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Amyotrophic Lateral Sclerosis (ALS)

Stem Cell treatments for ALS. An overview on all possible treatments and then what we currently specifically offer at Cedar Stem Cell Institute.
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Overview: Amyotrophic lateral sclerosis (ALS) is a rare, neurodegenerative disorder leading to the loss of motor neurons ultimately leading to death. After diagnosis, the average lifespan ranges from 3 to 5 years, and death usually results from respiratory failure. Although the pathogenesis of ALS remains unclear, multiple factors are thought to contribute to the progression of ALS, such as network interactions between genes, environmental exposure, impair molecular pathways and many others. The neuroprotective properties of neural stem cells (NSCs) and the paracrine signaling of mesenchymal stem cells (MSCs) have been examined in multiple pre-clinical trials of ALS with promising results. The data from these initial trials indicate a reduction in the rate of disease progression. The mechanism through which stem cells achieve this reduction is of major interest. Here, we review the to-date preclinical and clinical therapeutic approaches employing stem cells, and discuss the most promising ones and the ones currently used at the Cedar Stem Cell Institute.

List of ALL KNOWN POSSIBLE TREATMENTS:
Preclinical advances in stem cell therapies for ALS
Neural stem cells
Mesenchymal stem cells
Embryonic stem cells
Induced pluripotent stem cells
Human umbilical cord blood cells
Olfactory ensheathing stem cells

Clinical advances in stem cell therapies for ALS
Clinical application of NSCs for ALS therapy
Clinical application of BM-MSCs for ALS therapy

What we DO at Cedar Stem Cell Institute at PRESENT TIME:

1- BMAC harvest then give **Intravenous BM-MSCs alone**
2- BMAC harvest then give **Intrathecal BM-MSCs alone**
3- BMAC harvest then give **Combo intravenous and intrathecal BM-MSCs**
4- BMAC harvest then give **Combo Intravenous (BM-MSCs and PRP) plus intrathecal (BM-MSCs and PRP).** The rationale of adding PRP to the mix is for its benefits from the addition of many growth factors and cytokines found in the platelets.

SCIENTIFIC SUPPORT & RATIONNALE:

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent stromal cells that can be easily derived from various sources, such as the umbilical cord, adult bone marrow (the best described origin of MSCs), Wharton's jelly, the placenta, adipose tissue, fetal liver and others.

Subsequently, MSCs give rise to osteoblasts, chondrocytes, and adipocytes (Prockop, 1997). MSCs have been administered as a therapeutic strategy in treating many types of diseases, including neurodegenerative disorders, and can be recognized by negative and positive profiling of different hematopoietic surface markers. Their positive impact after transplantation involves the release of neurotrophic and immunomodulatory molecules (cytokines and growth factors such as IL-6 and IL-10, TGF-!, insulin-like growth factor (IGF-1) and VEGF). When delivered regularly, they migrate to the damaged tissue sites exhibiting inflammation (Aggarwal and Pittenger, 2005; Suzuki et al., 2008). What is more, MSCs have the possibility to transdifferentiate into neuron-like cells. So far, the

protocols for inducing neuron-like cell differentiation used several chemicals which are toxic and cannot be applied in humans (Mao et al., 2015). Conversely, growth factors, such as the epidermal growth factor (EGF), VEGF and hepatocyte growth factor (HGF), are naturally secreted in the human organism and may

be safety used to induce differentiation. Nevertheless, employing these neuronal cells in clinical trials, especially for the questionable formation of functional neurons, continues to raise doubts (Bae et al., 2011). There is a need for long-term preclinical studies on in vitro differentiation and biological activity of human

MSCs.

Animal model studies revealed that the most promising candidates for ALS therapy are bone marrow-derived MSCs (BM-MSCs), which successfully improve the clinical and pathological features of the disease. This is associated with the availability and quantity of BM-MSCs in relation to other stem cell classes. G93ASOD1 mice **receiving intra-venous, intra-thecal, intra-cerebral and**

intra-spinal MSC grafts exhibit favorable effects on the courseof ALS, namely the recovery of motor function, decreased loss of MNs and extended lifespan (Lunn et al., 2014; Zhao et al., 2007; Uccelli et al., 2012; Boulis et al., 2011). In turn, the intraspinal administration of BM-MSCs in G93A-SOD1 mice confers a range of beneficial effects on neuroinflammation, astrocytosis, and the activation of microglial cells (Vercelli et al., 2008; Boido et al., 2014). MSCs, apart from the delivery of neuroprotective factors to the CNS, are also involved in the regulation of inflammation and activation of endogenous cells to participate in tissue repair. In the G93A-SOD1 mice, the intra-cerebroventricular application of BM-MSCs expressing glucagon-like peptide 1 (withantioxidant properties) prolonged lifespan for 13 days, reduced neuroinflammation, astrocytosis, and activation of microglial cells, and delayed the onset of ALS by 15 days (Knippenberg et al., 2012a).

Moreover, the **intra-muscular application** of G93A-SOD1 rats with BM-MSCs expressing higher levels of glial-derived neurotrophic factor (GDNF) leads to the recovered health of MNs and lengthens lifespan by 28 days (Suzuki et al., 2008). In addition, Kwon et al. (2014) showed that BM-MSCs (intra-thecally delivered) exert immunomodulatory action in ALS patients via the regulation of immune cells, such as T regulatory cells, which secrete higher levels of IL-4, IL-10 and TGF-! (Kwon et al., 2014). In turn, there is evidence to suggest that human BM-MSCs intra-

cerebroventricularly injected into ALS mice do not always bring about benefits in regard to neuroinflammatory response or motor neuron (MN) lifespan
(Morita et al., 2008). This may be related to the fact that BM-MSCs also exert their immunomodulation by inhibiting the activation and function of different cells of the specific and nonspecific immune system, such as dendritic cells, T/B lymphocytes, macrophages, neutrophils and natural killer cells (Wang et al.,
2014).
There are also reports concerning **adipose-derived MSCs** and their use in the treatment of ALS (Marconi et al., 2013; Kim et al., 2014). The systemic administration of MSC to SOD1-mutant mice at the clinical onset delayed motor deterioration by 4–6 weeks, maintained the strength and function of lumbar motor neurons (MNs), and upregulated levels of GDNF and basic FGF in the spinal
cord (Marconi et al., 2013). From the presented preclinical data, it seems that MSCs, owing to their therapeutic plasticity, suite the complex character of ALS quite well. This feature predisposes them to being a powerful candidate for the treatment of ALS.

PRP
Platelet-rich plasma may be a novel treatment for central nervous system diseases. It can help promote remyelination etc. It has been shown that the potent restorative function of PRP is mainly based on neurotrophic capacity. May be helpful in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and ALS. (Shen, 2009).

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