The next chapter in regenerative medicine for osteoarthritis: From real-world evidence to regulatory shifts

openaccessgovernment.org/article/the-next-chapter-in-regenerative-medicine-for-osteoarthritis-from-real-world-evidence-to-regulatory-shifts/198137

Emily Warrender September 12, 2025

Osteoarthritis (OA) remains one of the leading causes of disability worldwide, yet the therapeutic landscape is evolving faster than ever

In a previous article, I outlined how stromal vascular fraction (SVF), exosomes, platelet-rich fibrin (PRF), and early findings in blood-derived stem cells were reshaping the field of regenerative medicine. Since then, two new clinical and translational studies have provided important real-world evidence, helping to move the discussion from theory toward practice.

Exosomes: Large-scale safety evidence

Exosomes, nanosized extracellular vesicles secreted by stem cells, have attracted increasing attention for their ability to modulate inflammation, stimulate repair, and enhance tissue homeostasis without the risks of uncontrolled differentiation. While early case series suggested encouraging clinical results, questions remained about long-term safety.

In our recent publication, Amniotic-Derived Exosomes in Clinical Practice: Safety and Outcomes in 608 Patients [(1)], we reported outcomes from one of the largest patient cohorts treated with exosomes to date. Patients received both intravenous and local delivery. Across 608 patients and over 1,000 treatments, no serious adverse events were recorded. Reported side effects were mild, self-limiting, and transient, typically injection-site soreness or mild flu-like symptoms lasting under 48 hours.

These findings provide strong reassurance for both clinicians and patients: when properly screened, amniotic-derived exosomes offer a safe therapeutic option. Importantly, exosomes may bypass immunological and regulatory challenges associated with cell therapies, since they exert effects through paracrine signaling rather than engraftment.

Small pluripotent stem cells: A novel frontier

In parallel with exosome research, attention has turned toward a new class of cells, Small Pluripotent Stem Cells (SPSCs), that may redefine autologous regenerative therapy. Unlike mesenchymal stem cells from fat or bone marrow, SPSCs are isolated directly from adult peripheral blood, making them far less invasive to obtain.

In our study, Isolation and Characterization of Small Pluripotent Stem Cells (SPSCs) from Human Peripheral Blood: A Novel Cold-Enrichment Protocol [(2)], we described a reproducible cold-storage enrichment method that significantly increased yield. Immunocytochemistry confirmed expression of pluripotency markers such as OCT4, SOX2, NANOG, and SSEA-4 – demonstrating their ability to differentiate into all three germ layers.

SPSCs combine the safety and accessibility of autologous cells with a pluripotent profile traditionally reserved for embryonic or induced stem cells. Because they can be harvested with a simple blood draw and require minimal manipulation, SPSCs may also fit within existing “minimally manipulated autologous cell” regulatory definitions, potentially easing clinical translation.

Regulatory realities: Diverging frameworks

Despite mounting evidence, regulatory frameworks continue to lag scientific advances. The European Union still requires that stem cell therapies for OA be autologous, a measure meant to reduce risk but one that may paradoxically limit standardized, safer allogeneic options.

By contrast, regulatory flexibility is emerging across other regions. In the United States, several states, including Florida, Nevada, and Utah, have enacted legislation allowing clinical use of regenerative therapies with donated stem cells under defined conditions. Japan employs an accelerated approval system that supports conditional use of promising regenerative products, balancing innovation with safety [(3)].

Most recently, Dubai and the broader UAE have begun establishing frameworks to accelerate access to advanced biologics.

These differences matter. Patients increasingly travel across borders for regenerative care, and clinicians must carefully navigate the interplay between science and legal compliance. A more harmonized global approach would foster innovation while safeguarding patient safety.

The road ahead: Integration and personalization

The emerging trend in OA therapy centers on integration, combining complementary modalities for a more robust effect. Exosomes can offer systemic anti-inflammatory and signaling benefits. PRF provides a scaffold for retention and growth factor release. SVF brings multipotent repair capacity. SPSCs promise same-day, autologous pluripotent therapy without complex processing.

Meanwhile, advanced biomaterials are maximizing delivery precision. Recent reviews highlight how injectable hydrogels with stimuli-responsive, injectable designs are disrupting OA treatment by ensuring localized, sustained release of drugs and biologic agents [(4)]. Such smart carriers could serve as ideal vehicles for combining exosomes, SPSCs, and PRF in a unified treatment.

Imagine a therapy where systemic exosome infusion resets inflammation, followed by local delivery of SPSCs embedded within a PRF/hydrogel scaffold, providing both systemic and localized regenerative impetus.

From possibility to practice

Regenerative medicine for osteoarthritis is advancing from possibility to practice. The large-scale safety data on exosomes and the discovery of SPSCs as a new pluripotent cell type from blood represent significant milestones. Regulatory divergence continues to pose both challenges and opportunities for translation.

If OA was once considered an irreversible, degenerative condition, it is now increasingly recognized as biologically modifiable. With continued collaboration among scientists, clinicians, and regulators and with integrated, personalized therapies atop smart biomaterials, the future may deliver safer, more effective, and more accessible joint regeneration.

References

1. Ogéus T. Amniotic-Derived Exosomes in Clinical Practice: Safety and Outcomes in 608 Patients. Journal of Orthopaedics and Sports Medicine. 2025.
2. Ogéus T. Isolation and Characterization of Small Pluripotent Stem Cells (SPSCs) from Human Peripheral Blood: A Novel Cold-Enrichment Protocol. Archives of Clinical and Biomedical Research. 2025.
3. Yoon J. Brief summary of the regulatory frameworks of regenerative medicine across the world. Frontiers in Pharmacology. 2025.
4. Chen J. Recent advances in injectable hydrogels for osteoarthritis treatment. Frontiers in Bioengineering and Biotechnology. 2025.

Primary Contributor

Torbjörn Ogéus
Stockholms Led- & Smärtspecialist