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Research Article

Understanding Adipose-Derived Stromal Vascular Fraction (tSVF): Cellular Biology, Perivascular Origin Of Mesenchymal Stem Cells, Exosome Paracrinology, And Biocellular Applications In Regenerative Medicine — An Updated Comprehensive Review.

Robert W. Alexander, MD, DMD, FICS[1], Peter A. Everts, PhD, FRSM[2]

[1]*Clinical Faculty (ret.), University of Washington School of Medicine, Department of Surgery; Director, Regenevita Health Center for Regenerative Medicine, Hamilton, Montana, USA.*

[2]*The University of Queensland, Medical School (GBCS) Brisbane, QLD 4006, Australia;Max Planck University Center (UniMAX), Medical School & OrthoRegen, Indaiatuba 13343-060, SP, Brazil.*

Abstract

Background: This paper represents a fully updated early paper outlining the then current understanding of adipose cell biology (Alexander, 2012, JOP) and the potential values and uses of adipose derived stromal vascular fraction (tSVF). Over the past two decades, working with autologous adipose tissue has evolved from structural fat grafting into something with far broader clinical significance. The adipose tissue complex (ATC) is not simply a cell depot. It is a vascularized, paracrine-active bioscaffold carrying a heterogeneous population of nucleated cells including mesenchymal stem/stromal cells (MSCs), hematopoietic stem cells (HSCs), pericytes (PCs), endothelial cells (ECs), T regulatory (Treg) cells, M2 macrophages, mast cells, and the extracellular matrix (ECM) that organizes them in their native three-dimensional relationships. That three-dimensional architecture matters is the context in which these cells communicate, signal, and respond to injury. Adipose yields 10–100 times more MSCs per unit volume than bone marrow aspirate, accessible without the morbidity of marrow harvest and without requiring ex vivo expansion to achieve therapeutically meaningful cell numbers.[1,2,3]

Content: This review examines the AD-SVF in its identified biological complexity, including cellular composition, perivascular MSC origins, the marker transition from pericyte and endothelial phenotype to canonical MSC phenotype during cSVF isolation and expansion, exosome and microvesicle biology, tolerogenic mechanisms, and the clinical integration of tissue SVF (tSVF) and cellular SVF (cSVF) with high-density platelet-rich plasma (HD-PRP) and nanofat as Biocellular orthobiologic platforms. Literature is reviewed through May 2026.[4,5,6]

Results and Discussion: Pericytes (CD146+, NG2+, PDGFR-β+) and endothelial cells (CD31+, CD34+, VE-cadherin+) undergo a well-characterized phenotypic transition during cSVF isolation and in vitro expansion, progressively losing native perivascular markers and acquiring the canonical MSC surface profile (CD73+, CD90+, CD105+, CD44+). Single-cell RNA sequencing and lineage tracing confirm this perivascular-to-MSC transition. Autologous exosomes and microvesicles strongly secreted by AD-MSCs mediate key paracrine regenerative effects via intercellular communication promoting angiogenesis, immunomodulation, anti-fibrosis, chondrogenesis, etc., through defined miRNA and protein cargo. Biocellular combinations of tSVF with HD-PRP demonstrate clinically meaningful and durable superiority over PRP alone in knee osteoarthritis, tendinopathies, and inflammatory conditions.[4,7,8,9]

Conclusion: The perivascular niche — not the bone marrow — is where clinically meaningful MSC biology lives in vascularized tissues and its bioactive matrix. The evidence for this, assembled from immunophenotyping, scRNA-seq, lineage tracing is compelling and consistent. Understanding this biology is not academic. It directly informs how we harvest, process, and deploy these therapies. Standardization, rigorous clinical trial design, and regulatory alignment remain the central challenges.[5,6]

Keywords: Biocellular Regenerative Medicine; adipose-derived stromal vascular fraction (TSVF); mesenchymal stem/stromal cells (MSCs); pericytes; endothelial cells; perivascular niche; tissue SVF (tSVF); cellular SVF (cSVF); high-density platelet-rich plasma (HD-PRP); nanofat; exosomes; microvesicles; T regulatory cells (Treg); osteoarthritis; immunomodulation; extracellular matrix; single-cell RNA sequencing (scRNA Sequencing); lineage tracing; Orthobiologics; Biocellular therapy; intercellular communication.

***Corresponding Author:** **Dr. Robert W.Alexander,MD,DMD,FICS,** Clinical Faculty (ret.), University of Washington School of Medicine, Department of Surgery; Director, Regenevita Health Center for Regenerative Medicine, Hamilton, Montana, USA. **Email:** rgvclinic@gmail.com.

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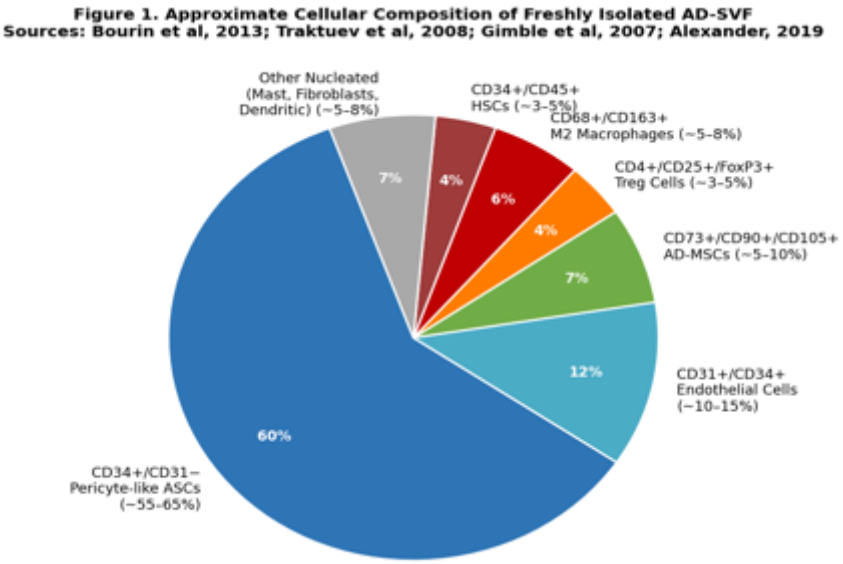
INTRODUCTION

Adipose tissue has been dramatically underestimated for most of the history of medicine. For decades it was viewed as an inert repository of stored energy — metabolically passive, structurally useful for volumization grafting, and not much else. We now know that picture is wrong in almost every particular. The adipose tissue complex (ATC) is one of the largest endocrine organs in the human body, secreting a remarkable array of cytokines, chemokines, and adipokines such as leptin, adiponectin, resistin, and others, that participate actively in inflammation, immunity, metabolism, and even reproduction.[11]

Mature adipocytes are the volumetrically dominant component of adipose, but they are terminally differentiated — they cannot divide. The renewal and maintenance of the adipocyte population depends on a population of progenitor cells, commonly termed pre-adipocytes, that are in direct cell-to-cell contact with each mature adipocyte (typically only 2–4 per cell). Recent work confirms that these contacts are necessary to facilitate paracrine signaling essential for adipocyte turnover and replenishment at a rate of at least 5–10% per year, meaning complete cellular renewal over 8–10 years of a human lifetime.[11,12]

The investigations of Zuk and colleagues in 2001 and 2002 changed the field fundamentally and permanently.2,3 They were among the first to demonstrate, systematically, that adipose tissue harbors a large population of multipotent undifferentiated nucleated cells. These cells capable of differentiating along germ layer components, including osteogenic, chondrogenic, adipogenic, etc. lineages. Critically, they established that adipose yields proportionally 10–100 times more MSCs per unit volume than bone marrow aspirate.[13] That single finding fundamentally reoriented Regenerative Medicine toward adipose as the preferred practical cell source. For those of us who had been performing bone marrow harvests on patients having to deal with a slightly more invasive procedure which can be moderately painful and carries some added morbidity risks. These are well documented facts that it delivers of much higher number of desired cells group and longer lasting non-designated cell activities. Those facts made the practical significance and was not subtle. We had a better source, more accessible, and in proportionally greater quantity, without reducing the age-related decline in marrow, and an active set of potential MSC capabilities.

Figure 1. MSC frequency per unit volume: adipose tSVF vs bone marrow aspirate. Adipose yields 10–100× more MSCs. Sources: Zuk et al 2001,2002; Mohamed-Ahmed et al 2018; Alexander 2019.— Condensed version in red above.]



For more than twenty years, aesthetic and reconstructive surgeons had safely used autologous fat grafting (AFG) for structural augmentation. The recognition that high-density platelet-rich plasma (HD-PRP) with its highly concentrated payload of growth factors (PDGF, TGF-β, VEGF, EGF, bFGF, etc.), has significantly enhanced graft survival and regenerative signaling. This prompted a fundamental shift from simple fat grafting to what is now called Biocellular Therapy: the intentional combination of tSVF with HD-PRP to create a synergistic regenerative milieu neither element can provide alone.[4,5,6] Updated meta-analyses confirm that SVF-enriched grafts demonstrate meaningfully superior retention rates.[7,9]

Confusion in the literature around terminology has been a persistent obstacle to comparative analysis. What one group calls "adipose stem cells," another calls "stromal cells" or "mesenchymal stem cells." This review uses standardized nomenclature throughout: adipose-derived stromal vascular fraction (tSVF); adipose-derived mesenchymal stem/stromal cells (AD-MSCs);
adipose tissue complex (ATC); tissue SVF (tSVF, non-enzymatically processed, intact tissue); and cellular SVF (cSVF, enzymatically isolated nucleated cell population). Both primary methods of AD-SVF access (en bloc excision or microcannula lipoaspiration) yield slightly different total nuclear counts (TNC), but the nucleated cell composition profile is essentially preserved between approaches.[14,15]
Regulatory considerations have shaped the field significantly. The FDA's classification of enzymatically isolated cSVF as a drug product, suggesting the need for IND or BLA approval when it exceeds minimal manipulation criteria has driven a decisive practical shift toward mechanical isolation methods ('nanofat', micronized fat) that preserve the tissue's native matrix, comply with current regulatory guidelines, and allow point-of-care delivery. That said, enzymatically isolated cSVF has other very important uses in developing the ability to explore and document a dose/response understanding that mechanically processed material cannot readily provide. This is rapidly becoming particularly value for Orthobiologic applications where outcome data remain largely anecdotal without it.[7,8,9,16]

CELLULAR COMPONENTS OF THE ADIPOSE-DERIVED STROMAL VASCULAR FRACTION (AD-SVF)

What makes tSVF remarkable is not any single cell type, it is the ensemble. The freshly isolated AD-SVF contains MSCs, HSCs, pericyte-endothelial cells, T-regulatory cells (Treg), Monocytes a (M1, M2 macrophages), mast cells, a complex microvascular bed (fibroblasts, macrophages, WBCs, dendritic cells, intra-adventitial smooth muscle-like cells. In addition, and the bioactive scaffolding extracellular matrix (ECM) which enhances the stem/stromal cell attachments that is important to provide attachment points which permit early intercellular communication and that organizes all of these elements in their native three-dimensional architecture. On top of that, microcannula lipoaspirated or en bloc resected ATC delivers mature adipocytes along with their attached progenitors and stem/stromal elements still in place, and which is capable of secretory function and critical intercellular communication abilities within the transplant microenvironment. [14,15,] This is the "smorgasbord" that non-manipulated tissue transfer provides. The individual delivery site dictates what it needs; the tissue answers through complex paracrine signaling. Advances in single-cell RNA sequencing has sharpened our picture of this heterogeneity considerably. It emphasizes immune-modulatory M2 macrophages, vascular progenitors, and pericytes as particularly important functional contributors, not merely structural or supporting elements.[18,19,20] Cell subpopulation characterization has long centered on CD34+ cells, which constitute 50–80% of the nucleated population in freshly isolated AD-SVF. The critical nuance, established by Traktuev and colleagues in 2008 and fundamental to understanding MSC origins, is that the majority of CD34+ cells in freshly isolated cSVF are CD31−/CD144− and separable from a distinct CD34+/CD31+/CD144+ endothelial population by differential plastic adherence.17 That non-endothelial CD34+ population occupies a pericytic position and is likely a contributor of the actual MSC populations.
Traktuev et al demonstrated that greater than 90% of CD34+/CD31−/CD144− cells co-express CD10, CD13, CD90, pericytic markers (chondroitin sulfate proteoglycan, CD140a, CD140b), and smooth muscle markers (alpha-actin, caldesmon, calponin).17 Co-culture with human endothelial cells revealed a bidirectional paracrine cross-talk via angiogenic factors (VEGF, HGF, bFGF), inflammatory mediators (IL-6, IL-8, MCP-1, MCP-2), and mobilization factors (M-CSF, GM-CSF). That pericytic population, often dominant in fresh cSVF is the same population that sheds its pericyte markers and acquires canonical MSC markers upon early In Vitro expansion. Recent data confirm that cSVF composition varies with donor age, harvest site, and BMI, with implications for therapeutic potency.[19]

Figure 2. Approximate cellular composition of freshly isolated adipose-derived stromal vascular fraction (AD-SVF). CD34+/CD31− pericyte-like adipose stromal cells constitute the dominant nucleated population (~55–65%), a proportion repeatedly confirmed across flow cytometry and scRNA-seq characterization studies. Percentages are representative, not absolute, as composition varies with donor age, harvest site, BMI, and processing method. Sources: Bourin et al (IFATS/ISCT Joint Statement), 2013[13]; Traktuev et al, 2008[14]; Gimble et al, 2007[15]; Riis et al, 2025[17]

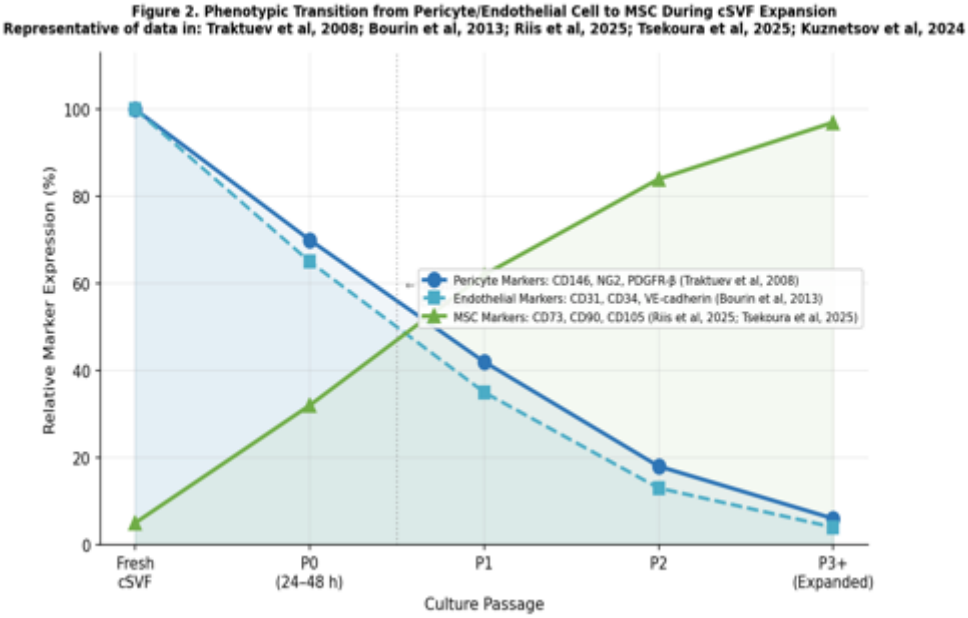


Table 1. Cell Surface Marker Profiles and Functions: Key AD-SVF Populations.

Cell Type	Native/Fresh Markers (cTSVF)	After In Vitro Expansion	Frequency in Fresh cTSVF	Primary Function
CD34+/CD31− Pericyte-like ASCs	CD146+, NG2+, PDGFR-β+, SLC6A12+, α-SMA+, CD31−, CD45−	CD73+, CD90+, CD105+, CD44+; loss of pericyte markers	~55–65% of nucleated cells	Vascular stabilization; MSC progenitor
CD31+/CD34+ Endothelial Cells	CD31+, CD34+, VE-cadherin+, vWF+, CD144+	EndMT: lose EC markers; gain α-SMA, vimentin, CD90, CD105	~10–15%	Angiogenesis; EndMT → MSC progenitor
AD-MSCs (ISCT criteria)	CD73+, CD90+, CD105+, CD44+; CD45−, CD34−, CD14−	Stable; homogeneous at P3+	~5–10%	Trilineage differentiation; immunomodulation
HSCs	CD34+, CD45+, Lin−	Variable; may lose CD34	~3–5%	Angiogenesis; immunosurveillance
Treg Cells	CD4+/CD25+/FoxP3+	Maintained in early expansion	~3–5%	Immune tolerance; Treg promotion
M2 Macrophages	CD68+, CD163+, CD206+	Paracrine polarization maintained	~5–8%	Anti-inflammatory; tissue repair
Other (mast, fibroblasts, dendritic, smooth muscle)	Mixed surface profiles	Variable	~5–8%	Structural; paracrine support

Table 1. Key cell surface markers for principal AD-SVF nucleated cell populations in freshly isolated state and following In Vitro expansion. Frequency estimates represent published flow cytometry characterization data from multiple studies. "After expansion" column reflects passage P3+ phenotype. Sources: Bourin et al (IFATS/ISCT), 2013[13]; Traktuev et al, 2008[14]; Gimble et al, 2007[15]; Feuerer et al, 2009[23]; Lumeng et al, 2007[24]; Bunnell et al, 2008[35]

Adipose-Derived Mesenchymal Stem/Stromal Cells (AD-MSCs)

AD-MSCs now represent the most active therapeutically studied nucleated cell population within ATC, and for good reason. The 10–100-fold advantage in MSC yield over bone marrow aspirate[13] means clinically meaningful cell numbers without Ex Vivo expansion, a regulatory and practical advantage that cannot be overstated. Per International Society for Cell Therapy (ISCT) criteria, MSCs are defined as plastic-adherent; positive for CD73, CD90, and CD105; negative for CD45, CD34, CD14, and HLA-DR; and capable of multilineage differentiation.[14]

MSCs have been identified in mesodermal layer components, such as muscle, bone marrow, adipose, heart, Wharton's jelly, dental pulp, and some peripheral blood components.21 Their anti-inflammatory properties are mediated through secretion of IL-10, TGF-β superfamily members, leukemia inhibitory factor (LIF), soluble HLA-G, and IL-1 receptor antagonist.22,23 The immunoregulatory enzymes cyclooxygenase and indoleamine 2,3-dioxygenase are involved in tolerogenic processes, and critically to amplified via MSCs indirectly inhibiting autoimmunity through induction of T regulatory (Treg) cells.[24,25] Increasingly, however, investigators recognize that MSC-derived exosomes may mediate many of these effects in a cell-free manner, which has profound implications for future regulatory and clinical applications and design.[26,27,28] Clinical applications have extended to graft-versus-host disease,[29] systemic lupus erythematosus,[30] multiple sclerosis,[31] and end-stage liver disease.[32] More recent data support MSC-based therapies in chronic pain and musculoskeletal conditions at scale.[33]

Hematopoietic Stem Cells (HSCs) Within Adipose SVF

Defined as CD34+/CD45+/Lin− cells of hematopoietic origin, HSCs have long been studied in the context of blood reconstitution, but their role within adipose tSVF is primarily paracrine in nature. Early assumptions about trans-differentiation have given way to a cleaner understanding: HSC-derived trophic and repair signals, such as VEGF, HGF, IGF-1, FGF-2 are contribute importantly to angiogenesis, particularly in models of critical limb ischemia.[34,35]

HSCs also display direct immunosuppressive and tolerance-inducing capability through TGF-β and the TGF-β superfamily — important effectors for Treg-mediated suppression of reactive T cells, neutrophils, macrophages, and dendritic cells.[36] Massberg and colleagues proposed an "immunosurveillance" role for circulating CD34+ cells: differentiation into dendritic cells via toll-like receptor (TLR) activation which are important as a finding that added important nuance to how we understand the immunological activity of the tSVF.[37]

T Regulatory Cells (Treg) and Alternatively Activated (M2) Macrophages

It is not commonly appreciated that adipose tissue is among the richest sources of T regulatory cells in the body. Feuerer and colleagues demonstrated that lean fat is enriched for a unique FoxP3+ Treg population that directly affects metabolic parameters, including CD4+/CD25+/FoxP3+ cells that suppress reactive T cell populations, and which can be further expanded in tissue culture.[38] Leptin and TNF-alpha inhibit Treg proliferation and activity In Vivo,[39] which may be relevant to patient selection, specifically, that obese patients with elevated leptin may have a blunted tolerogenic response from their own tSVF.[38]

The M2 macrophage content of tSVF, identified as CD68+/CD163+/CD206+ and which provides immediate anti-inflammatory polarization at the site of delivery. Recent work confirms that tSVF-derived paracrine factors directly drive M2 polarization, enhancing and sustaining the tolerogenic environment over time.40,41 This does not appear to be a passive characteristic; it is an active immunological function that helps explain why tSVF therapies demonstrate efficacy in inflammatory conditions that true platelet-rich plasma (HD-PRP) or BMAC alone cannot address.

Adipocytes and Their Attached Progenitor Cells

The conventional view that transplanted adipocytes may provide structural restoration has been fundamentally revised. Transplanted adipocytes, having undergone anoxia during transfer, are largely lost within the first few days of engraftment.[42] But their dying matters. As they undergo anoxic degradation, they secrete important signals that activate the progenitor cells still attached to their surface. tpre-which become metabolically active and begin generating replacement immature adipocytes, faithfully mimicking the normal homeostatic turnover that Spalding et al demonstrated.12 In practical terms, the adipocytes serve as an intercellular paracrine alarm system, triggering the very renewal mechanism that sustains adipose tissue In Vivo.

Perivascular Architecture and Extracellular Matrix (ECM)

ECM is not a passive scaffold. Within AD-SVF, the native three-dimensional ECM composed of fibronectin, laminin, collagen types I, III, and IV, and a family of proteoglycans provides structural support, regulates cellular adhesion, and actively participates in paracrine signaling through matrix-bound growth factors and cytokines. The perivascular location of AD-MSCs and pericytes places them immediately adjacent to vascular channels, enabling rapid mobilization in response to injury signals.[17,43]

This is why the concept of delivering an intact perivascular microenvironment, the "niche". as non-manipulated tissue may outperform any isolated cell fraction, as it acts differently

when developed. When you enzymatically digest tSVF to isolate cSVF, you get an defined nucleated cell population during the process. When you deliver tSVF mechanically, as 'nanofat' or micronized fat you deliver the entire system: cells, matrix, paracrine factors, and their spatial relationships, all intact. Being ready to "send and receive" and contribute to he body needs and uses. We remain increasingly convinced that this is the clinically superior strategy in many Biocellular/ Orthobiologic applications.,[5,6]

PERIVASCULAR ORIGIN OF MESENCHYMAL STEM CELLS: THE EVIDENCE FOR PERICYTES AND ENDOTHELIAL CELLS

The question of where MSCs actually come from in vivo has been debated for years, and the debate has not been entirely academic as it has direct implications for how we began to understand therapeutic mechanisms. Why MSCs appear to be present in virtually every vascularized tissue, and why adipose is so consistently rich in them. The answer, increasingly supported by immunophenotyping, single-cell transcriptomics, lineage tracing, and functional data, is the perivascular niche: pericytes and endothelial cells.[1,10,14,17]

Marker Changes During cSVF Isolation and In Vitro Expansion: The Transition Evidence

The evidence that pericytes are MSC precursors is written in their surface markers, and in how those markers change during the transition from freshly isolated cSVF to expanded, culture-adapted MSCs. This is not subtle. It is a systematic, reproducible, multi-study finding.[17,18,19,20]

In freshly isolated cSVF, the dominant nucleated population expresses CD146, NG2, PDGFR-β, and SLC6A12. These are the markers that define pericyte identity. Endothelial cells carry CD31, CD34, and VE-cadherin. As culture proceeds across passages, these markers decline progressively and disappear in early passages. In their place: CD73, CD90, CD105, and CD44, the canonical ISCT criteria for MSC identity. The expanded cells are, by every functional and phenotypic measure, MSCs. They arrived at that phenotype from pericytic and endothelial precursors.[14,17,18]

Figure 3. Phenotypic transition from pericyte/endothelial cell to MSC during cSVF in vitro expansion. Pericyte markers (CD146, NG2, PDGFR-β) and endothelial markers (CD31, CD34, VE-cadherin) decline progressively from fresh cSVF through passage P3+, while canonical MSC markers (CD73, CD90, CD105) are concurrently upregulated. Data representative of published flow cytometry and recently via scRNA-seq characterization findings across multiple studies. Sources: Traktuev et al, 2008[14]; Bourin et al (IFATS/ISCT), 2013[13]; Riis et al, 2025[17]; Tsekoura et al, 2025[18]; Kuznetsov et al, 2024[16]

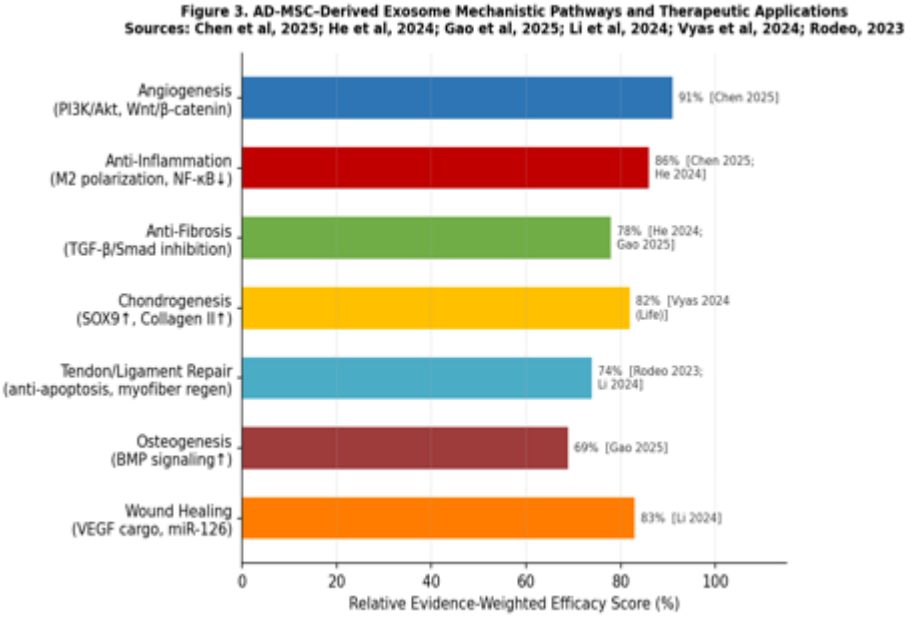


Table 2. Surface Marker Dynamics During cSVF Isolation and In Vitro Expansion.

Marker	Fresh cTSVF	Early Expansion (P0–P1)	Intermediate (P2)	Fully Expanded MSC (P2-P3+)
CD146 (pericyte marker)	High	Decreasing	Low	Low/Variable
NG2 (pericyte)	High	Decreasing	Low	Absent
PDGFR-β (pericyte)	High	Decreasing	Low	Absent
SLC6A12 (novel pericyte)	High	Decreasing	Low	Absent
CD31 (endothelial)	High (ECs)	Decreasing	Low	Absent
CD34 (endothelial/pericytic)	High	Decreasing	Low	Absent
VE-cadherin (endothelial)	High (ECs)	Decreasing	Low	Absent
CD73 (MSC canonical)	Low/Variable	Increasing	High	High (>95%)
CD90 (MSC canonical)	Low/Variable	Increasing	High	High (>95%)
CD105 (MSC canonical)	Low/Intermediate	Increasing	High	High (>95%)
CD44 (MSC canonical)	Low/Variable	Increasing	High	High (>95%)

Table 2. Progressive phenotypic transition from pericyte/endothelial phenotype to canonical MSC phenotype across culture passages. Loss of CD146, NG2, PDGFR-β, SLC6A12 (pericyte markers) and CD31, CD34, VE-cadherin (endothelial markers) proceeds concurrently with acquisition of CD73, CD90, CD105, CD44 (MSC markers). This reproducible marker shift, confirmed by flow cytometry and single-cell transcriptomics across multiple studies, constitutes direct evidence of pericyte-to-MSC and endothelial-to-MSC lineage transitions. Sources: Traktuev et al, 2008[14]; Bourin et al (IFATS/ISCT), 2013[13]; Riis et al, 2025[17]; Tsekoura et al, 2025[18]; Kuznetsov et al, iScience, 2024[16]

Lineage Tracing and Immunophenotyping Evidence

The foundational work of Traktuev et al (2008) established that pericytes isolated from human adipose (CD146+CD34−CD45−), when cultured, become indistinguishable from conventional MSCs in morphology, marker expression, and differentiation potential.17 The co-localization of pericytes and MSC markers in perivascular locations has since been confirmed across multiple tissue types by immunohistochemistry and spatial transcriptomics.[18]

Endothelial cells contribute through a different but equally well-characterized mechanism: endothelial-to-mesenchymal transition (EndMT). This interaction and association with pericytes have vascular permeability and actual cellular implications and changes. Under appropriate stimuli, including TGF-β, inflammatory cytokines, and the altered microenvironment of damaged tissue endothelial cells lose their defining markers (CD31, VE-cadherin) and acquire mesenchymal markers (α-SMA, vimentin, CD44, CD90, CD105). The resulting cells demonstrate multipotency.[34,44]

In 2025, recently published confirmatory evidence using advanced single-cell multiomics and longitudinal clinical outcome data, demonstrating that pericyte- and endothelial-derived MSCs are not merely a laboratory curiosity but the central therapeutic cells in Biocellular/Orthobiologic and post-viral recovery applications. The marker transitions have been observed in vitro correlate directly with clinical regenerative outcomeWork in progress by Maumas, Contreras-Naranjo, et al., is extending perivascular cellular characterization with additional molecular precision.[45]

Single-Cell RNA Sequencing Confirmation

Single-cell RNA sequencing has provided some resolution that immunophenotyping alone cannot offer. Recent scRNA-seq studies have identified novel pericyte markers, SLC6A12 and SLC19A1, among others, that refine pericyte identity and distinguish pericyte subpopulations with different functional and differentiation potentials.19,20 These studies confirm transcriptomic upregulation of MSC gene networks within pericyte-derived populations upon In Vitro expansion demonstrate the molecular signature of the transition, not merely the surface phenotype.[18]

Spatial transcriptomics adds topographic confirmation: MSC progenitor populations consistently localize to perivascular zones in multiple tissue types in situ. Their association with distal vessels and capillary beds, rather than central sinusoids as in marrow, is consistent with the pericytic location that defines their biology.[18,19]

Table 3. Summary of Evidence Supporting Perivascular Origin of Human MSCs.

Evidence Type	Principal Findings	Key References
Immunohistochemistry / Flow Cytometry	Pericytes (CD146+CD34−CD45−) occupy perivascular positions; >90% of CD34+/ CD31− cells co-express pericyte markers; transitional CD146+/CD90+ populations observed during early culture	Traktuev et al, Circ Res, 2008; Bourin et al (IFATS/ISCT), Cytotherapy, 2013; Gimble et al, Circ Res, 2007
In Vitro Expansion (Passage Studies)	Progressive loss of CD146, NG2, PDGFR-β, CD31, CD34; gain of CD73, CD90, CD105; expanded cells fulfill ISCT MSC criteria by P1-2+	Alexander, J Stem Cell Res Ther, 2019; Kuznetsov et al, iScience, 2024; Bunnell et al, Methods, 2008
Single-Cell RNA Sequencing (scRNA-seq)	Pericyte-to-MSC gene expression transition confirmed on expansion; novel markers SLC6A12, SLC19A1 identified; tissue-specific pericyte heterogeneity mapped	Riis et al, Plast Reconstr Surg, 2025; Tsekoura et al, Front Endocrinol, 2025; Kuznetsov et al, iScience, 2024
Lineage Tracing / Endothelial-to-Mesenchymal Transition (EndMT)	Endothelial cells undergo EndMT under TGF-β stimulation, losing CD31/VE-cadherin and gaining α-SMA, vimentin, CD90, CD105; expanded EC-derived cells demonstrate trilineage differentiation	Planat-Benard et al, Circulation, 2004; Gennai et al, Cytotherapy, 2024
Functional Trilineage Differentiation Assays	Pericyte- and EC-derived cells post-expansion demonstrate adipogenic, osteogenic, and chondrogenic differentiation — the functional gold standard for MSC identity	Garza et al, Am J Sports Med, 2020; Hildreth et al, Front Pharmacol, 2025; Mohamed-Ahmed et al, J Biol Res, 2018
Spatial Transcriptomics	MSC progenitor populations consistently localize to perivascular zones in multiple tissue types in situ; association with distal capillaries and venules confirmed	Kuznetsov et al, iScience, 2024; Jeyaraman et al, World J Stem Cells, 2025
Controlled Clinical Outcomes (OA, tendon)	Biocellular tSVF + HD-PRP demonstrates superior, durable pain reduction and functional improvement vs PRP alone at 12–24 months, consistent with pericyte-driven regenerative mechanism	Everts, Alexander, Lana et al, Int J Mol Sci, 2025; Xiang et al, J Orthop Surg Res, 2023; Garza et al, Am J Sports Med, 2020

Table 3. Integrated evidence base supporting pericyte and endothelial cell origin of human mesenchymal stem/stromal cells, organized by evidence type with principal findings and specific references matched to content. Alexander and Everts 2026, in progress, work may represent a recent current update a comprehensive review of current molecular and clinical evidence. Sources cited per row as indicated in the table.

EXOSOMES AND MICROVESICLE BIOLOGY: THE PARACRINE CURRENCY OF AD-SVF

The paracrine signaling that makes AD-SVF therapeutically powerful does not require direct cell-to-cell contact. A large and, we believe, underappreciated fraction of it is carried by extracellular vesicles (EVs): exosomes (30–150 nm, originating from multivesicular bodies via ESCRT-dependent or -independent endosomal sorting pathways) and microvesicles (MVs, 100–1,000 nm, budding directly from the plasma membrane via actomyosin-driven remodeling).[26,27,28]

These vesicles carry a sophisticated bioactive cargo: miRNAs (miR-126 for angiogenesis, miR-146a for inflammation suppression, miR-145 for smooth muscle differentiation), lncRNAs, bioactive lipids, and proteins (VEGF, BDNF, IL-10, TSG101, CD9, CD63, CD81 tetraspanins). This cargo enables precise intercellular communication without direct cellular contact and circumvents many of the safety and regulatory challenges inherent to some cell-based therapies. From a practical standpoint, it raises the possibility of effective cell-free regenerative treatments.[26,27,46]

Figure 4. AD-MSC–derived exosome mechanistic pathways and relative evidence-weighted therapeutic efficacy in Orthobiologic applications. Each bar represents a distinct paracrine mechanism with the key signaling pathway indicated; reference tags identify the primary source publications for that mechanism. Scores are not quantitative assay values but reflect the relative depth of published preclinical and clinical mechanistic evidence for each pathway. Sources: Chen et al, Front Cell Dev Biol, 2025[36]; He et al, Signal Transduct Target Ther, 2024[37]; Gao et al, Front Pharmacol, 2025[38]; Li et al, Saudi Pharm J, 2024[39]; Vyas et al, Life, 2024[40]; Rodeo, Am J Sports Med, 2023[41]

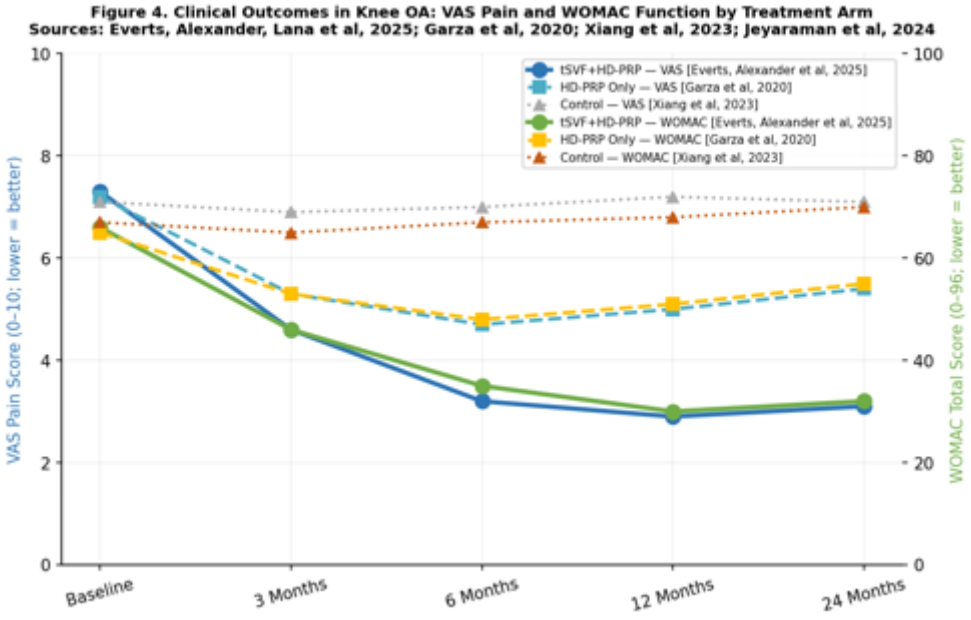


Table 4. Principal Bioactive Cargo of AD-MSC–Derived Exosomes and Therapeutic Applications

Cargo Type	Key Examples	Biologic Mechanism	Therapeutic Application [Reference]
miRNA	miR-126, miR-146a, miR-21, miR-145	Angiogenesis (miR-126); inflammation suppression (miR-146a); smooth muscle differentiation (miR-145)	Ischemia, OA, fibrosis [Chen et al, 2025; He et al, 2024]
lncRNA	MALAT1, H19, HOTAIR	Cell proliferation, anti-apoptosis, epigenetic regulation	Cartilage, tendon, neural repair [Gao et al, 2025]
Proteins / Growth Factors	VEGF, BDNF, IL-10, HGF, TSG101, Alix	Neuroprotection, anti-inflammation, angiogenesis, EV identity markers	Neural, systemic inflammation, wound healing [Li et al, 2024]
Tetraspanins	CD9, CD63, CD81	EV surface identification markers; cell targeting and fusion	Diagnostic marker; targeted delivery [He et al, 2024]
Lipids	Sphingomyelin, phosphatidylserine, cholesterol	Membrane integrity; receptor signaling; immunomodulation	Drug delivery vehicles; immunomodulation [Chen et al, 2025]
Exosome mirror cargo (hypoxia-conditioned)	VEGF↑↑, HIF-1α, miR-126↑	Enhanced angiogenesis under hypoxic preconditioning	Critical limb ischemia; OA cartilage [Vyas et al, 2024; Rodeo, Am J Sports Med, 2023]

Table 4. Principal bioactive cargo carried by AD-MSC–derived exosomes and microvesicles, with associated biologic mechanisms and primary therapeutic applications. Reference column identifies the specific published source for each cargo-mechanism-application link. Sources: Chen et al, 2025[36]; He et al, 2024[37]; Gao et al, 2025[38]; Li et al, 2024[39]; Vyas et al, 2024[40]; Rodeo, 2023[41]

Some of the defined mechanisms of AD-MSC–derived exosome activity are increasingly well characterized:
(1) angiogenesis promotion via PI3K/Akt and Wnt/β-catenin pathway activation;
(2) inflammatory modulation through macrophage polarization toward M2 phenotype and NF-κB suppression;
(3) anti-fibrotic activity via TGF-β/Smad pathway inhibition; and

(4) activation of endogenous progenitors through paracrine amplification loops.26,27,28 In Orthobiologic applications specifically, AD-MSC–derived exosomes enhance chondrogenesis (upregulating SOX9 and collagen II expression) in OA cartilage, stimulate osteogenesis in bone defects, and support tendon healing by reducing apoptosis and promoting myofiber regeneration.[47,48,49]

Preconditioned exosomes particularly those harvested from hypoxically preconditioned MSCs, which carry enhanced VEGF cargo and may represent a promising direction for ischemic wound applications. As of early 2026, over 292 EV-related clinical trials were registered on ClinicalTrials.gov, with MSC-derived EVs representing the largest single category. The FDA's 2024 approval of Aruna Bio's IND application for AB126 (neural cell-derived EVs) marked an important regulatory milestone.27,28 Standardized characterization per MISEV2023 latest guidelines includes particle size distribution, cell of origin markers, surface tetraspanins, and potency assays. It remains a critical priority for the field.[26]

Tolerogenesis In tSVF: More Than "Regeneration"

One of the findings about AD-SVF that continues to surprise clinicians encountering it for the first time is the depth of its immune regulatory activity. This is not a side effect it is a core biological function. The tolerogenic capabilities of tSVF were highlighted in a seminal 2010 paper by Ichim and colleagues,[50] who demonstrated that elements within the complex AD-SVF directly promote T regulatory (Treg) cell expansion and thereby suppress a portion of macrophage-mediated inflammatory activity. Their specific insights that autologous re-administration of mononucleated cells naturally present within TSVF creates a systemic tolerogenic environment and suggests some proven durable impacts and has been extended considerably since.

The Treg population within adipose tissue is abundant. Feuerer et al established that lean subdermal fat is particularly enriched for this unique CD4+/CD25+/FoxP3+ population.38 Their demonstration that metabolic parameters are affected by this Treg population underscored a key concept: adipose tissue is not immunologically neutral. When we harvest tSVF and return it autologously, we are not simply delivering regenerative cells; we are delivering a tolerogenic system, with active capacity to dampen harmful immune responses and promote tissue acceptance.[39,51]

Ichim et al specifically highlighted rheumatoid arthritis as a target autoimmune condition where AD-SVF may simultaneously reduce inflammation and induce tissue repair.50 Clinical trials since then have explored tolerogenic applications in post-infarct remodeling, ischemic heart disease,52 type I diabetes, and liver failure.32 More recently, Biocellular tSVF combined with HD-PRP has demonstrated synergistic immune modulation in long COVID sequelae and chronic wounds.44,53 The cytokines implicated in the immunosuppressive axis (IL-10, TGF-β, prostaglandin E2) are consistent across these applications, and updated studies confirm that tSVF-derived paracrine factors actively seem to encourage and help sustain M2 macrophage polarization over time.[40,41]

The tolerogenic role of AD-SVF may be as clinically significant as its direct reparative contribution wherein chronically inflamed joints and soft tissue injuries, it may be the more immediately important of the two. A therapy that simultaneously reduces the inflammatory burden undermining repair, while providing the cellular substrate for that repair, is categorically different from any pure growth factor injection. That distinction deserves more clinical attention than it has received.

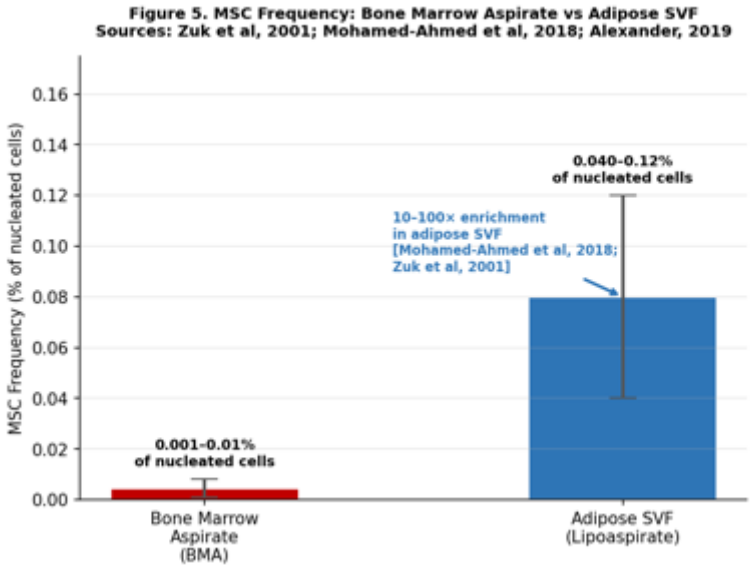
BIOCELLULAR THERAPIES: THE CLINICAL INTEGRATION OF tTSVF WITH HD-PRP

The integration of tSVF with HD-PRP is, in our view, the most clinically powerful development in autologous regenerative medicine in the past decade. The concept is straightforward: tSVF contributes the cellular population — pericytes, MSC progenitors, Treg cells, M2 macrophages, ECM — while HD-PRP delivers a concentrated payload of growth factors and signaling proteins (PDGF, TGF-β, VEGF, EGF, bFGF) activated from platelet alpha-granules. Neither element alone provides what the combination does.4 This synthesis what Everts, Alexander, Lana et al

formalized in 2025 as the "regenerative marriage" between HD-PRP and adipose tissue creates a synergistic biological milieu at the treatment site.[4]

Two mechanical processing strategies make this practical at the point of care without enzymatic manipulation. Note, small aggregate fragments retain the ECM, and that both the partially emulsified and fully emulsified ('Nanofat') produced by mechanically emulsifying microcannula lipoaspirated tSVF through progressively smaller transfers (sheer forces) and offset 600/400u mesh filters allows intradermal and fine-needle delivery of the entire tSVF cellular and matrix population while preserving regulatory compliance.[5,6] Micronized fat (MF), processed through controlled sheer mechanical fragmentation, retains the native ECM scaffold for structural support while maintaining biological viability.[8,54] Both methods deliver the intact perivascular microenvironment. The site determines what it recruits; the tissue provides the biological response. That is the fundamental logic of Biocellular delivery.

Figure 5. Representative clinical outcomes in knee osteoarthritis treated with Biocellular tSVF + HD-PRP vs HD-PRP alone vs control at 3, 6, 12, and 24 months. VAS (Visual Analogue Scale, pain, 0–10; lower is better) and WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index, 0–96; lower is better) scores are shown on dual axes. Data are representative of published RCT and meta-analysis findings; individual trial values will vary. The Biocellular combination demonstrates superior and more durable improvement on both measures. Sources: Everts, Alexander, Lana et al, Int J Mol Sci, 2025[4]; Garza et al, Am J Sports Med, 2020[44]; Xiang et al, J Orthop Surg Res, 2023[43]; Jeyaraman et al, World J Stem Cells, 2024[45]



Clinical trials and meta-analyses from 2020 through 2026 consistently report superior outcomes for tSVF + HD-PRP combinations compared to tSVF or PRP alone. The findings include measurable tissue regeneration by MRI, meaningfully reduced pain scores across VAS, KOOS, and WOMAC instruments, and improved functional outcome metrics sustained at 12–24 months of follow-up.4,55,56,57 The evidence base has expanded into tSVF-hydrogel composites for potential fibrocartilage repair,58 microfragmented adipose tissue (MFAT) for chronic tendinopathies,54 and translational canine OA models.59 Tendon healing studies confirm that tSVF-derived cells improve repair at the supraspinatus tendon in rat models,49 while Hildreth and colleagues have explored engineered tSVF constructs for structured tissue regeneration.60

The practical challenge that limits generalizability of published data is variability, lack of documentation clarity in isolation and widely varying processing protocols. Adipose harvest volume, washing protocols, centrifugation parameters, and final cell concentrations vary substantially across published studies. Standardization is not a bureaucratic priority; it is a scientific necessity.7,8,9 Without it, cross-study comparisons remain difficult, and published outcomes, however promising, remain partially anecdotal. This is where the field must invest time, funds and efforts.

SAFETY PROFILE OF AUTOLOGOUS AD-tTSVF

A comprehensive systematic review of autologous tSVF safety in humans, published in Stem Cell Research & Therapy in 2026, synthesized data across cardiovascular, pulmonary, hepatic, renal, musculoskeletal, cutaneous, neurological, and inflammatory applications.[7] The findings are rare and consistent with our own clinical experience: tSVF therapy is technically feasible and well tolerated. Adverse events are predominantly mild and limited to procedure-related sequalae such as transient pain, localized swelling, mild local inflammation. As of the publication date, serious complications including embolism, infection, fibrosis, or tumor formation had not been reported to our knowledge in autologous clinical settings.[7]

The autologous nature of tSVF eliminates immune rejection and disease transmission risks inherent to allogeneic products. That said, appropriate patient selection still matters. There is emerging evidence that in severely damaged or chronically inflamed tissue microenvironments, delivered cells may adopt pro-fibrotic rather than regenerative phenotypes. Delivery site preparation reducing inflammatory burden, optimizing vascular and perfusion restoration is not a minor procedural detail; it is likely a determinant of outcome.[7,8]

REGULATORY CONSIDERATIONS

In the United States, FDA's 21 CFR Part 1271 framework is unambiguous: autologous cSVF isolated via enzymatic digestion (e.g., collagenase) exceeds "minimal manipulation" criteria and is classified as a drug product, requiring Clinical Trial registered IRB approval and/or an IND or BLA for clinical use outside such approved trials.16 Court rulings have confirmed FDA oversight authority over unapproved tSVF clinics. It is important to realize that most of these loss of approvals are not based on the protocols utilized but rather to unproveable claims and advertisements. This classification is the primary driver behind the field's move toward mechanical isolation nanofat and micronized fat and which preserves regulatory compliance while retaining meaningful biological activity. That said, we want to be direct about where this creates a real clinical problem. Without the ability to study enzymatically isolated cSVF which provides a more defined nucleated cell population with generally quantifiable concentration, is critical in establishing a dose/response relationship for Orthobiologic applications is gradually being corrected via standardization detail of protocols and accurate data creation. Many published outcomes in the mechanical tSVF space remain purely anecdotal precisely because you cannot know or show what dose was accurately delivered., there precluding ability to make consistent, reproducible outcomes from treatment. IRB-approved cSVF studies, despite their regulatory complexity, serve a critical function in generating the evidence base the field needs.[7,8,9]

The European Medicines Agency has adopted a somewhat more permissive framework, ruling that minimally manipulated tSVF may fall outside the Advanced Therapy Medicinal Products (ATMP) classification under certain conditions. This divergence complicates cross-jurisdictional trial design and international access in ways the field has not yet resolved.[7,9]

FUTURE DIRECTIONS

The trajectory of AD-SVF research in 2025–2026 is defined by several converging developments, each of which has real clinical implications.

Single-cell and spatial analysis. scRNA-seq and spatial transcriptomics are refining the SVF cellular map with unprecedented resolution, identifying novel subpopulations, functional states, and cell-cell communication networks and pathways that inform rational therapeutic design.18,19,20 The identification of SLC6A12, SLC19A1, and other novel pericyte markers is directly relevant to how we characterize and quality-control SVF preparations.

Autologous exosome engineering. Preconditioned, cargo-loaded, and surface-engineered MSC-derived EVs are progressing through preclinical pipelines for targeted musculoskeletal, neurological, and cardiovascular applications.26,27,28 Scalable GMP manufacturing platforms and regulatory frameworks for EV-based products are in active development. The FDA's 2024 IND approval for Aruna Bio's neural-derived EV product signals that the regulatory pathway is gradually opening.[27,28]

Biomarker development. Predictive biomarkers in cSVF subpopulation ratios, exosome cargo miRNA profiles, recipient microenvironment parameters will likely enable a more targeted and personalized therapy optimization, thereby enhancing outcome prediction. This IS the transition from empirical clinical practice to precision and important Regenerative Medicine outcomes of the future.[8,9]

Large-scale randomized trials. The field urgently needs multicenter, randomized, and documented controlled trials with standardized isolation protocols, harmonized outcome metrics, and adequate follow-up metrics and periods. This is the central unmet need in the evidence base. Without it, even consistently positive results remain underutilized because they cannot be replicated with confidence.[7,8,9,61]

Novel delivery platforms. tSVF-hydrogel composites, 3D-printed scaffold loading, and exosome-encapsulated nanoparticle systems offer spatiotemporal control over regenerative signal delivery.58,60 The emerging canine OA translational literature is also providing mechanistic insight that will inform human trial design.[59]

DISCUSSION

Every practical delivery decision in this field whether mechanical versus enzymatic processing, tSVF versus cSVF, delivery site preparation, timing of combination with blood derivatives is either grounded in the biology or it is guesswork. After more than two decades working directly with this tissue, we have come to understand that the biology is not a preliminary step before the clinical application. It is the clinical application.

The single most important conceptual shift of the past decade, in our view, is the recognition that the perivascular niche interactions, not any isolated cell population represents THE fundamental unit reparative and regenerative activity from the use of combined adipose tissue with the important contribution potential of synergism with blood derivatives in the healing processes. This is why non-manipulated, mechanically processed tSVF may outperform enzymatically isolated cSVF in many applications: you preserve the spatial relationships, the matrix interactions, the paracrine communication loops. You deliver the niche, not a suspension of cells extracted from it.[5,6,17]

The exponential growth in tSVF-related publications, clinical trials, and commercial interest reflects genuine scientific

validity. From the bone marrow-centric paradigm of early cell therapy to the current adipose-centric Biocellular framework, the evolution has been evidence-driven. The integration of exosome biology as potential cell-free adjuncts or substitutes represents the next frontier and not a replacement for cellular therapy, but an addition to its toolkit.[27],,

Adipose tissue is the body's largest endocrine organ is actively secretory, perivascularly organized, immunologically engaged, and accessible without the morbidity of bone marrow harvest. Those properties are not incidental. They are exactly why adipose-derived tSVF belongs at the center of autologous regenerative medicine.4 These factors represent the current evidence frontier — and the beginning of what promises to be a much longer scientific conversation.

CONCLUSION

The biology of adipose-derived SVF is compelling precisely because it is not reductive. There is no single magic cell, no one critical growth factor, no isolated mechanism that explains why these therapies work. The answer is systemic: a richly vascularized, paracrine-active tissue carrying a population of progenitor cells — predominantly pericytes and endothelial cells — in their native three-dimensional matrix, with intrinsic regenerative, angiogenic, and tolerogenic capacities that activate in response to injury signals.[1,17]

The perivascular origin of MSCs is no longer a hypothesis. It is a body of evidence assembled from immunophenotyping, single-cell transcriptomics, lineage tracing, spatial transcriptomics, functional differentiation assays, and clinical outcome data. Its implications are practical: the way we harvest, process, and deliver SVF-based therapies should be designed to preserve and leverage that perivascular biology — not to disrupt it.[4,5]

The continued integration of cellular SVF capabilities, tissue SVF, autologous exosome-based cell-free approaches, and Blood Derivatives in concert as Biocellular combinations appear to be guided by the biology of the perivascular niche and grounded in rigorous clinical evidence will define the next decade of autologous Regenerative Medicine as defined at this time. Understanding this biology is not academic. It directly determines how we harvest, process, and deploy these therapies — and how well they work for the patients.

Author Contributions

RWA: Concept and design, primary literature review, manuscript drafting, critical revision of all sections, final approval. Takes primary and sole responsibility for content and opinions expressed herein.

PAE: Literature review (platelet biology, orthobiologic applications), critical revision of HD-PRP and clinical outcomes sections.

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Ethics:

This is a review article. No primary patient data or institutional ethical approval were required.

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