SCE 0702 Public Evidence Appendix

Immunomodulation

Literature review date: September 9, 2026

Controlling principle. Immunomodulation is a context-dependent network effect rather than uniform immune suppression; product-specific effects on innate and adaptive immunity must be demonstrated and kept separate from proof of clinical benefit.

Mechanistic evidence map

Domain	Mechanistic evidence	Interpretive boundary
Inflammatory signaling	Changes in cytokines, chemokines, lipid mediators, metabolites, enzymes, or EV-mediated signaling.	Direction and magnitude depend on product, priming, dose, timing, tissue environment, and recipient state.
T-cell regulation	Effects on activation, proliferation, trafficking, cytokines, and effector/regulatory T-cell balance.	In-vitro suppression or circulating subset changes do not establish clinically meaningful immunosuppression.
Macrophage phenotype	Measured changes in transcription, cytokines, efferocytosis, antigen presentation, or repair behavior.	M1/M2 shorthand oversimplifies in-vivo macrophage states; function should be measured directly.
Dendritic-cell modulation	Changes in maturation, antigen processing/presentation, migration, costimulation, or cytokine production.	A single marker change does not establish tolerogenic function or beneficial immune tolerance.
Natural-killer-cell effects	Changes in NK activation, proliferation, receptor expression, cytokines, or cytotoxicity.	MSC-NK interactions are bidirectional; NK suppression is not uniformly desirable because of antiviral/antitumor surveillance.
Complement interactions	Activation, regulation, deposition, opsonization, phagocytosis/clearance, and coagulation interactions.	Complement effects may influence both efficacy and safety and are product-, route-, and recipient-dependent.

Key evidence conclusions

Immunomodulation is not synonymous with generalized immune suppression. Both proinflammatory and anti-inflammatory effects can occur, depending on biological context.

Innate and adaptive immunity are integrated. T cells, macrophages, dendritic cells, NK cells, complement, B cells, neutrophils, endothelium, and coagulation pathways influence one another.

Potency assays support mechanism but do not replace clinical endpoints. A useful immune potency assay should be quantitative, reproducible, indication-relevant, and sensitive to meaningful product changes.

Safety must be measured. Excessive or poorly targeted immune modulation could impair antimicrobial or antitumor surveillance or alter inflammatory, complement, or coagulation responses.

Principal references

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

2. 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.

3. 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.

4. Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood. 2007;110:3499-3506.

5. Relevant contemporary consensus and review literature concerning MSC/EV interactions with T cells, macrophages, dendritic cells, NK cells, complement, and inflammatory signaling.