Modern Medicine and Surgery: Stem Cell Treatment of Spinal Cord Injury

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Abstract
Spinal cord injury is an important cause of morbidity worldwide, with associated significant reduction in quality adjusted life years (QALY). Stem cell therapy has perhaps been viewed by aspects of the profession as the experimental pathway with the greatest degree of optimism. That being said, the technique has now been explored for 20 – 30 years and despite this length of time the technique has not achieved any widely accepted cases of curative success (Eck & Marks, 2016; EUSTC, 2015; Kumar & Clark, 2016; Fehlings, 2012; Ronaghi).

This report explores potential explanation for the lack of curative, or restorative, success. The report then details potential pathways forward.

Keywords (Terms): ESCs; Injury; Neuron; MSCs; NPCs; NGF; Spinal Cord

1 Introduction
Spinal cord injury is an important cause of morbidity worldwide, with associated significant reduction in quality adjusted life years (QALY) (AAOS, 2016; Eck & Marks, 2016; EUSTC, 2015; Ronaghi, 2010). Despite the important advances in the understanding of spinal cord injuries, to date, almost all therapies that have shown promise at the preclinical stage of study have failed to translate into clinically effective treatments (Eck & Marks, 2016; EUSTC, 2015; Fehlings, 2012). There still remains no cure for spinal cord injury (Eck & Marks, 2016; EUSTC, 2015; Kumar & Clark, 2016).

Experimental research has investigated a number of techniques including stem cell therapy, neuro grafting, and other regenerative techniques (AAOS, 2016; EUSTC, 2015; Ronaghi, 2010). However, success has been very limited and as aforementioned no cure for spinal cord injury has been achieved (Eck & Marks, 2016; EUSTC, 2015; Kumar & Clark, 2016).

Stem cell therapy has perhaps been viewed by aspects of the profession as the experimental pathway with the greatest degree of optimism. That being said, the technique has now been explored for 20 – 30 years and despite this length of time the technique has not achieved any widely accepted cases of curative success (Eck & Marks, 2016; EUSTC, 2015; Kumar & Clark, 2016; Fehlings, 2012; Ronaghi).

This report explores potential explanation for the lack of curative, or restorative, success. The report then details potential pathways forward.

2 Development of the Nervous System
Neuronal development typically involves a neuron sending out an axon toward distant targets to which signals are delivered and several dendrites which receive signals from other neurons in addition to circulating messengers (Alberts, 2002; Ronaghi, 2010; Vawda, 2012). The path of axons and dendrites are led by growth cones (which propagate the axons and dendrite along their path) and receive structural support from a substratum of extracellular matrix or cell surface (Alberts, 2002; Lodish, 2000; Saladin, 2001). Pioneering neurites may already have traversed the pathway (Ronaghi, 2010; Saladin, 2001). The growth cones sense guidance cues from the surroundings (example, extracellular environment) for what are termed guidance cues. The growth cones respond to these guidance cues through what is termed a chemotropic response. Guidance molecules include: Netrins; Slits (Sli); Ephrins; Semaphorins; Cell Adhesion Molecules (CAMs); BMPs, GABA; FGFs; BMPs; L1; and, others. Of particular note is that target tissues release important chemicals and factors including NGF which facilitate nerve growth and development toward the target (Saladin, 2001; Vawda, 2012). Continued neuronal development, differentiation and attainment of function involves complex and intricate chemical, physiological and biological reactions (Saladin, 2001).

3 Spinal Cord Injuries
SCI causes myelopathy, damage to white matter, and myelinated fiber tracts that carry sensation and motor signals to and from the brain (Saladin, 2001). The gray matter damage causes segmental losses of interneurons and motoneurons and restricts therapeutic options (Ronaghi, 2010).
Different sources and types of cells have been tested in clinical trials for SCI, including embryonic stem cells (ESCs), neural progenitor cells (NPCs), mesenchymal cells (MSCs; and, BMSCs), olfactory ensheathing cells and Schwann cells (Ronaghi, 2010; Vawda, 2012).

4 Problem Identification

Stem cell therapy has perhaps been viewed by aspects of the profession as the preferred experimental pathway to pursue. That being said, the technique has now been explored for 20 - 30 years and despite this length of time the technique has not achieved any widely accepted cases of curative success.

It is important that the scientific community direct concerted attention to the key factors having negated stem cell therapy from having achieved any accepted cases of curative success.

Key barriers to success include:

1. The transplanted stem cells fail to achieve the intended growth into the desired neuronal form
2. The stem cell derived neuron (or, nerve) fails to function appropriately
3. Inflammation
4. Glial scarring

The report now systematically works its way through the above key factors hindering success to date with stem cell therapy of SCI, focusing on factors 1 and 2.

With respect to factors 1 and 2 above, one challenge is that in nature the development, differentiation, and attainment of desired function with respect to neurons (nerves) occurs over many years, and involves very complex chemical, electrical, physiological and biological reactions (Barrett, 2015). In order to achieve restorative (and curative) stem cell treatment of SCI, it would likely require the mimicking of this ‘long complex developmental process.’ Current techniques do not appear to achieve this.

The neurons need to learn:

1. The ability to grow, differentiate and learn
2. The ability to attain and utilize the desired function

The scientific community needs to address the above issue adequately in order to achieve restorative and curative success in the stem cell treatment of SCI. It would seem worth considering measures including the following:

- Exogenous growth of nerves using complex (perhaps multidimensional) computer simulated (and guided) chemical signaling designed to mimic that occurring with neuronal development in humans in nature. The likely commencement being that of stem cells (Examples: ESCs; NPCs; MSCs). The other aspect is to achieve functional capabilities of the nerve, again using complex computer simulations to facilitate the nerve to learn the functions it needs to perform.
- Three dimensional printer technology may also be assistive with respect to the above. Whether computer technology could be developed such as to implant devices to simulate (and stimulate) such chemical signaling with the objective to achieve endogenous growth of the nerve would be worth considering. It would seem that the current technology (produced through three dimensional printing) designed in USA that, in the main, provides only structural support for guidance of growth of the nerve would be unlikely by itself to achieve any restorative (curative) success.

It is reiterated that nerve growth be viewed as a ‘long complex developmental process.’ In terms of achieving the technological capabilities to carry out the required nerve growth process as espoused, whilst it may seem extensive, there is optimism in programs of USA revolving around mind mapping (BRAIN Initiative) that could potentially merge to further facilitate the progress of restorative (and curative) spinal cord injury repair (Pappas, 2013; WH, 2014).

One further consideration with the predicted advent of downloadable consciousness is the development of an implant to transfer the consciousness of the CNS from an area higher than the SCI to an area lower than the SCI. This would need to take into account anatomical considerations. Given that a person appears, from an external perspective, unconscious if either suffering brainstem damage or widespread cortical damage (Kumar & Clark, 2016; Lindsay et. al., 2010; Talley & O’Connor, 2014) the commencement (point of origin) of the implant would likely have to be at the level of the brainstem or higher and insert into a site at a location below the SCI (or, traverse through it).

5 Conclusions

Stem cell therapy has perhaps been viewed by aspects of the profession as the experimental pathway with the greatest degree of optimism in
respect of achieving restorative (and curative) success in SCI repair, yet despite 20 – 30 years of exploration the technique has not achieved any widely accepted cases of curative success. The current report has detailed potential pathways forward.

References