

What is the Real Mechanism of Stem Cells in ASD Patients?

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Received: October 23, 2026; **Published:** October 29, 2026

Abstract

ASD (Autism Spectrum Disorder), is a heterogeneous neurodevelopmental disorder in which no etiology is identified in the majority of cases.

The proposed mechanism of action of umbilical cord blood stem cells in ASD is not believed to be the replacement of brain cells. Instead, researchers think any potential benefit would occur through paracrine and immunomodulatory effects—that is, the cells release signaling molecules that may influence inflammation, immune function, and neural connectivity.

Several mechanisms have been proposed: 1- Modulation of neuroinflammation, 2- Regulation of the immune system, 3- Secretion of neurotrophic factors, 4- Improvement of cerebral blood flow and 5- Effects on neural connectivity.

Early open-label trials reported improvements in some children, particularly in social communication. However, stem cell therapies for ASD are generally experimental. Larger, well-designed clinical trials are still needed.

Keywords: *Autism Spectrum Disorder; Stem Cells; Mechanism; Clinical Trials*

ASD (Autism Spectrum Disorder), is a heterogeneous neurodevelopmental disorder in which no etiology is identified in the majority of cases. Clinical presentation varies widely, and regression may occur in a significant subset of patients.

Early diagnosis, systematic etiological investigation, and evidence-based intervention are essential to optimize outcomes. Advances in genetic testing are improving diagnostic yield, while addressing misconceptions remains crucial for appropriate clinical management.

Therapy with stem cells from the umbilical cord blood, is a promising tool for the patients with ASD and may improve their communications and social behavior.

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Several mechanisms have been proposed:

1. **Modulation of neuroinflammation:** Many studies have found evidence of altered immune activation and neuroinflammation in some individuals with ASD. Cells from cord blood may release anti-inflammatory cytokines and growth factors that could reduce excessive inflammatory signaling in the brain.

2. **Regulation of the immune system:** Umbilical cord blood contains stem and progenitor cells capable of interacting with immune cells. Researchers hypothesize that these cells may help normalize immune dysregulation observed in some autistic individuals.
3. **Secretion of neurotrophic factors:** Cord blood cells can produce factors such as:
 - Brain-derived neurotrophic factor (BDNF)
 - Vascular endothelial growth factor (VEGF)
 - Nerve growth factor (NGF)

These molecules may support neuronal survival, synaptic plasticity, and brain connectivity.

4. **Improvement of cerebral blood flow:** Some researchers suggest that cord blood cells may promote angiogenesis (formation of blood vessels) and improve microvascular function, potentially enhancing oxygen and nutrient delivery to brain tissue.
5. **Effects on neural connectivity:** ASD has been associated with atypical neural network connectivity. Growth factors released by cord blood cells may theoretically support synaptic remodeling and communication between brain regions [7-18].

What does the clinical evidence show?

Early open-label trials reported improvements in some children, particularly in social communication. However, stem cell therapies for ASD are generally experimental. Larger, well-designed clinical trials are still needed.

Others clinical trials are:

- A. Dawson G, Sun JM, *et al.* (2020). A Phase II Randomized Clinical Trial of the Safety and Efficacy of Intravenous Umbilical Cord Blood Infusion for Treatment of Children with Autism Spectrum Disorder. *Journal of Pediatrics*, 222:164-173.e5.

This was the main randomized, double-blind, placebo-controlled trial. The infusion was considered safe, but did not demonstrate a significant benefit in the overall study population. Some subgroups showed signs of improvement that warrant further investigation.

- B. Villarreal-Martínez L, *et al.* (2022). Stem Cell Therapy in the Treatment of Patients With Autism Spectrum Disorder: A Systematic Review and Meta-analysis. *Stem Cell Reviews and Reports*, 18(1):155-164.

The authors concluded that the preliminary results are promising, but the methodological quality of the studies does not yet allow for definitive conclusions.

- C. Nour-Eldine W, *et al.* (2022). In search of immune cellular sources of abnormal cytokines in the blood in autism spectrum disorder: A systematic review.

This review provides support for the hypothesis of immunological and inflammatory alterations in some individuals with autism, one of the main mechanisms by which cord cells could act [1-17].

- D. Zhang Z., *et al* (2026). Efficacy and safety of allogenic umbilical cord blood mononuclear cells therapy in children with autism spectrum disorder and immune dysregulation: a single-center, double blinded, randomized, placebo-controlled trial.

The inclusion criteria considered was: (1) diagnosed with ASD as specified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V); (2) aged 3 to 8 years, with no restriction on gender; (3) with laboratory evidence of peripheral immune dysregulation, defined as having at least one serum cytokine (including IL-1, IL-2, IL-6, IL-8, or TNF- α) level exceeding 1.5 times the upper limit of the normal reference range; (4) guardian who can fully understand the study's informed consent and voluntarily sign it.

This was the first study using allogeneic UCB-MNCs for the treatment of ASD. In Dawson., *et al.* study, autologous (n = 56) and allogeneic (n = 63) UCB infusions were administered. This study is the first to utilize allogeneic MNCs as the sole intervention, providing a basis for the compositional optimization of subsequent cell therapies. While both our study and previous research hypothesize immunomodulation as the therapeutic mechanism, we specifically enrolled children with peripheral blood evidence of immune dysregulation. Considering that previous animal experiments and clinical studies have shown that multiple infusions yield more potent anti-inflammatory and immunomodulatory effects, we administered four infusions at one-week intervals, as opposed to a single infusion. Furthermore, no prophylactic medications were administered in this study, enabling a clear and unbiased assessment of infusion-related adverse events.

In this trial, the results demonstrated that allogeneic UCB-MNCs treatment was both safe and potentially clinically beneficial, as evidenced by week 13 outcomes: the UCB-MNCs group had lower total scores and social cognition domain scores on the SRS-2 than the control group and also elevated cytokine levels [19].

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Volume 15 Issue 11 November 2026

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