SCE 0705 Public Evidence Appendix

Fibrosis and remodeling

Literature review date: September 9, 2026

Controlling principle. Normal repair requires matrix formation and remodeling; antifibrotic benefit depends on restoring appropriate matrix quantity, organization, mechanics, and organ function rather than simply suppressing fibroblasts or collagen.

Mechanistic evidence map

Domain	What is evaluated	Interpretive boundary
Fibroblast activity	Proliferation, migration, inflammatory signaling, extracellular-matrix synthesis, and matrix degradation.	Reduced fibroblast activity is not automatically beneficial because normal repair requires adequate fibroblast function.
Myofibroblast differentiation	Contractile phenotype, alpha-smooth-muscle actin, matrix production, TGF-beta signaling, and mechanical cues.	A single marker does not establish beneficial or harmful remodeling; persistence, function, and tissue context matter.
Collagen deposition	Collagen quantity, type, organization, cross-linking, turnover, and tissue mechanics.	Less collagen is not necessarily better if tissue strength or organization is impaired.
Matrix metalloproteinases	MMP activity, TIMP balance, proteolysis, and extracellular-matrix turnover.	Too little matrix degradation can promote fibrosis; excessive degradation can damage tissue.
Scar remodeling	Changes in scar cellularity, collagen alignment, vascularity, stiffness, tensile strength, and function over time.	A smaller or thinner scar does not by itself establish regeneration or restored normal tissue function.
Organ-specific fibrosis	Lung, liver, kidney, heart, skin, musculoskeletal, and other tissue-specific fibrotic biology.	Evidence from one organ or disease model should not be transferred automatically to another.

Key evidence conclusions

Fibrosis is not simply excess collagen. Matrix organization, cross-linking, stiffness, cell state, inflammation, and organ architecture influence function.

Prevention and reversal are different claims. Limiting early scar formation is biologically different from removing mature, highly cross-linked fibrosis that has been present for years.

Normal repair must be preserved. Excessive suppression of fibroblasts, collagen formation, or matrix remodeling could impair wound healing and tissue strength.

Organ specificity matters. Antifibrotic findings should be demonstrated for the exact product, organ, disease, stage of fibrosis, dose, route, and clinically meaningful functional outcome.

Principal references

1. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nat Med. 2012;18:1028-1040.

2. Henderson NC, Rieder F, Wynn TA. Fibrosis: from mechanisms to medicines. Nature. 2020;587:555-566.

3. Hinz B. Formation and function of the myofibroblast during tissue repair. J Invest Dermatol. 2007;127:526-537.

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

5. Relevant contemporary literature concerning MSC/EV effects on fibroblasts, TGF-beta signaling, extracellular-matrix turnover, matrix metalloproteinases, scar remodeling, and organ-specific fibrosis.