Allogeneic vs. Autologous Cell-Based Therapy: What the Immunogenicity and Safety Literature Shows

Why "autologous is automatically safer" doesn't hold up in the comparative trial data — and why cell-free allogeneic products like Cellavé sit outside the primary rejection mechanism entirely

Prepared for RCX Network Partner Clinics — Hair Restoration & Regenerative Aesthetics

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Purpose

This reference is written for physicians, PAs, NPs, and estheticians who encounter the common assumption that autologous ("from your own body") regenerative products are inherently safer than allogeneic (donor-derived) ones. It summarizes the comparative safety literature on allogeneic vs. autologous MSC-based therapy, and addresses the distinct question of whether a cell-free allogeneic secretome product like Cellavé carries the same immunogenicity considerations as allogeneic whole-cell transplantation.

The Core Clinical Question

The intuitive assumption is that autologous material, being the patient's own tissue, avoids immune complications that donor-derived (allogeneic) material might trigger. The comparative clinical trial evidence does not straightforwardly support that assumption for whole-cell MSC therapy. Separately, and more relevant to a cell-free product, the primary mechanism behind allogeneic immune rejection — donor cell surface antigens (MHC/HLA molecules) being recognized as foreign — requires a living, intact donor cell to be present. A cell-free secretome product contains no such cells.

The Mechanism

MSCs were historically believed to be "immune-privileged" — invisible to the recipient's immune system regardless of donor source. More recent evidence has shown this is not fully accurate for allogeneic whole-cell transplantation: donor MSCs can express MHC molecules capable of triggering measurable anti-donor cellular and humoral immune responses in some settings. Whether this same mechanism applies to MSC-derived extracellular vesicles (EVs) and secretome — which carry no intact donor cell surface for the immune system to directly recognize — is a distinct and less-resolved question addressed directly in the evidence below.

The Published Evidence

1. Head-to-head randomized trial: allogeneic was not less safe than autologous

The POSEIDON trial (Hare et al., 2012, *JAMA*) directly randomized patients with ischemic cardiomyopathy to receive allogeneic or autologous bone-marrow MSCs by transendocardial injection. The allogeneic group had numerically fewer adverse events than the autologous group (6 AEs, 0.4 per patient vs. 17 AEs, 1.13 per patient), and no patient in either group experienced a reaction suggestive of acute immunogenic rejection (fever, urticaria, hemolysis, hypotension, liver dysfunction, or thrombocytopenia). The trial met its primary safety endpoint documenting allogeneic MSC safety.

2. Broader review: therapeutic differences between the two sources remain inconclusive

Li, Zhao, Cheng, and Wang's 2021 review in *Cell & Bioscience* concludes that therapeutic benefits of autologous vs. allogeneic MSCs remain inconclusive overall, and identifies donor and subpopulation heterogeneity — not source (self vs. donor) alone — as a key driver of uncertainty in safe and effective use, consistent with the donor-variability findings addressed in this series' companion Donor Age reference.

3. The key nuance: whole-cell rejection risk is documented, EV/secretome-specific risk is still being characterized

Lohan, Treacy, Griffin, Ritter, and Ryan's widely cited 2017 review in *Frontiers in Immunology* is the most direct treatment of this question. The authors document that allogeneic whole-cell MSCs are not fully immune-privileged and can elicit specific anti-donor cellular and humoral immune responses in some contexts. Critically, they separately note that whether MSC-derived EVs carry comparable immunogenic risk is an open question: EVs may contain MHC molecules, but at the time of that review it remained unclear whether MSC-derived EVs actually transfer such molecules to recipient cells or induce an allo-immune response — the authors frame this explicitly as an area requiring further study, not a settled finding of risk or safety.

> **Clinical translation for Cellavé:** The most well-documented allogeneic immune-rejection mechanism — donor cell surface antigens triggering recipient immune recognition — requires an intact, living donor cell to be present. Cellavé is cell-free by design, containing no living donor cells for this mechanism to act on. This is a mechanistic rationale for why cell-free allogeneic products sit outside the primary documented risk pathway, not a claim that Cellavé itself has been directly tested in a published immunogenicity trial — the EV/secretome-specific literature (Lohan et al., above) is honest that this remains a less mature body of evidence than the whole-cell safety data.

Key Takeaways for Practitioners

- "Autologous is automatically safer" is not supported by the strongest available head-to-head trial data — the POSEIDON RCT found allogeneic whole-cell MSC therapy at least as safe as autologous, with no immunogenic reactions in either arm
- Allogeneic whole-cell MSCs are not fully immune-privileged and can trigger documented anti-donor immune responses in some settings — this is real and should not be minimized when discussing live-cell allogeneic products
- The mechanism behind that whole-cell rejection risk requires an intact donor cell surface, which a cell-free secretome product does not contain — a mechanistic, not clinically proven, reason to expect lower immunogenic risk
- The EV/secretome-specific immunogenicity literature is honest that this remains an open, actively studied question rather than a fully resolved one

A Note on Scientific Framing

Nearly all of the comparative safety and immunogenicity literature above concerns live, whole-cell MSC transplantation delivered by injection or infusion — not cell-free secretome products like Cellavé. The absence of donor cells in Cellavé is a legitimate mechanistic reason to expect it sits outside the primary documented allogeneic rejection pathway, but this is an inference from mechanism, not a citation to a published immunogenicity trial of Cellavé itself. Practitioners should present this as "here is why cell-free allogeneic sourcing avoids the main risk mechanism seen in whole-cell studies," not as "Cellavé has been clinically proven hypoallergenic or non-immunogenic."

References

- Hare JM, Fishman JE, Gerstenblith G, DiFede Velazquez DL, Zambrano JP, Suncion VY, Tracy M, Ghersin E, Johnston PV, Brinker JA, et al. Comparison of Allogeneic vs Autologous Bone Marrow-Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy: The POSEIDON Randomized Trial. *JAMA*. 2012;308(22):2369-2379. doi:10.1001/jama.2012.25321.
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