EDITORIAL

Secretome as an Alternative Therapy for Pain Intervention in Musculoskeletal Disorders

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Pain is one of the factors that may impair a person's quality of life, and persistent pain is difficult to manage. Recently, pain management that focuses solely on symptom relief has been shown to potentially lead to chronic pain. Nowadays, clinicians face several potential approaches that may help prevent or break the cycle of pain. One of these potential approaches is stem cell therapy. Although the evidence base supporting this approach is still limited, preliminary studies—such as in vitro, in vivo, and translational studies—show positive and encouraging effects on tissue regeneration in cases of degenerative tissue damage.

The secretome is one modality of stem cell therapy that offers several advantages, including a lower risk of allergic reactions and the ability to stimulate the tissue-healing process. Secretome-based, cell-free therapy has moved from a peripheral topic in regenerative medicine to a mainstream translational strategy for musculoskeletal disorders, including osteoarthritis, ligament and tendon injury, sarcopenia, and peripheral nerve entrapment syndromes such as carpal tunnel syndrome. This reflects a broader shift toward a present-and-future translational framing of stem cell secretome across tissue repair applications (Da Silva et al., 2025). This shift deserves attention because the field is at an inflection point: preclinical data are accumulating faster than standardized clinical protocols, and manuscripts submitted for review vary widely in how they define, characterize, and dose "secretome." These notes are intended to guide editorial assessment of submissions in this area and to outline where future-oriented, design-driven research is most needed.

Current Evidence Landscape

Osteoarthritis (joint disorders). A 2025 rat-model study induced osteoarthritis and compared saline, whole adipose-derived stem cell (ASC) transplantation, and ASC-secretome treatment. Whole-cell transplantation was associated with more severe cartilage damage and abnormal bone remodeling, while the secretome arm produced only mild-to-moderate degeneration, comparable to controls (Palombella et al., 2025). This finding is editorially significant: it challenges the assumption that cell-based and cell-free (secretome) approaches are interchangeable, and it strengthens the rationale for secretome as a safer, first-line acellular alternative.

Ligament and tendon healing. A 2026 systematic review of preclinical ligament-healing studies concluded that secretome application improves graft revascularization, collagen deposition, and biomechanical strength of the healing graft (Febyan et al., 2026). The recency of this review, published in early 2026, reflects how quickly the evidence base for soft-tissue applications is expanding beyond joint and bone.

Sarcopenia and muscle disorders in elderly populations. A widely cited review identifies mitochondrial dysfunction and age-related inflammation as central drivers of muscle loss, and notes that exercise remains the only intervention with consistently demonstrated clinical benefit, while nutraceutical and pharmacological approaches have produced mixed results (Lo et al., 2020). Because exercise-based interventions have limited reach in immobile or frail patients, the same review proposes stem-cell secretome as a scalable adjunct therapy for this harder-to-treat subgroup (Lo et al., 2020). Supporting animal data show that intramuscular secretome injections in aged mice increased lean mass,

reduced fat mass, and improved physical function (grip strength, activity levels), with effects attributed to bioactive signaling factors and extracellular-vesicle-carried microRNAs in the product (Fennel et al., 2024).

Nerve entrapment (carpal tunnel syndrome). This indication remains comparatively underrepresented in the literature relative to joint and muscle applications, and editorial submissions here should be evaluated with the awareness that the evidence base is still largely preclinical or early translational, relying on mechanistic extrapolation from broader peripheral nerve and CNS secretome literature (e.g., Pinho et al., 2020) rather than CTS-specific trials.

Manufacturing and delivery. A recurring theme across reviews is that secretome-based acellular therapy carries a lower immunogenic profile than cell transplantation, since the product contains fewer of the surface proteins that typically trigger immune responses (Zohora et al., 2023). The same review points to a manufacturing advantage: secretome can be harvested continuously from culture, similar to fed-batch fermentation, rather than requiring repeated resuscitation of new cell batches as whole-cell therapy does (Zohora et al., 2023)—a cost and scalability advantage editors should expect well-designed manuscripts to address, particularly for readerships in health systems where affordability determines real-world adoption.

Future Challenges for Secretome Therapy

There is still limited evidence-based data on secretome therapy. Several studies have shown positive effects in reducing pain in cases of knee osteoarthritis; however, an optimal dosage has not yet been established.

Cell vs. cell-free distinction. Given emerging evidence that whole-cell MSC transplantation may produce worse histopathological outcomes than secretome alone in some osteoarthritis models, further research is needed to evaluate the adverse events of secretome therapy.

Population specificity. Focusing on elderly populations and sarcopenia, age-related comorbidity, frailty status, and baseline inflammatory profile materially affect secretome responsiveness and should be reported as covariates, not incidental demographics.

Outcome standardization. Musculoskeletal secretome studies vary in outcome measures (histology, biomechanical strength, patient-reported pain/function, imaging). Future submissions should be encouraged to focus at least on functional and adverse-event reporting to support future meta-analyses.

Safety reporting. Narrative reviews acknowledge that secretome-based therapy, while generally favorable, may still produce negative side effects that limit its use in some diseases. Manuscripts should report adverse events transparently rather than defaulting to a “no complications” framing.

Future Design Research: Priorities and Study Architecture

Standardized product characterization protocols. The field needs a shared minimum reporting standard specific to musculoskeletal secretome products—covering donor cell source, passage number, priming/preconditioning method, storage, and potency assay. Standardizing characterization for each secretome product should be a higher-level priority given the inconsistent characteristics across products.

Head-to-head, indication-specific randomized trials. Most current evidence is preclinical or single-arm early-phase. Future design research should prioritize randomized, double-blind, placebo (or active-comparator) controlled trials structured by indication:

- Osteoarthritis: secretome vs. whole-cell MSC vs. standard-of-care injection (e.g., corticosteroid or hyaluronic acid), with cartilage imaging (MRI T2 mapping) and WOMAC/KOOS as co-primary endpoints.
- Sarcopenia: secretome as an adjunct to resistance exercise vs. exercise alone, specifically in frail or partially immobile elderly cohorts—a population underrepresented in current exercise-only trials, which have so far favored ambulatory hybrid-exercise designs such as combined tai chi and strength training (Guo et al., 2024)—with dual-energy X-ray absorptiometry (DEXA)-based lean mass, grip strength, and gait speed as endpoints.
- Ligament/tendon injury: secretome-improved graft healing vs. standard graft, with biomechanical and revascularization imaging endpoints drawn from the ligament-healing systematic review framework.
- CTS and nerve entrapment: studies remain very limited for CTS given the potential for histological changes. The key challenges are dose-finding and delivery route (local injection vs. perineural) studies, since comparing these two delivery approaches would help identify which yields the more effective result.

Dose and delivery optimization. Future protocols should systematically vary dose, delivery route (intra-articular, intramuscular, perineural, systemic), and formulation (whole conditioned medium vs. isolated EV fraction vs. lyophilized product) within the same indication, which almost no current study does.

Mechanistic biomarker-linked designs. Trials should incorporate mechanistic biomarkers (inflammatory cytokine panels, myokine/osteokine profiles, EV-cargo microRNA signatures) alongside clinical endpoints, enabling future studies to link responder/non-responder status to baseline biological profile—particularly relevant for elderly populations with heterogeneous inflammatory aging ("inflammaging") status.

Health-system and cost-effectiveness research. Given the manufacturing-cost advantage of secretome over cell-based therapy, future research should include formal cost-effectiveness modeling, particularly for health systems (such as Indonesia's) where scalable, lower-cost regenerative options would materially affect access for elderly and musculoskeletal disorder populations outside major urban academic centers.

Longitudinal and combination-therapy designs. Nearly all current data are short-term (weeks to months). Future design research should include longer follow-up (≥12 months) and combination arms (secretome plus exercise, plus nutraceutical support) to reflect realistic elderly-care pathways rather than isolated pharmacological framing.

Conclusion

Given the Indonesian healthcare context this editorial content is intended for, framing should emphasize: (1) secretome as a cell-free, potentially lower-cost and lower-risk regenerative option relevant to health systems with limited access to cell-therapy infrastructure, and (2) the current evidence gap specifically for elderly, multimorbid, and CTS/nerve-entrapment populations, positioning this as a call for locally relevant translational research rather than only summarizing international preclinical findings.

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