SCE 0701 Public Evidence Appendix

Cell replacement versus signaling

Literature review date: September 9, 2026

Controlling principle. Durable cell replacement is only one possible mechanism; engraftment, differentiation, paracrine signaling, immune-mediated effects, and matrix remodeling must be distinguished and demonstrated rather than inferred from clinical outcome alone.

Mechanism map

Mechanism	What would support it	Major interpretive limitation
Direct engraftment	Viable administered cells persist, integrate into target tissue, and contribute to function over an appropriate time frame.	Short-term label detection or biodistribution signal does not prove durable engraftment.
Differentiation	Rigorous lineage evidence shows administered cells acquire the required specialized phenotype in vivo and contribute functionally.	In-vitro differentiation, marker expression, cell fusion, label transfer, or nonspecific staining can mislead.
Paracrine effects	Secreted cytokines, chemokines, growth factors, extracellular vesicles, or other mediators are linked to a measured biological response.	Plausible signaling does not establish which factor dominates or prove clinical benefit.
Immune-mediated effects	Changes in innate/adaptive immune cells or host response are measured and linked to the administered product.	Immune effects may be indirect, transient, context-dependent, or partly driven by clearance of administered cells.
Matrix remodeling	Measured changes in extracellular matrix, collagen deposition, matrix metalloproteinases, myofibroblasts, or fibrosis are linked to tissue function.	Remodeling can be adaptive or maladaptive; structural change alone does not prove regeneration.

Key evidence conclusions

Mechanism cannot be inferred from outcome alone. Clinical improvement, if observed, does not by itself reveal whether benefit arose from cell replacement, differentiation, signaling, immune effects, or matrix remodeling.

Persistence and replacement are separate questions. Many MSC preparations show limited long-term persistence after systemic administration, so short-term cell tracking should not be interpreted as durable tissue replacement.

Paracrine and immune mechanisms are biologically plausible but product-specific. The relevant mediators, target cells, dose, timing, and disease context should be demonstrated for the actual product.

Matrix remodeling can help or harm. Changes in fibrosis, collagen, and matrix turnover must be interpreted alongside tissue structure and function.

Principal references

1. Galipeau J, Sensebé L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. Cell Stem Cell. 2018;22:824-833.

2. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell. 2011;9:11-15.

3. Prockop DJ. Concise review: two negative feedback loops place mesenchymal stem/stromal cells at the center of early regulators of inflammation. Stem Cells. 2013;31:2042-2046.

4. de Witte SFH, Luk F, Sierra Parraga JM, et al. Immunomodulation by therapeutic mesenchymal stromal cells is triggered through phagocytosis of MSCs by monocytic cells. Stem Cells. 2018;36:602-615.

5. Relevant contemporary consensus and review literature concerning MSC biodistribution, persistence, paracrine signaling, immune interactions, extracellular vesicles, and tissue remodeling.