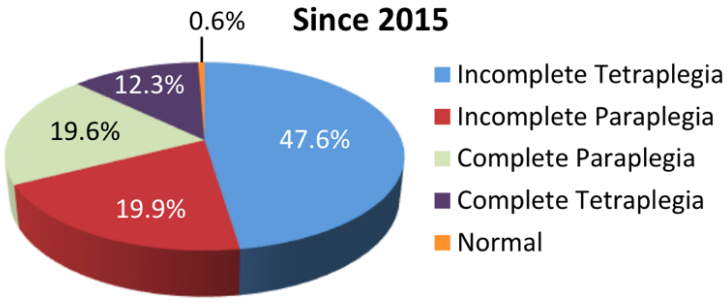


Figure 2: Neurological Level



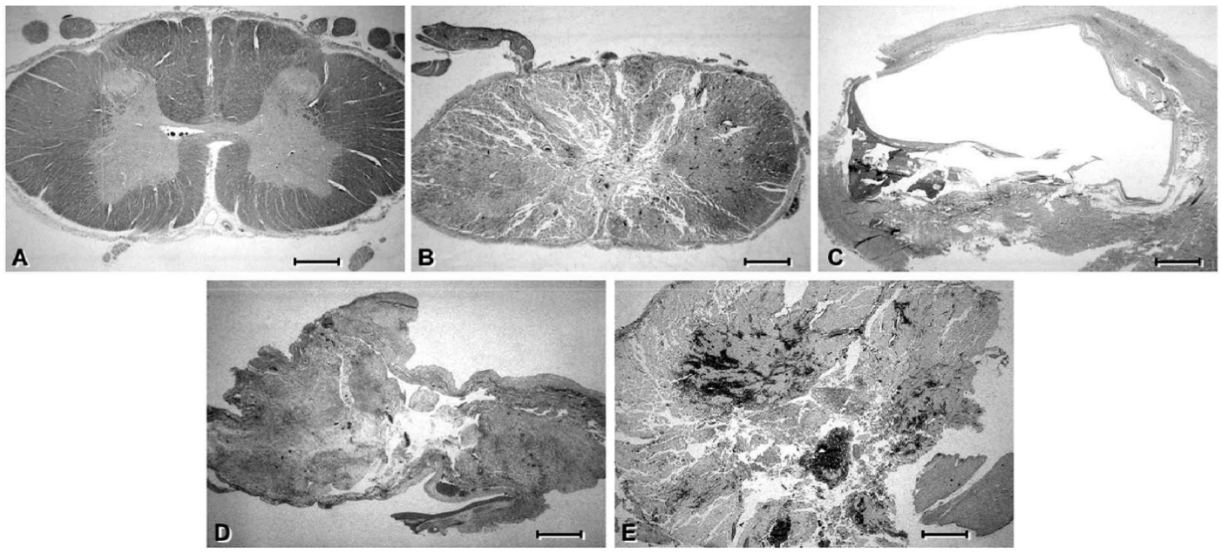
Source: National spinal cord injury statistical center

SCI 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

[1] National spinal cord injury statistical center.
[2] Jain NB, Ayers GD, Peterson EN, et al. Traumatic spinal cord injury in the United States, 1993-2012. JAMA. 2015;313(22):2236-2243.
[3] Economic Impact of SCI published in the journal Topics in Spinal Cord Injury Rehabilitation, Volume 16, Number 4, in 2011.

collagenous connective tissue. In massive compression, the cord is pulpified to a varying degree with extensive fibrous scarring[1].

Figure 3: "The Pathology of Human Spinal Cord Injury: Defining the Problems"



(A) Cross section of normal spinal cord (LFB-PAS). **(B)** Solid cord injury showing loss of the normal architecture and myelin loss (LFB-PAS). **(C)** Contusion/cavity in which the cord has been largely replaced by a cyst (H&E). **(D)** Laceration injury in which the pial surface has been breached (H&E). **(E)** Massive compression showing fragmentation, distortion and hemorrhage (H&E). Bar = 2 mm.

The initial primary injury causes neuronal death (axons and oligodendrocytes), increase in the level of pro-inflammatory cytokines, and recruits 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, and syrinx, and Schwannosis [1] (**Figure 4 and 5** below).

Figure 4: Norenberg et al.
Pathophysiology of traumatic. SCI

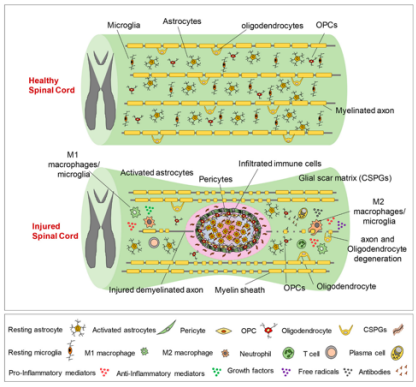


Figure 5: [2]
Main cellular targets of cell therapy in SCI

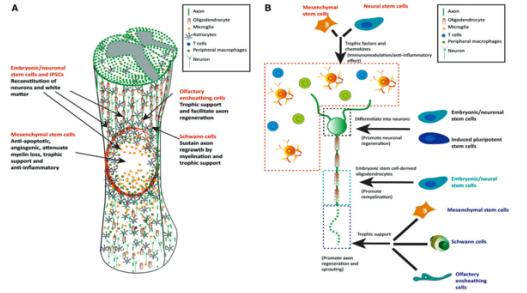
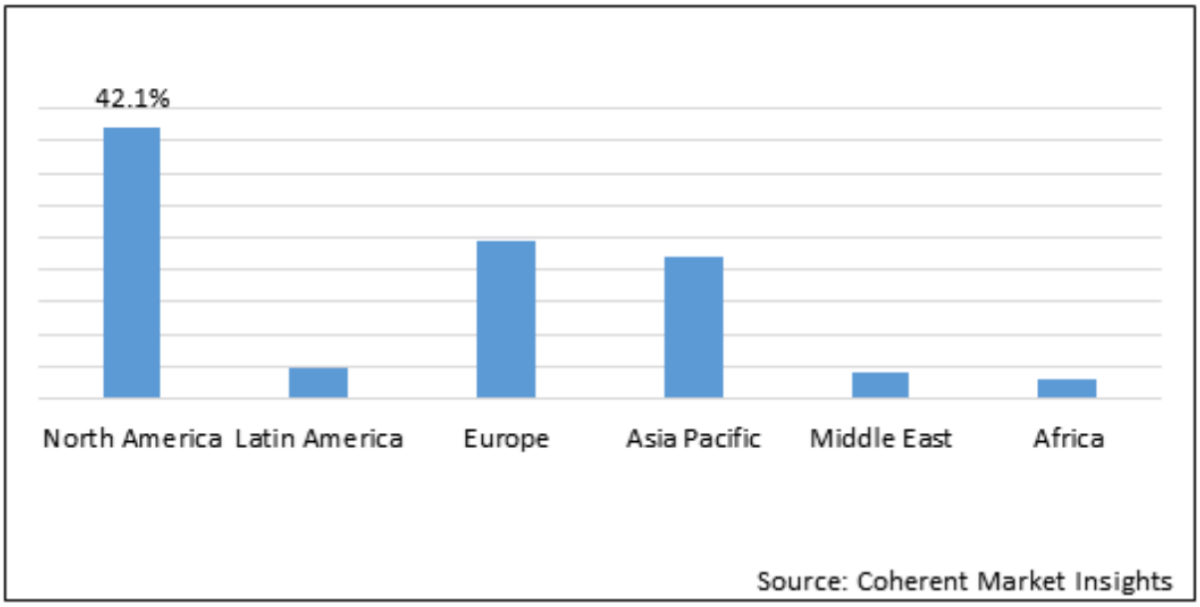


FIG. 5. Schematic illustration showing the main cellular targets of cell therapy in SCI and how this works (**A**), with particular focus on the mechanism by which stem cells ac to achieve immunomodulatory action, differentiation into neurons and oligodendrocytes, or providing trophic factors that can support axonal regeneration (**B**). Reproduced wit permission from Vismara *et al.*[2] Color images are available online.

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%.

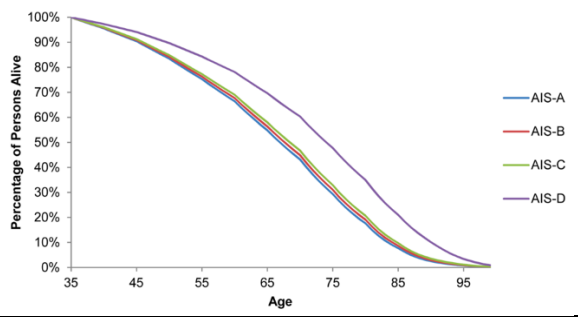


Neuro-Spinal graft targets patients who have suffered a thoracic AIS (American Spinal Injury Association Impairment scale) A traumatic spinal cord injury at neurological level of injury of T2-T12. Compared to a neurological "incomplete" injury (AIS-B, C or D), AIS-A has the least potential improvement, the lowest lifetime survival [3](**Figure 6** below). In term of costs, Medicaid is the only national program covering services that SCI survivors require. Mean annual cost oof hospitalization are the highest among persons with AIS-A, AIS-B, or AIS-C injuries with a daily cost of $2601 (2015 US$) [3] (**Figure 7** below).

Figure 6: ASIA Impairment Scale Grade

	AIS-A	AIS-B	AIS-C	AIS-D	Total N
Year 1	931 (59%)	153 (10%)	193 (12%)	295 (19%)	1572 (100%)
Year 5	676 (65%)	99 (9%)	128 (12%)	144 (14%)	1047 (100%)
Year 10	720 (71%)	80 (8%)	124 (12%)	97 (10%)	1021 (100%)

Figure 7: Estimated lifetime expectancy



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.

References:

[1] M. D. Norenberg, J. Smith, and A. Marcillo, "The Pathology of Human Spinal Cord Injury: Defining the Problems," *Journal of Neurotrauma*, vol. 21, no. 4, pp. 429–440, Apr. 2004, doi: 10.1089/089771504323004575.

[2] J. Desai, S. Steiger, and H.-J. Anders, "Molecular Pathophysiology of Gout," *Trends in Molecular Medicine*, vol. 23, no. 8, pp. 756–768, Aug. 2017, doi: 10.1016/j.molmed.2017.06.005.

[3] E. M. Dukes, S. Kirshblum, A. A. Aimetti, S. S. Qin, R. K. Bornheimer, and G. Oster, "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, pp. 445–451, Sep. 2018, doi: 10.1093/neuros/nyx425.