

Adipose Derived Extracellular Vesicles in Regenerative Medicine from Biological Potential to GMP Manufacturing

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ABSTRACT

Extracellular vesicles released by adipose-derived stem cells attracted interest as mediators of tissue repair and candidates for cell-free regenerative therapies. Experimental studies indicate effects on fibroblast activity, extracellular matrix remodeling and cartilage protection. Translation nevertheless requires a defined product whose biological activity remains reproducible during manufacturing and storage. The narrative mini-review examines selected preclinical evidence and the principal steps connecting laboratory preparations with manufacturing under Good Manufacturing Practice. Particular attention is given to source-cell control, scalable separation, complementary analytical methods and indication-specific potency assays. Particle concentration alone cannot establish identity, purity or therapeutic value, while an acellular composition does not establish clinical safety. A development strategy linking product attributes to biological function and clinically meaningful outcomes provides a rational basis for evaluating these candidates. Progress should therefore be measured by reproducible activity and credible clinical evidence as well as by production yield.

Keywords: Extracellular Vesicles; Adipose-Derived Stromal Cells; Regenerative Medicine; Good Manufacturing Practice; Potency; Clinical Translation

Introduction

Adipose-derived stem cells (ASCs) provide a source of extracellular vesicles (EVs) to investigate paracrine mechanisms of tissue repair. EVs are lipid bilayer-delimited particles released by cells and participate in intercellular signaling. The term exosome denotes a specific endosomal origin and should not be inferred solely from particle size or commonly detected surface markers. Accordingly, EV or small EV is preferable when biogenesis has not been established [1]. The distinction matters when comparing published preparations and defining a reproducible therapeutic candidate. The central translational question evaluates whether an ASC-derived EV preparation deliver consistent biological activity at a clinically feasible dose. My focused narrative review considers representative wound and cartilage studies alongside EV characterization and manufacturing guidance, not a systematic assessment of clinical efficacy.

Regenerative Potential and Limits of the Evidence

In a preclinical wound-healing study, Zhang and colleagues reported that ASC-derived preparations described as exosomes enhanced fibroblast proliferation and migration and supported wound repair, with evidence implicating PI3K/Akt signaling [2]. Data findings support further investigation of EV-mediated stromal responses whereas not establishing an occurrence of equivalent benefits in chronic human wounds, where vascular impairment, infection and persistent inflammation influence treatment response. Woo and colleagues examined human ASC-derived small EVs in osteoarthritis models, increasing the type II collagen synthesis while reducing several catabolic mediators in stimulated human osteoarthritic chondrocytes. Intra-articular administration also attenuated cartilage degeneration in rat and mouse models [3]. All observed data connect matrix preservation with modulation of the joint inflammatory environment but

does not either determine an effective human dose or demonstrate durable clinical cartilage regeneration. Together, all findings support a biological rationale rather than a class-wide efficacy claim. Preparations obtained using different cells, culture conditions and separation procedures should not be assumed equivalent. Comparisons require both analytical and functional evidence, particularly when moving from exploratory experiments to a proposed clinical product [1,4].

Manufacturing a Reproducible Product

Good Manufacturing Practice (GMP) development begins upstream of EV collection. Donor eligibility, tissue traceability, source-cell identity, passage history and microbiological control establish the foundation of the process. Culture conditions and harvest timing are documented and controlled since producing cells directly contribute to product variability. Medium components also require attention: externally introduced particles and proteins complicate both characterization and interpretation of biological activity [1,4]. Scaling production requires a downstream process that balances recovery, impurity removal and retention of function. Visan and colleagues compared tangential flow filtration followed by size exclusion chromatography with ultracentrifugation followed by the same chromatographic step. All results supported advantages of the filtration workflow in yield and scalability under investigated conditions [5]. This evidence informs process development but does not make one separation method universally optimal or demonstrate GMP suitability for every ASC-derived product. A practical development program will evaluate the complete manufacturing sequence, including concentration, buffer exchange, formulation and filling. Transfer to a contract development and manufacturing organization requires defined operating procedures, analytical methods and acceptance criteria, together with comparability evidence when equipment or scale changes. Such a framework links manufacturing decisions to product quality instead of treating increased particle recovery as a sufficient development endpoint [4,5].

Characterization and Biological Potency

Complementary methods are needed to assess the workflow for an EV preparation. Particle sizing and counting are usually combined with morphological and molecular characterization and assessment of relevant co-isolated material. Nanoparticle tracking analysis alone cannot distinguish all EVs from non-vesicular particles. Likewise, detection of CD9, CD63 or CD81 does not demonstrate exosomal biogenesis or exclude contaminants [1]. Research characterization and routine batch release serve related but distinct purposes while release methods must be suitable for consistent use. Potency testing addresses biological function. An assay reflects an activity relevant to the intended therapeutic mechanism, with a measurable response across an appropriate dose range. A fibroblast migration assay support wound-product development, while modulation of inflammatory or catabolic responses reflects a crucial information for a cartilage-di-

rected candidate. Neither assay becomes a validated predictor of clinical benefit merely because a statistically significant effect is observed [2,3,6]. The 2026 ISEV task-force perspective emphasizes alignment between product characteristics, laboratory activity and the intended clinical effect [7]. For development teams, this supports early selection of a reference preparation, suitable controls and reproducible assay conditions. Potency methods should be able to detect meaningful process-related changes and deterioration during storage. Particle number contribute to dose description but cannot substitute for a functional measure as well as preparations with similar counts differ in activity [6,7].

Clinical Translation and Development Priorities

An acellular preparation avoids administering viable stromal cells but does not establish safety or regulatory simplicity. Nonclinical evaluation will address the proposed route, exposure, biodistribution and relevant toxicological risks. Clinical development requires a justified starting dose, explicit escalation and stopping rules, and follow-up appropriate to the intended indication [8]. Product quality and the involved material in supporting studies must remain sufficiently comparable for those studies to inform clinical decisions. Stability would be demonstrated in the intended formulation and container, including relevant handling conditions. Refrigeration, freezing or lyophilization cannot be assumed to preserve biological activity without supporting data. Functional testing alongside physical measurements is particularly valuable when evaluating storage-related changes [4,7]. For ASC-derived EVs, a focused indication, a controlled manufacturing process and a mechanism-informed potency strategy provide a coherent basis for prospective trials with clinically meaningful outcomes.

Conclusion

ASC-derived EVs warrant further investigation as regenerative therapeutic candidates, supported by experimental findings in wound repair and cartilage protection. Their translation depends on defining the preparation, preserving its activity during scale-up and demonstrating benefit in appropriately designed clinical studies. Coordinated biological and manufacturing development can help establish which preparations merit clinical evaluation and which quality attributes are essential for reproducible performance.

Declarations

Ethics Approval and Data Availability

This narrative review reports no new experiments involving human participants or animals and generates no new datasets.

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