

# AMYOTROPHIC LATERAL SCLEROSIS & STEM CELLS: FACT SHEET

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a relentless and incurable disease that involves the death of motor neurons in the brain and spinal cord that control voluntary movement, eventually leading to complete paralysis. While progression can range from rapid to slow, the average time course from disease onset to death is about three years. One of the most difficult parts of the disease arises when the motor neurons that control breathing are affected, and the patient needs to decide whether to use the support of an artificial breathing machine. Many choose not to.

A genetic cause contributes to about 10-15% of ALS cases, for which therapies to correct the mutated gene are being explored using antisense oligonucleotides and viral methods. Most patients, however, have a sporadic form of the disease. Currently, active development is underway for therapeutic drugs targeting sporadic ALS but, as of now, approved drugs only provide a minimal extension of lifespan. One area that has received a lot of attention is cell-based therapies for ALS.

## RATIONALE FOR USING CELL-BASED THERAPIES FOR ALS

The most obvious cellular approach is to generate new motor neurons from stem cells to replace the ones lost in ALS. It is possible to make new motor neurons from a patient's own stem cells, and these can survive transplantation into the brain and spinal cord. The problem with this approach is that placing these cells throughout the length of the spinal cord and cortex is currently not possible, nor can we get these cells to connect to their original targets.

An alternative approach is to protect diseased motor neurons using stem or progenitor cells that can be isolated from various tissues, such as the bone marrow or fetal brain or a new technology using adult-derived induced pluripotent stem cells (iPSC)<sup>1</sup>. Once stem or neural progenitor cells are transplanted into the brain or spinal cord, they can differentiate into a glial phenotype and may take up deleterious factors from the milieu, reduce disease-related inflammation, and release potent growth factors that nourish diseased motor neurons. Genetically engineered neural progenitor cells, modified to make the protein glial cell line-derived neurotrophic factor (GDNF), present a promising approach for delivering support cells and GDNF directly to the spinal cords and brains of patients with ALS.

A final approach is the intravenous infusion of autologous T-regulatory (Treg) lymphocytes, which may reduce ALS-related inflammation<sup>2-3</sup>.

## CLINICAL STATUS OF CELL-BASED THERAPIES AND CLINICAL TRIALS FOR ALS

There are no clinical trials aimed at replacing the motor neurons lost in ALS for the reasons given above. However, there are a few completed and ongoing trials using stem cells to modulate disease progression in ALS. These trials have generally used bone marrow-derived mesenchymal stem cells (MSCs), which are typically expanded in culture and then transplanted into the cerebral spinal fluid (CSF). Currently, there are over 40 trials, either completed or started, using MSCs to treat ALS in this way ([ClinicalTrials.gov](https://clinicaltrials.gov)).

In some cases, there have been signs of effect, but these are mainly Phase I safety studies. Therefore, any claims for efficacy need to be viewed with great caution. In a recent Phase II study, the company Brainstorm harvested and differentiated adult MSCs that secrete neurotrophic factors, reporting some positive results ([NCT02017912](https://clinicaltrials.gov/ct2/show/study/NCT02017912)). This has led to an ongoing larger Phase III efficacy trial by Brainstorm ([NCT03280056](https://clinicaltrials.gov/ct2/show/study/NCT03280056)). The treatment is repeated at three bi-monthly intervals as the cells only remain viable for a few months. These cells could help reduce inflammation through modulation of cytokines and the release of several neurotrophic factors, including GDNF. However, this Phase III trial failed to reach clinical significance.

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## ADDITIONAL RESOURCES

[About Stem Cells](#)  
[www.aboutstemcells.org](http://www.aboutstemcells.org)

[The ALS Association](#)  
[www.als.org](http://www.als.org)

[Motor Neurone Disease Association](#)  
[www.mndassociation.org](http://www.mndassociation.org)

[North East ALS Consortium](#)  
[www.neals.org](http://www.neals.org)

Several clinical trials in the USA ([NCT01348451](#); [NCT01730716](#)) have administered injections of human fetal spinal cord-derived neural stem cells, known as NSI-566, into the spinal cords of ALS patients<sup>4-5</sup>. The aim of this treatment is to introduce new interneurons and potentially stimulate the release of growth factors, thereby offering protection to motor neurons. However, although safe, there were no significant positive effects on secondary outcomes using this approach and the company has since stopped working in this space. A similar Phase I trial ([NCT01640067](#)) has been performed in Italy using human fetal-derived neural stem cells<sup>6</sup>. A more recent Phase I/IIa trial ([NCT02943850](#)) is assessing genetically engineered neural progenitor cells that stably release GDNF for a combined cell and gene therapy approach<sup>7-8</sup>. These cells, termed CNS10-NPC-GDNF, have been transplanted into the spinal cord of ALS patients and the trial met the endpoint of safety<sup>9</sup>. The cells were only given once and were shown to survive and release GDNF for the lifetime of the patient. Based on product safety and preclinical studies<sup>10</sup>, a subsequent trial is ongoing ([NCT05306457](#)) to deliver this same cell and gene therapy to the motor cortex of ALS patients.

Finally a small Phase I trial using autologous Tregs has shown safety and preliminary positive effects, but this needs to be expanded to more patients and a Phase II study ([NCT03241784](#)).

## CENTERS WORKING ON THE CLINICAL APPLICATION OF STEM CELLS FOR ALS

Many centers globally are involved with stem cell-based trials for ALS. The ongoing stem cell trials in the USA are being conducted by Brainstorm, which includes numerous clinical sites across the country, and by the Cedars-Sinai Medical Center. One of the essential criteria for credible and responsible clinical trials for ALS is compliance with regulatory authorities, such as the FDA. Unfortunately, there are also many clinics offering ‘stem cell therapies’ that are not performed with appropriate regulatory permission or oversight.

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