Title: **Cell- Based Therapy for ALS: Past, Present and Future**

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Abstract:

Amyotrophic Lateral Sclerosis (ALS) is a fatal and uncurable neurodegenerative disease that targets motorneurons. ALS community is still searching for an effective disease-modifying treatment of ALS. Stem Cell Therapy (SC) is viewed as a promising option for ALS because these cells potentially target several of the putative pathogenic mechanisms involved in the onset and progression of the disease, Indeed, in the past two decades, transplantation of various SC products has been evaluated in numerous Phase I and II clinical trials designed to assess feasibility and safety, but also looking for indications of clinical benefit however no conclusive results have yet been reported. Very few trials are controlled, as inclusion of adequate sham controls for invasive procedures is problematic and often unethical. We can conclude that some types of adult SCs are sufficiently safe and may be proposed for large clinical trials. However, it cannot yet be established which treatments provide significant benefit, and whether positive effects on the disease are sufficiently lengthy to justify the risks and costs of cell therapy. Moreover, different stem cell types that have been tested both in pre-clinical and clinical experiments do not possess the bona fide properties of stem cell, that is self-renewing and pluri/multipotency and are more properly classified as precursors or even differentiated cells. Identification of appropriate good manufacturing process (GMP)-compliant human SC lines that exhibit similar efficacy and safety profiles is needed. We review the first generations of clinical trials of novel cell therapies applied to ALS. This in turn helps to determine the best strategies to be adopted and the potential chances for success in developing new cell therapies to clinical application in this disease. We then consider the scientific, technical, ethical, regulatory and logistic issues to be resolved in translating effective laboratory cell-based protocols to patients in clinical trials.