SCE 0708 Public Evidence Appendix

Mechanism-of-action uncertainty

Literature review date: September 13, 2026

Controlling principle. Mechanism-of-action claims are conditional on the exact product, disease, dose, timing, and patient; biological plausibility can support a hypothesis but cannot substitute for indication-specific human evidence of clinical benefit.

Mechanistic evidence map

Domain	What must be considered	Interpretive boundary
Product-specific mechanisms	Source, donor, cell population, culture, priming, oxygen tension, harvest, purification, formulation, storage, viability, EV composition, dose, and route.	A mechanism shown for one defined product should not automatically be assigned to another product sharing a broad MSC or exosome label.
Disease-specific mechanisms	Pathophysiology, tissue architecture, inflammation, vascular supply, extracellular matrix, disease duration, stage, phenotype, and standard treatment.	A mechanism relevant to one disease model may be irrelevant or undesirable in a different clinical disease.
Dose dependence	Exposure, dose-response, threshold effects, saturation, nonlinear responses, and toxicity.	Higher dose is not necessarily stronger or better; mechanistic and clinical dose-response relationships require direct study.
Timing	Disease stage, injury phase, treatment window, recipient state, and sequence relative to other therapies.	A mechanism observed during acute injury cannot automatically be extrapolated to chronic established disease.
Patient heterogeneity	Age, comorbidities, medications, immune phenotype, genetics, baseline severity, prior treatment, and responder subgroups.	Average group biology may conceal clinically important differences between patients.
Plausibility versus proof	Target engagement, causal inference, model validity, mechanistic biomarkers, clinical endpoints, and independent confirmation.	A coherent mechanism can fail clinically; meaningful human benefit requires direct clinical evidence.

Key evidence conclusions

Broad product labels are inadequate mechanistic identifiers. Product identity and characterization must precede transfer of mechanistic claims between studies.

Mechanisms can vary across disease, dose, time, and patient. These variables can change target engagement, biodistribution, clearance, and recipient response.

Negative mechanistic findings are informative. Null results can identify an incorrect target, inadequate exposure, wrong timing, nonresponsive subgroup, or invalid model assumption.

Mechanistic evidence, clinical efficacy, and regulatory status are separate dimensions. None should be used as a substitute for the others.

Principal references

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

2. Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: cell biology to clinical progress. NPJ Regen Med. 2019;4:22.

3. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. Cytotherapy. 2006;8:315-317.

4. Théry C, Witwer KW, Aikawa E, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018). J Extracell Vesicles. 2018;7:1535750.

5. Relevant contemporary literature concerning product heterogeneity, disease context, dose-response, treatment timing, patient heterogeneity, mechanistic biomarkers, translational validity, and causal inference.