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Regenerative Medicine in Hemophilic Arthropathy

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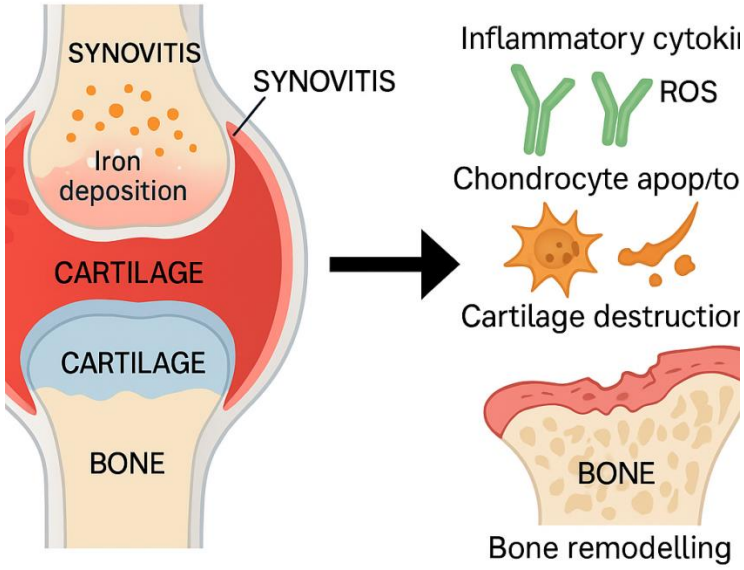
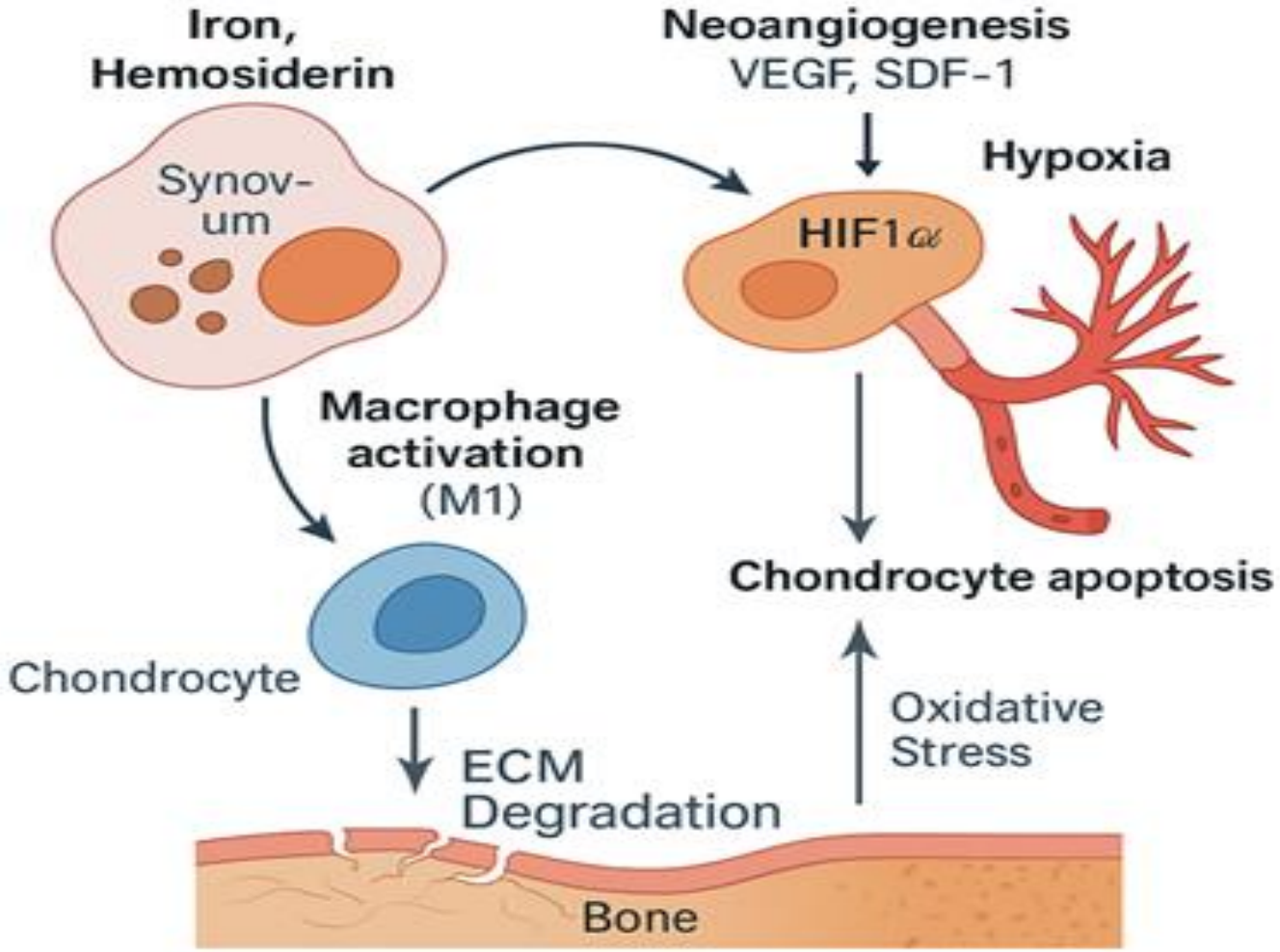
Pathophysiology of Joint Damage

- Most commonly affects ankles, knees, and elbows
- Hemarthrosis → iron deposition → synovial hypertrophy → inflammatory cytokines → chondrocyte apoptosis → ECM degradation → cartilage loss → bone remodeling → reduced mobility → pain



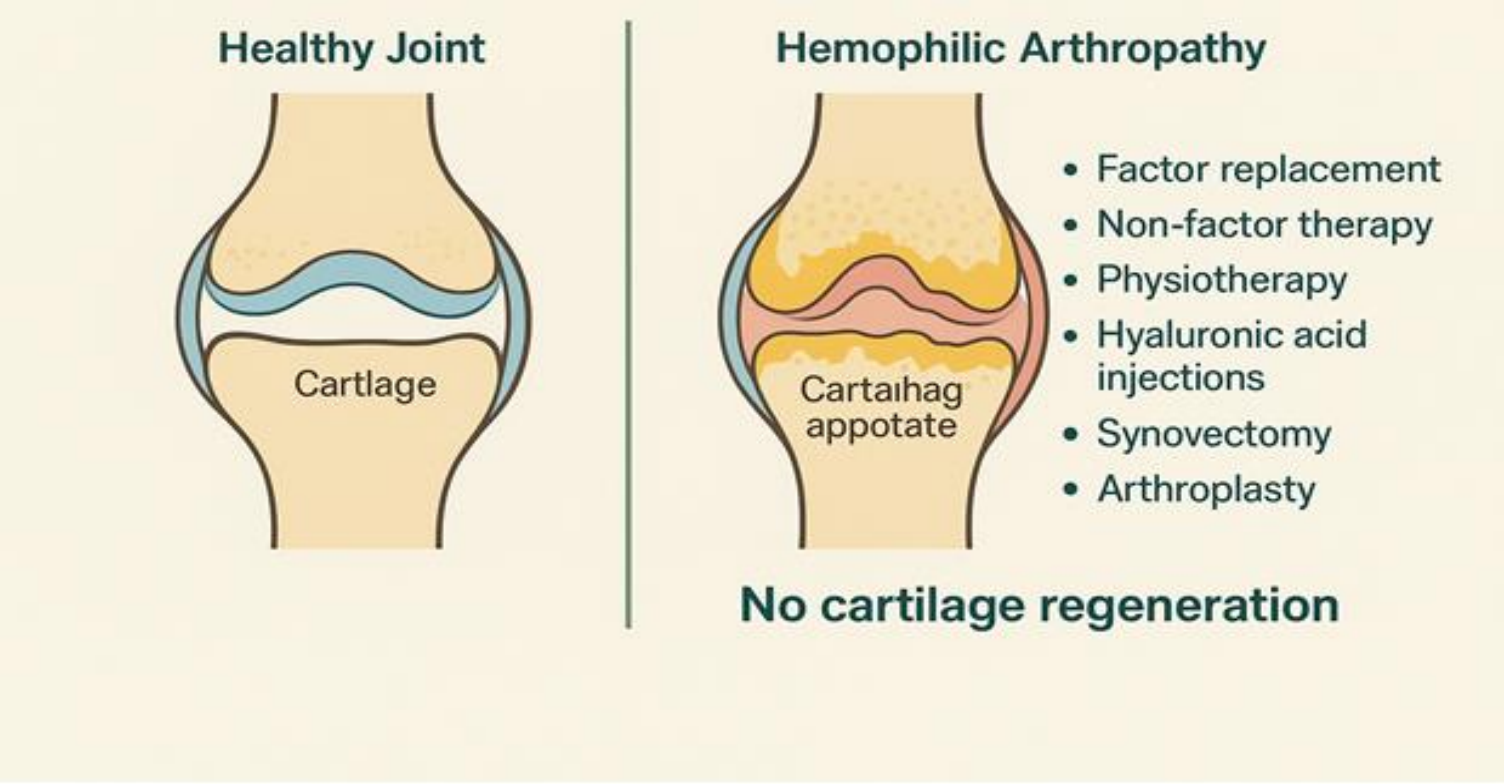
Osteoarthritis and Cartilage 32 (2024) 634–642

Cellular & Molecular Mechanisms



Current Standard Treatments & Limitations

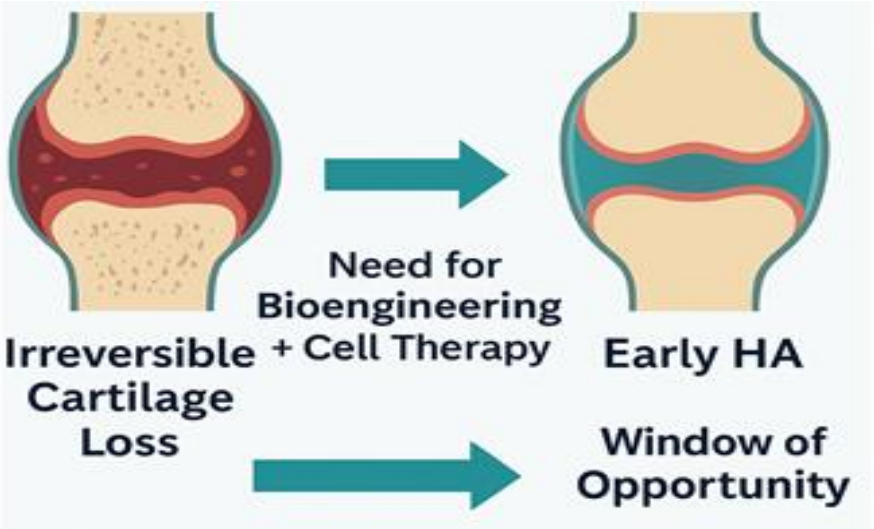
- Current treatment **focuses on slowing progression**; no reversal of cartilage loss



Rationale for Regenerative Therapies

Cell based therapy (PRP ،MSCs, SVF) :

- Target inflammation
- Tissue repair mechanisms
- Potential to slow or reverse early joint pathology



J Thromb Haemost. 2021;19:2112–2121

Regenerative therapies work best **after joint bleed frequency is minimized** using:

- Factor prophylaxis
- *Non-factor therapies* (e.g., emicizumab)

Once a **"low-bleeding environment**" is achieved:

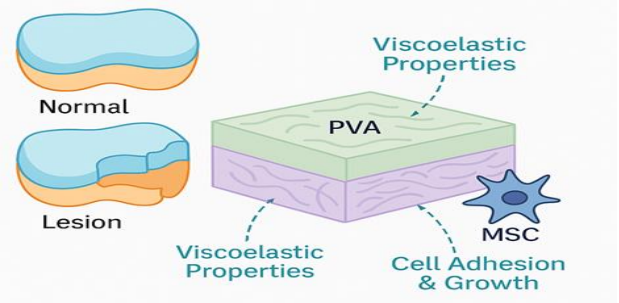
- MSCs / PRP / exosomes / scaffolds can perform far better.

Cell-Based Therapies:

- PRP and PLT-derived Exosome (Evs)
- Platelet Rich Fibrin (PRF)
- MSC and MSC derived Exosome (Evs)
- SVF (stromal vascular fraction)

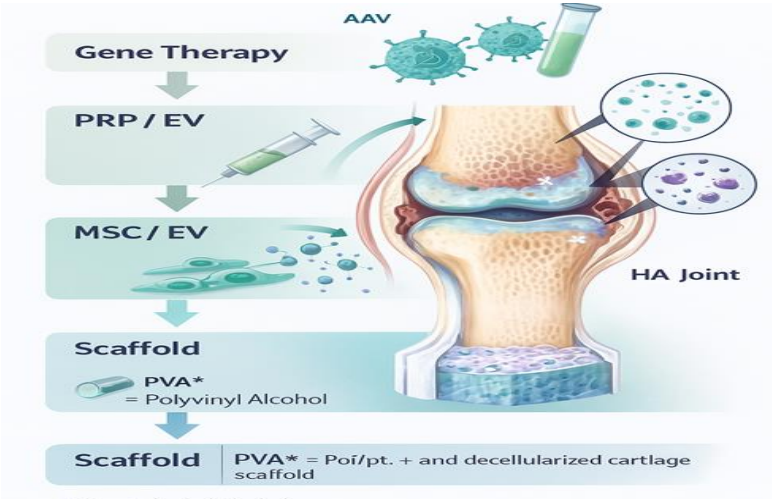
Non–Cell-based Therapies:

- Biomaterials & scaffolds

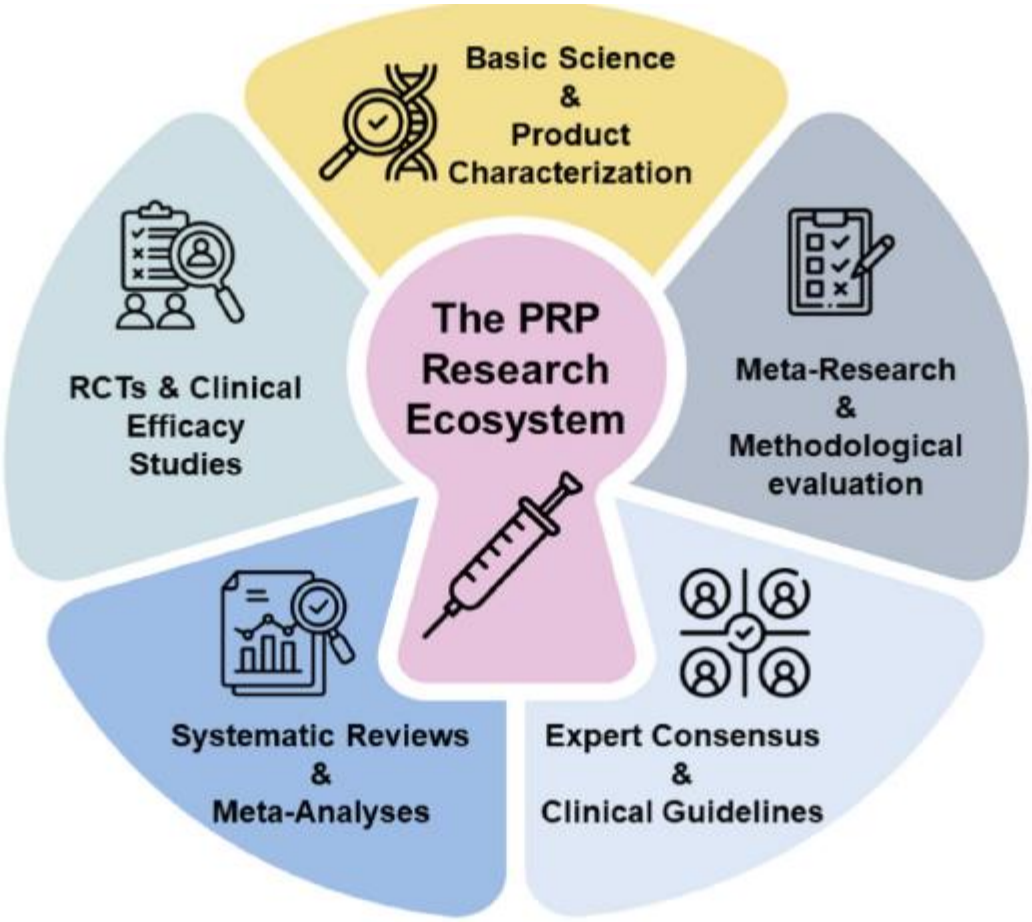


Multi-Modal Strategy:

- MSC + Gene Therapy
- MSCs+ PRP
- MSCs+ SVF
- Chondrocyte + Scaffold



PRP and PLT-derived Exosome (Evs)



The PRP research ecosystem

Domains of PRP research include basic science, product characterization, randomized controlled trials, systematic reviews, meta-research, expert consensus, and condition-focused studies, forming an interconnected framework that links biological mechanisms with clinical evidence.

Regenerative Therapy 30 (2025) 1036–1045

Transfusion and Apheresis Science 56 (2017) 160–164

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Transfusion and Apheresis Science 56 (2017) 226–232

DOI:10.31557/APJCP.2019.20.3.817

Autologous Platelet-Released Growth Factor and Sexual Dysfunction Improvement

RESEARCH ARTICLE

Editorial Process: Submission:08/10/2018 Acceptance:01/16/2019

BIOMEDICAL JOURNAL 42 (2019) 403–410

Available online at www.sciencedirect.com

ScienceDirect

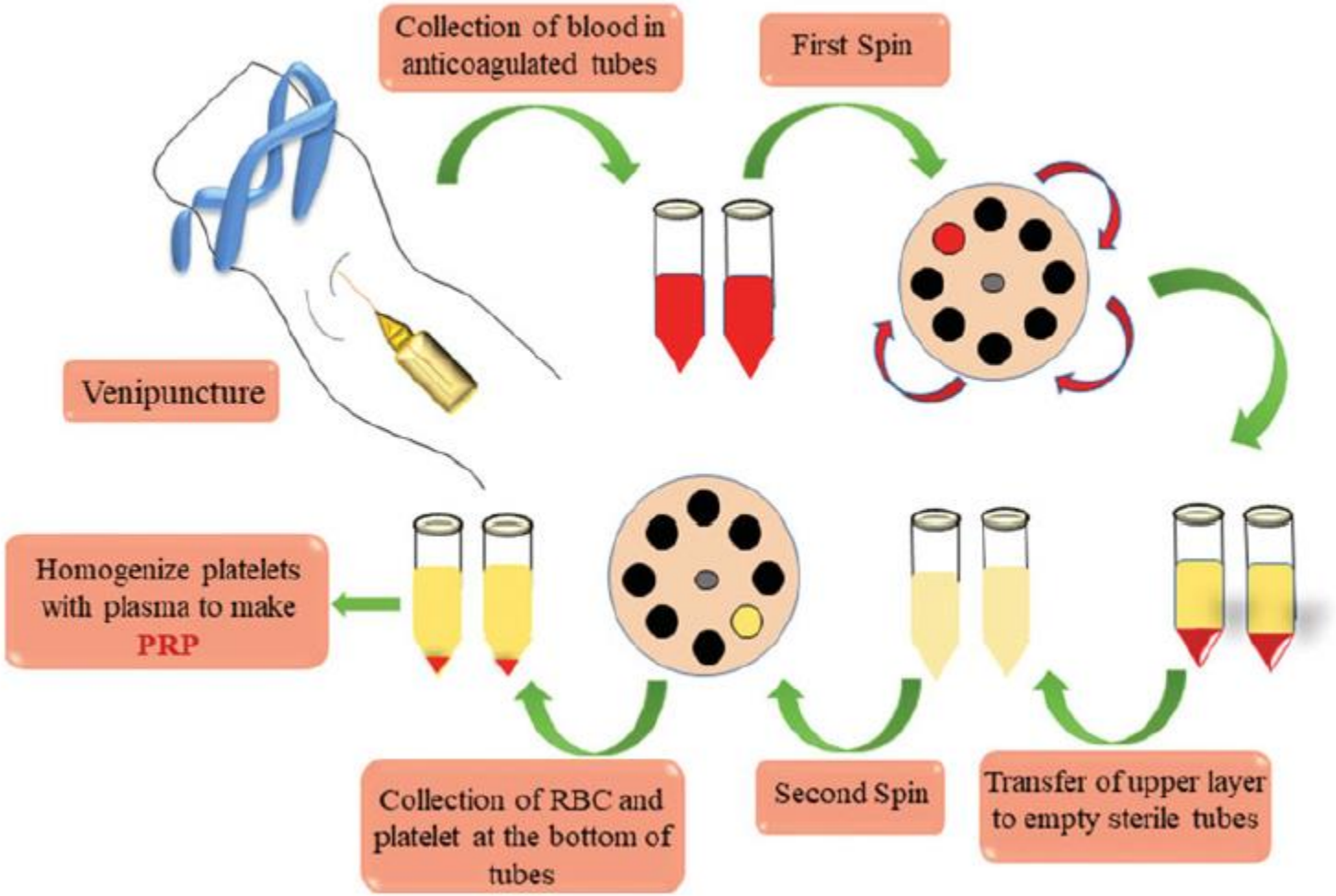
Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Original Article

A randomized controlled trial of effectiveness of platelet-rich plasma gel and regular dressing on wound healing time in pilonidal sinus surgery: Role of different affecting factors

Saeed Mohamadi [a,1], *Amir Hossein Norooznezhad* [b,c,1], *Shayan Mostafaei* [c,d], *Mohsen Nikbakht* [a], *Shirzad Nassiri* [e], *Hiva safar* [f], *Kamran Ali Moghaddam* [a], *Ardeshir Ghavamzadeh* [a], *Anoshirvan Kazemnejad* [g,*]



Regenerative Therapy 30 (2025) 1036–1045

IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

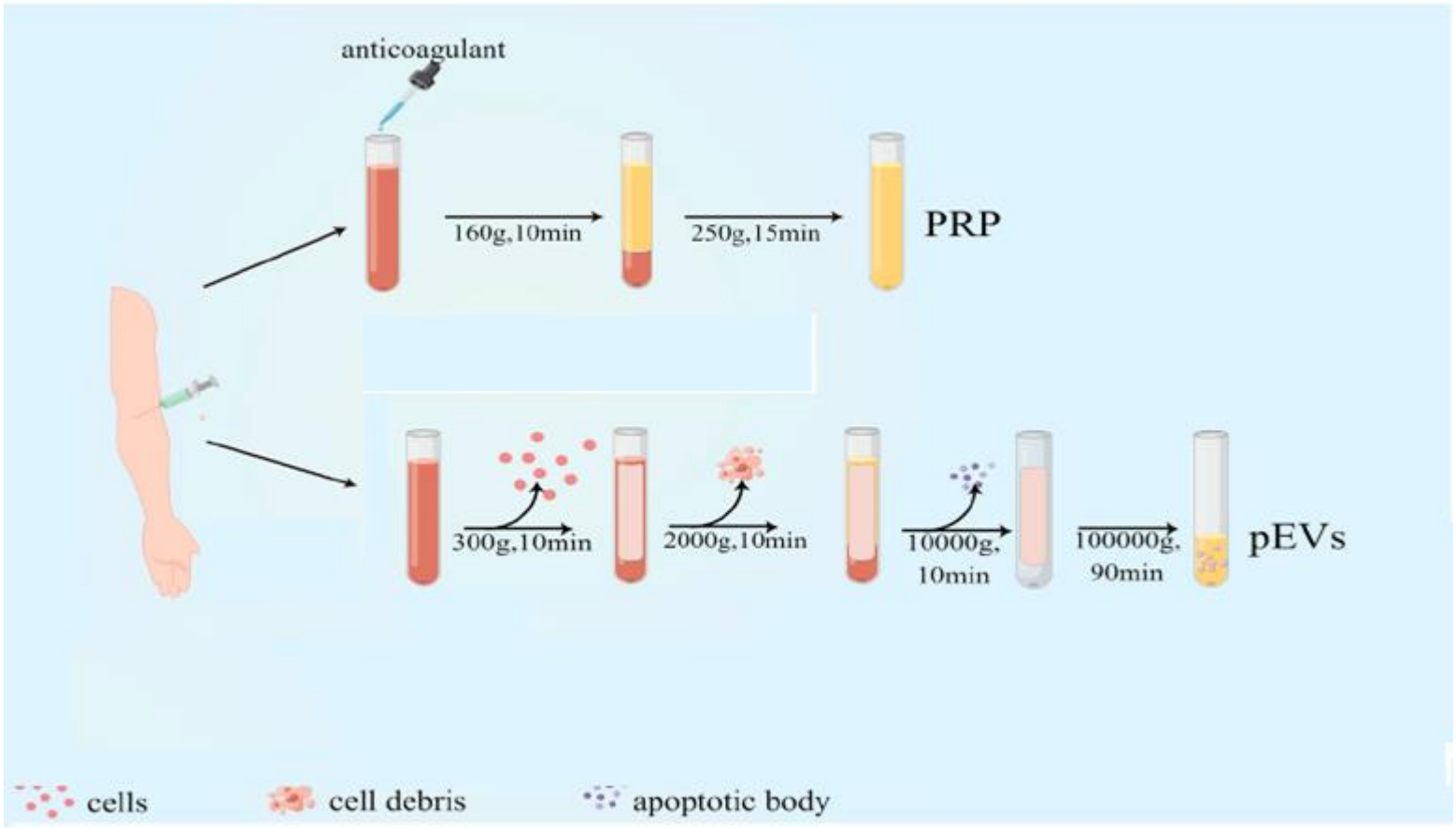
Human Platelet Lysate as a Xeno Free Alternative of Fetal Bovine Serum for the In Vitro Expansion of Human Mesenchymal Stromal Cells

Saeed Mohammadi[1], Mohsen Nikbakht[1], Ashraf Malek Mohammadi[1], Mahdi Zahed Panah[2], Mohammad Reza Ostadali[1], Hajar Nasiri[1], Ardeshir Ghavamzadeh[1]

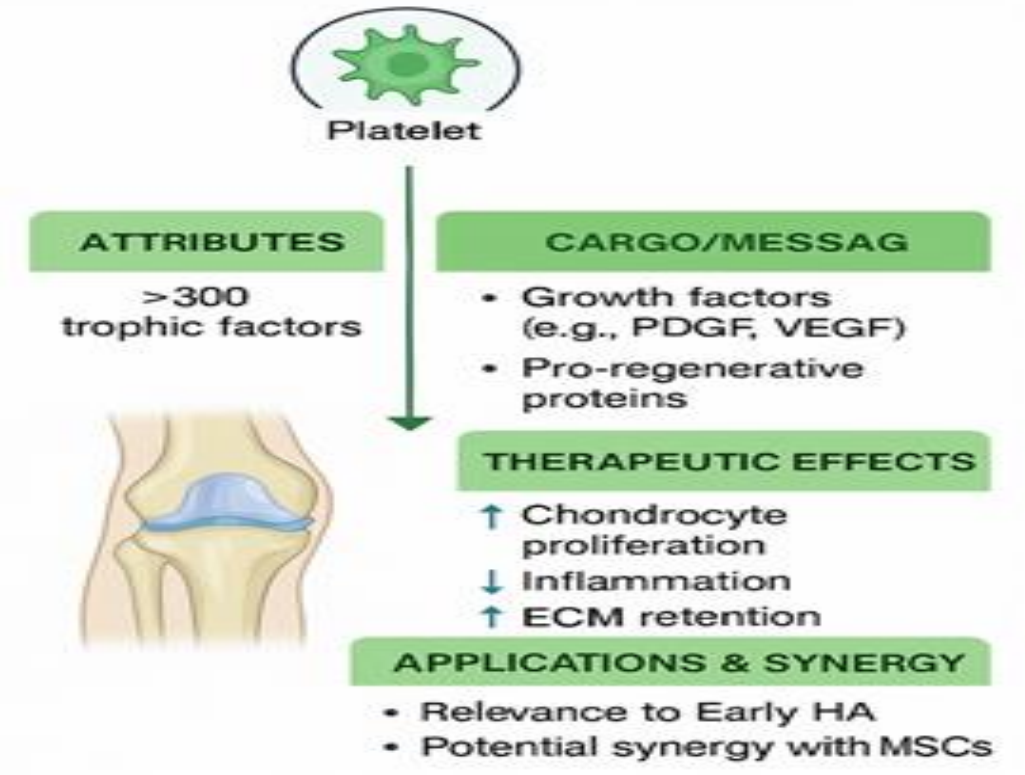
[1]Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
[2]School of Allied Medical Sciences, Qazvin University of Medical Sciences, Qazvin, Iran

Platelet-rich derivatives		Centrifuge process (centrifugal force or revolution per minute and time of centrifugation)	Special characteristics
first-generation platelet-rich derivatives: PRP	L-PRP	firstly, 250×g for 10 min, secondly 250×g for 10 min. (Jia et al., 2018)	the addition of an anticoagulant was required before centrifugation
	P-PRP	firstly, 160×g for 10 min, secondly 250×g for 15 min. (Jia et al., 2018)	

PLT-derived Exosome (Evs)

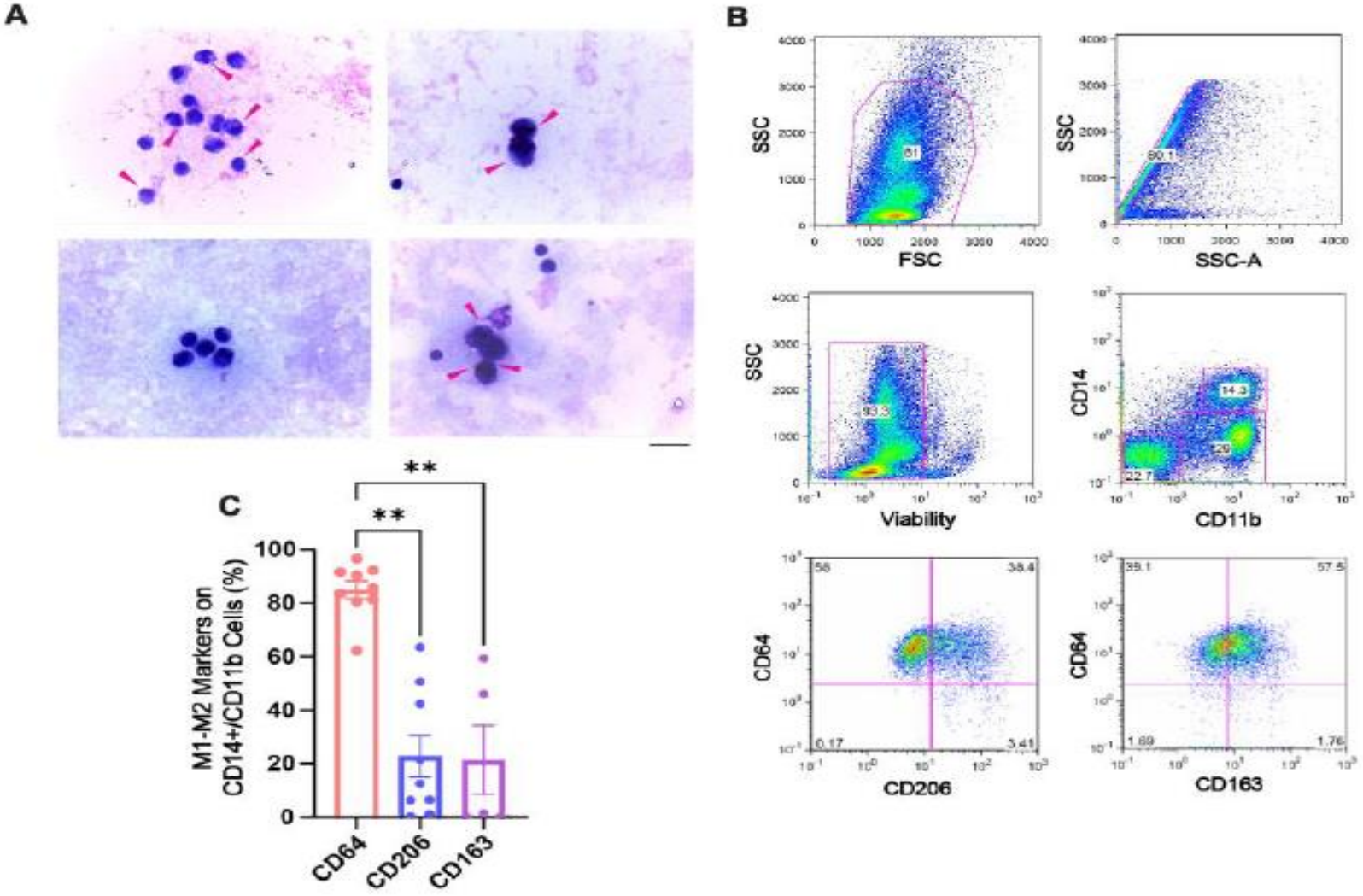


PRP in Joint Repair



ARTIFICIAL CELLS, NANOMEDICINE, AND BIOTECHNOLOGY 2019, VOL. 47, NO. 1, 882–890

PRP and PLT-derived Exosome (Evs)



Int. J. Mol. Sci. 2025, 26, 10616

list of studies regarding the application of PRP in patients with knee OA.

Type of therapy	Publication Year	Study type	Patient population	Study design	Follow-up	Outcome
PRP therapy	2012	Case-series	50	PRP	12 months	Improved pain, clinical scores and quality of life
	2013	Prospective cohort study	22	PRP	12 months	Improved pain, functional and clinical scores
	2013	Randomized controlled trial	78	PRP	6 months	Improved WOMAC score
	2014	Systematic review and meta-analysis	1543	PRP vs. HA	6 to 24 months	Improved function; more effective than HA
	2017	Meta-analysis	1069	PRP	Variable	Similar pain relief and functional improvement at 6 months; better improvements for PRP at 12 months; PRP is safe
	2018	Meta-analysis	1520	PRP vs. HA	6, 12 months	Similar effectiveness between PRP and HA
	2018	Randomized clinical trial	89	PRP vs. HA	3, 6 months	Better improvement in pain and functional status for PRP; Improved synovial hypertrophy and vascularity scores
	2018	Randomized clinical trial	42	PRP vs. PRL	6 months	PRP is more effective than PRL regarding pain, stiffness and functional limitations
	2018	Pilot study	132	Prior MP injection vs.	1, 3, 6, 12 months	Better clinical outcomes in prior MP injection

SVF: stromal vascular fraction; PRP: platelet-rich plasma; HA: hyaluronic acid; MRI: magnetic resonance imaging; VAS: visual analog scale; ECM: extracellular matrix; MSC: mesenchymal stem cell; ADSC: adipose-derived stem cell; WOMAC: Western Ontario and McMaster Universities osteoarthritis; FRI: functional rating index; ROM: range of motion; BM: bone-marrow; MP: methyl prednisone.

ARTIFICIAL CELLS, NANOMEDICINE, AND BIOTECHNOLOGY 2019(47), 1, 882–890

Study / Country	Number of Patients (Joints)	Type / Grade of Arthropathy	PRP Intervention	Main Clinical Outcome	Reference
Teyssler et al., Czech Republic	**6 patients, 8 ankles**	Chronic hemophilic synovitis of the ankle (early arthropathy; evaluated by HJHS)	**Single intra-articular PRP** injection (3–5 mL) in affected joint	**1.Pain reduction, 2. Decreased synovial thickness (MRI), 3.Improved Hemophilia Joint Health Score at 2-month follow-up**	Teyssler P. Acta Orthop Belg. 2014;80(1):11–17.
Caviglia et al., Argentina	**19 patients, 28 joints (knee, elbow, ankle)**	Chronic hemophilic synovitis; hemophilic arthropathy without complete ankylosis (Arnold–Hilgartner ≤4)	**Single intra-articular PRP** injection in affected joints	**1. Significant reduction in bleeding episodes,** **2. Pain reduction (VAS)** **3. Improved HJHS at up to 12-month** follow-up	Caviglia H. Haemophilia. 2017;23(4):613–619.
Landro et al., Argentina	**11 patients, 14 joints,**	Chronic synovitis / mild-to-moderate hemophilic arthropathy	**Three intra-articular PRP injections at 2-week intervals**	**1. Sustained reduction in pain and bleeding** **2. Improved function** at **12-month follow-up** **3. No serious adverse events reported**	Landro ME. Biomed J Sci Tech Res. 2019;12(5).

Study / Country	Number of Patients (Joints)	Type / Grade of Arthropathy	PRP Intervention Plan	Main Clinical Outcome	Reference
Li et al., Taiwan	**22 patients with painful hemophilic knee arthropathy**	Hemophilic knee arthropathy (mostly mild–moderate (Kellgren Lawrence / Arnold Hilgartner)	**RCT:** **1. 11 patients received single intra-articular PRP injection** **2. 11 patients received 5 weekly hyaluronic acid injections**	**Both groups :** **1. Improved in pain and WOMAC** **PRP group:** **1. Significantly greater pain reduction (VAS)** **2. Functional improvement (WOMAC),** **3. Decreased synovial hypertrophy (US) at 6 months**	Li TY. Haemophilia. 2019;25(3):484–492.
Caviglia / Oneto et al., Argentina (combined clinical + in vitro study)	**22 patients with 23 joints (1 ankle, 22 knees)**	Chronic hemophilic synovitis; hemophilic arthropathy grade 1–4 (Arnold Hilgartner)	**1. Single intra-articular PRP injection;** **2. Synovial fluid sampling before and after for macrophage and NETs analysis**	**Clinical level:** **1.Improved HJHS,** **2. Reduced pain and bleeding** **Cellular level:** **1. Decreased M1 macrophages (CD64+) and modulation of inflammatory signature in synovial fluid** **2. Anti-inflammatory and reparative mechanism of PRP**	Oneto P / Caviglia H. Int J Mol Sci. 2025;26(21):10616 Hemophilia 2024, “Treatment of Chronic Hemophilic Synovitis with PRP” (MDPI)

Platelet Rich Fibrin (PRF)

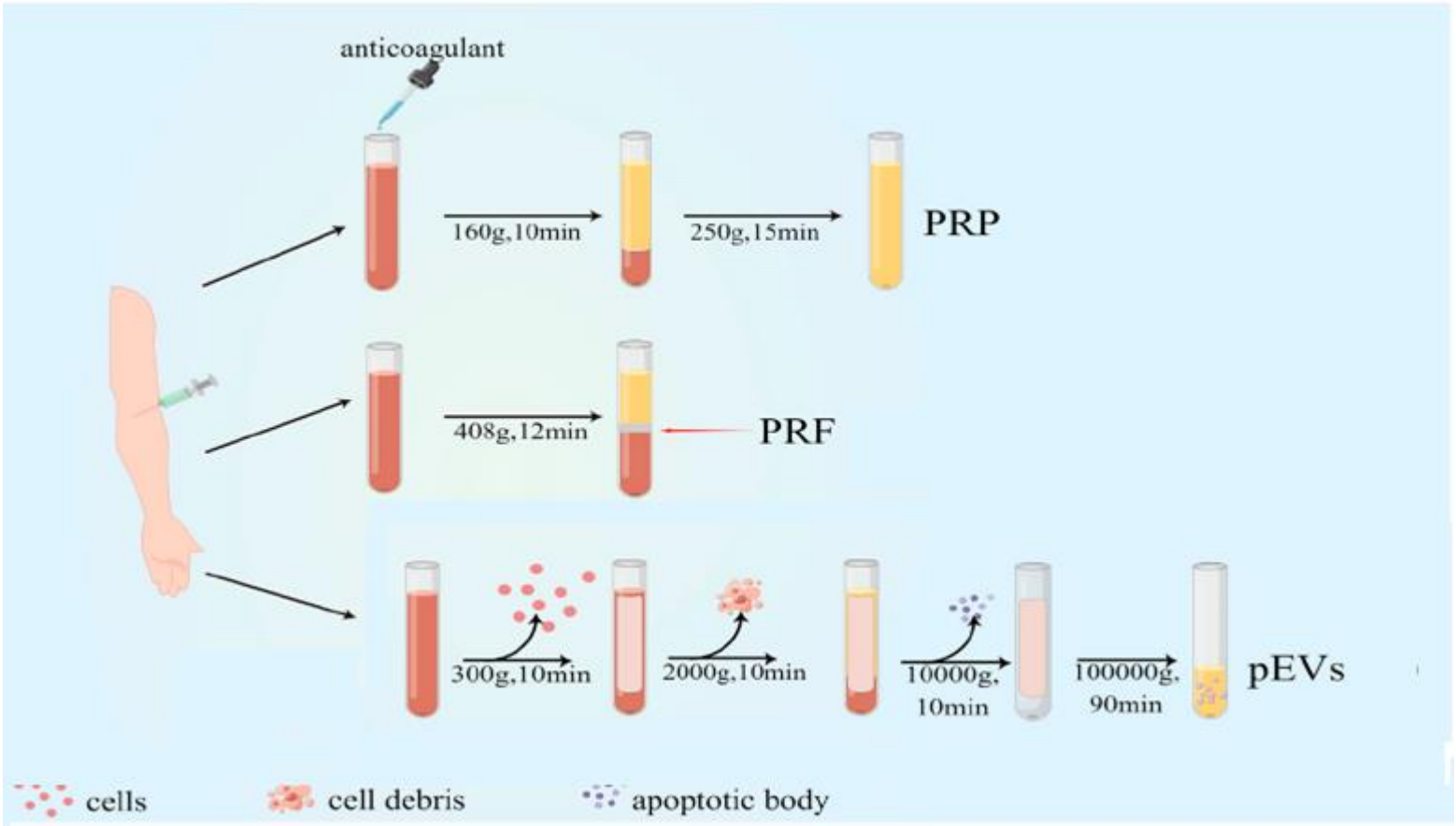
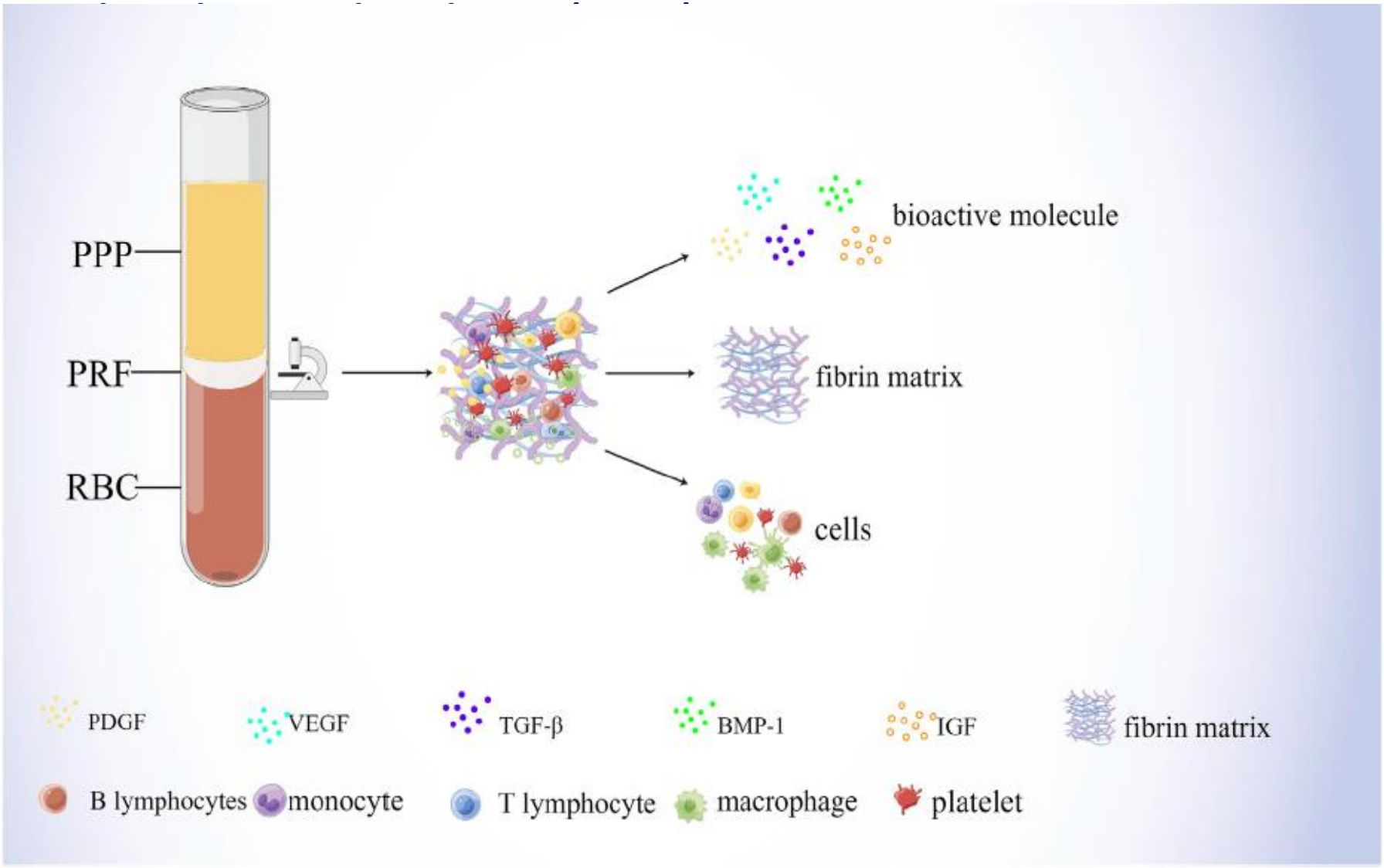


Table 2: Certain growth factors and cytokines present in PRF and their function

Transforming growth factor-β (TGF-β)	Stimulates angiogenesis, fibronectin, and collagen production; prevents collagen breakdown; induces fibroblast and immune cells chemotaxis; inhibits osteoclast formation and bone degeneration
Platelet-derived growth factor (PDGF)	Provokes migration and proliferation of mesenchymatous cell lineage; enables angiogenesis, macrophages chemotaxis, and activation; induces TGF-β secretion from macrophages
Insulin growth factor-1 (IGF-1)	Stimulates chemotaxis and activation of osteoblasts and bone formation; induces differentiation and mitogenesis of mesenchymal cells
Vascular endothelial growth factor (VEGF)	Initiates angiogenesis; enhances permeability of the vessels; induces endothelial cell proliferation and migration
Epidermal growth factor (EGF)	Promotes angiogenesis; stimulates proliferation and differentiation of epithelial cells; increases cytokine secretion in epithelial and mesenchymal cells
Interleukin-1β (IL-1β)	Increases expression of adhesive molecules on endothelial cells; stimulates helper T cell, chemotaxis of lymphocytes; activates osteoblasts
Interleukin-6 (IL-6)	Stimulates B-cell differentiation and antibody secretion; induces differentiation of naive T cells in cytotoxic T lymphocytes
Tumor necrosis factor-α (TNF-α)	Induces neutrophil cytotoxicity; stimulates cell survival and proliferation; enhances the remodeling capacities of fibroblasts
Interleukin-4 (IL-4)	Induces B-cell differentiation into plasmocytes, B-cell class switching to IgE, differentiation of naive helper T cells in Th2 cells

Open Medicine 2021; 16: 446–454



Open Medicine 2021; 16: 446–454

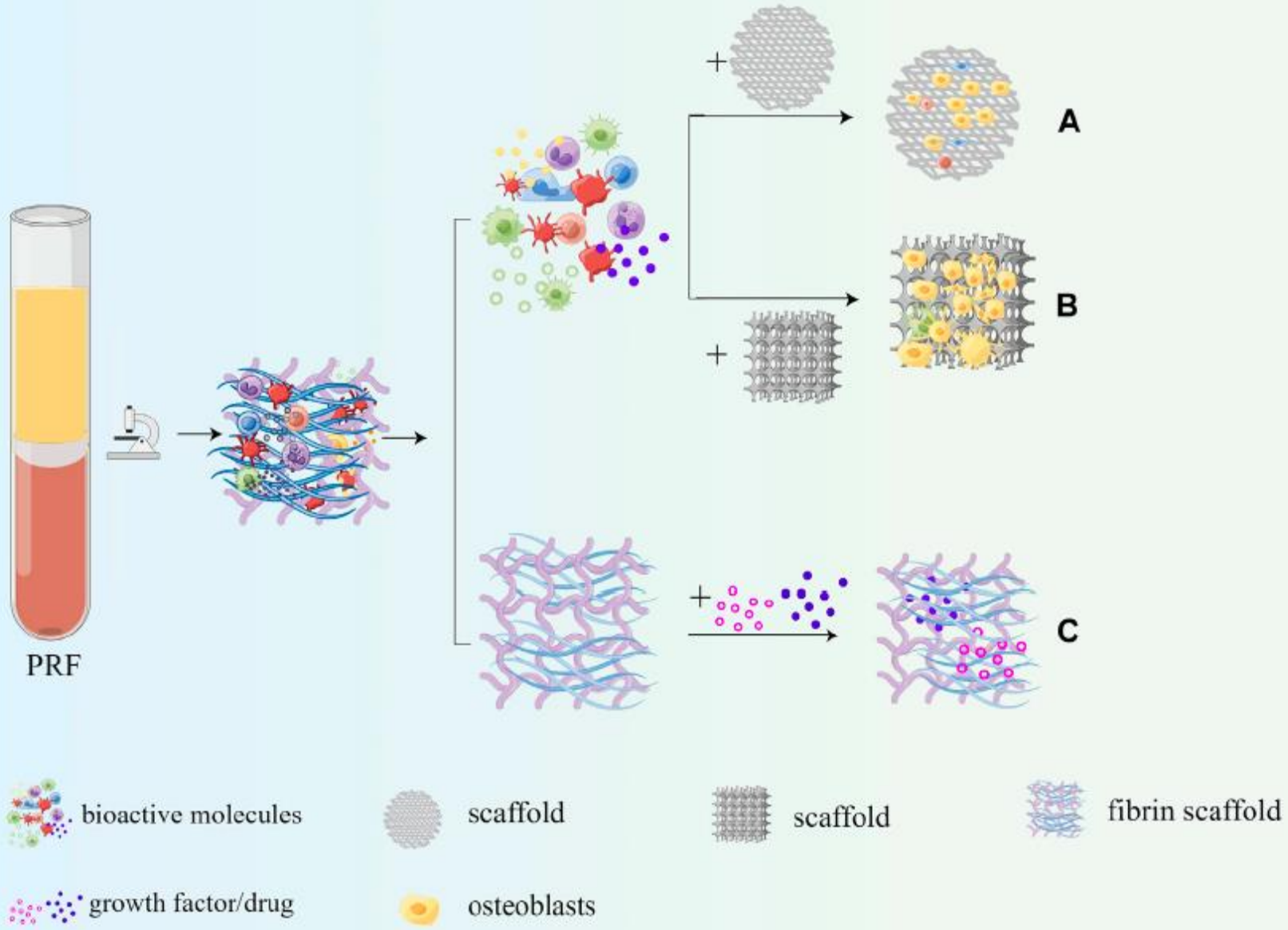


FIGURE 8
Application of PRF in bone tissue engineering. **(A)** PRF can enhance osteoinduction properties of the scaffold; **(B)** PRF can enhance biocompatibility of the scaffold; **(C)** PRF serves as a drug delivery system.

The evolution of platelet derivatives and their preparations.

Platelet-rich derivatives		Centrifuge process (centrifugal force or revolution per minute and time of centrifugation)	Special characteristics
first-generation platelet-rich derivatives: PRP	L-PRP	firstly, 250×g for 10 min, secondly 250×g for 10 min. (Jia et al., 2018)	the addition of an anticoagulant was required before centrifugation
	P-PRP	firstly, 160×g for 10 min, secondly 250×g for 15 min. (Jia et al., 2018)	
second-generation platelet-rich derivatives: PRF	L-PRF	400×g for 12 min (Ratajczak et al., 2018)	none
	H-PRF	700×g for 8 min (Feng et al., 2020)	horizontal centrifugation
	T-PRF	2,700 rpm for 12 min (Ercan et al., 2022)	titanium tubes
	i-PRF	60×g for 3 min (Ozsagir et al., 2020)	none
	A-PRF	100×g for 14 min (Kobayashi et al., 2016)	none
	Ly-PRF	400×g for 10 min (Ngah et al., 2021)	to prepare Ly-PRF, intact fresh PRF was frozen and stored at −80°C for 30 min before being freeze-dried overnight at −51°C to produce Ly-PRF.
third-generation platelet-rich derivatives: concentrated growth factor (CGF)		accelerate for 30 s, then 2,700 rpm for 2 min, 2,400 rpm for 4 min, 2,700 rpm for 4 min, 3,000 rpm for 3 min, finally, decelerate for 36 s and stop	acceleration and deceleration repeated centrifugation
platelet-derived extracellular vesicles (pEVs)		300–2,000×g for 20 min, 5,000–10000×g for 10 min, and 1,000,00×g for 1–3 h	none

L-PRP: Leukocyte Rich PRP

L-PRF: Leukocyte Rich PRF

A-PRF: advanced PRF

P-PRP: Pure PRP or leukocyte poor PRP

T- PRF: Titanium PRF

Lyo-PRF: lyophilized PRF

H-PRF: Horizontal centrfigate PRF

i- PRF: Injectable PRF

PRF Type	Final Form	Strengths (Advantages)	Weaknesses (Disadvantages)	Common Applications
L-PRF)	Solid gel/membrane **with leukocytes**	1. Dense fibrin structure 2. sustained release of growth factors 3. Simple and cost-effective protocol	1. Limited final volume 2. Sensitive to centrifugation time/speed	1. Periodontal regeneration 2. Cavity filling 3. Bone graft enhancement
A-PRF)	Gel/membrane with modified centrifugation **(lower speed)**	1. Different platelet and leukocyte distribution 2. Enhanced growth factor release and angiogenesis	1. Softer structure 2. Lower mechanical stability	1. Soft tissue integration 2. socket preservation 3. 3. regenerative procedures

PRF Type	Final Form	Strengths (Advantages)	Weaknesses (Disadvantages)	Common Applications
i-PRF	Liquid suspension **(injectable)**	1. Injectable 2. suitable for filling soft spaces 3. Rapid diffusion 4. Can be combined with fillers/grafts	1. Short lifespan before gelation (requires quick handling) 2. variable platelet content depending on protocol	1. Bioactive soft tissue absorption 2. combination with biomaterials
T-PRF	Gel/membrane prepared in **titanium tubes**	1. Denser fibrin matrix 2. Free of silica particles 3. Higher tissue stability	1. Requires special titanium tubes/instruments (higher cost) 2. Fewer long-term clinical studies	1. Periodontal cases 2. Soft/hard tissue grafts where longer stability is desired
H-PRF **Alb-PRF**	Hertz/albumin-enhanced	1. Increased strength 2. Prolonged release	1. May require additional steps or materials 2. Less standardized	1. Complementary or alternative use in surgical 2. Aesthetic 3. Regenerative procedures

What we have:

- PRF in HA has only been used as an adjunct in reconstructive surgeries
- High safety and good biocompatibility
- Stable source of growth factors (TGF-β, PDGF, VEGF)

What we don’t have :

- Independent intra-articular PRF injections in HA
- Human RCTs of PRF in HA
- Direct comparison of PRF vs PRP in hemophilia patients

Summary:

- PRF has so far only been used as a biological scaffold or surgical adjunct in human studies,
- Has not yet been clinically evaluated as a standalone intra-articular therapy in HA.

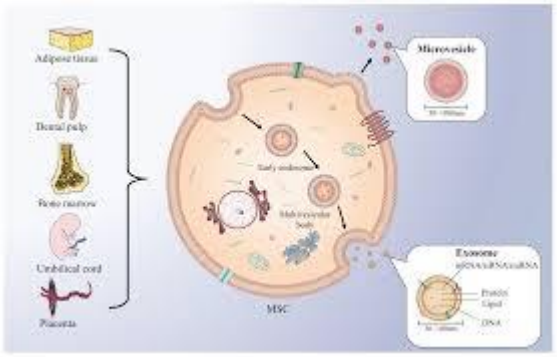
Table 3. Clinical application of PRF for cartilage repair.

End Use Destination	Hemocomponent/Experimental Groups	PRFPreparation Protocol	Characterization Parameters	Major Findings	Reference
Hemophilic ankle arthropathy (focal lesions)	n = 5 patients (mean age = 33 ± 6.78 years): collagen membrane loaded with BMDCs and PRF	Preparation according to the Vivostat® system	Mean follow up: 2 years The postoperative outcome was evaluated by: - AOFAS scores - radiographs - MRI and Mocart scores	- All patients showed complete filling of the talar defect - The implant borders were completely/partially integrated with the adjacent cartilage - In all patients presented inhomogeneous, hyperintense repair tissue was detected - Three patients had subchondral bone edema or cyst - Overall, the data showed good osteochondral regeneration and no progression of joint degeneration	Buda et al., 2015 [82]
Knee cartilage focal lesions	n = 15 patients: microfractures and PRF; n = 16 patients: microfractures and PRP; n = 17 patients: microfractures alone	-	Follow up: 2, 5 years Postoperative evaluation of patients was performed by: - clinical scores (i.e., IKDC, VAS pain) - MRI and Mocart scores	- Platelet concentrates allowed to achieved better clinical results compared to microfracture alone - The PRF was more effective than the PRP at 2 years, with loss of significance at 5 years - According to Mocart score, PRF gave better results earlier than the other two treatments	Papalia et al., 2016 [84]
Knee cartilage focal lesions	n = 25 patients (mean age = 29 ± 7.3 years): single-step AMIC procedure based on microfracture and application of autologous PRF called CLP-MB membrane, combined with an injectable collagen scaffold (Cartifill)	- Blood collection by apheresis - Separation of CLP and plasma - Cryoprecipitate formation from freeze/thawed plasma - Mixing of CLP and cryoprecipitate (CLP mix) - Activation of the CLP mix with calcium gluconate - Incubation at 37 °C for 10 min - Centrifugation (7333× g, 25 min)	Pre-implant characterization: - assessment of blood cell composition, $CD34^+/CD133^+/VEGFR2^+$ cell content, fibrinogen concentration during each preparation phase - release of PDGF-AB, TGF-β1 and VEGF -mechanical tests Clinical trial: Follow-up: 1, 6 and 12 months Patients were evaluated by: - NMR and/or radiographic scans - VAS pain - IKDC scores	- Quality control tests during each phase of CLP-MB preparation assured for the obtainment of a standardized, traceable and safe product - The treatment with the hemocomponent provided short-term pain relief and functional improvement	D'Antimo et al., 2017 [85]
Rhinoplasty (dorsal nasal augmentation)	n = 19 patients: cartilage scales-cartilage pâté compound graft with PRGF n = 21 patients: cartilage scales-cartilage pâté compound graft with i-PRF n = 8 patients: cartilage pâté graft with a-PRF	Preparation according to Choukroun et al., 2001 [3]	Follow-up controls every 3 months Medical records to assess the surgical outcome included: - follow-up notes - pre- and post-operative photographic documentation	- Satisfactory dorsal nasal augmentation in 47 patients - 1 mm-horizontal displacement of the graft in one patient 3 months after surgery, with no tendency for further displacement - No dorsal irregularities, nor signs of resorption, erythema, inflammation	Kovacevic et al., 2017 [86]

a-PRF, advanced PRF; AOFAS scores, American Orthopedic Foot and Ankle Society scores; BMDCs, Bone Marrow-derived Cells; CLP, leukocyte and platelet concentrate; CLP-MB, leukocyte- and platelet-rich fibrin membrane; i-PRF, injectable PRF; IKDC, International Knee Documentation Committee; MRI, Magnetic Resonance Imaging; NMR, Nuclear Magnetic Resonance; PRF, Platelet-rich Fibrin; PRGF, Platelet-rich Growth Factors; PRP, Platelet-rich Plasma; VAS, Visual Analog Scale.

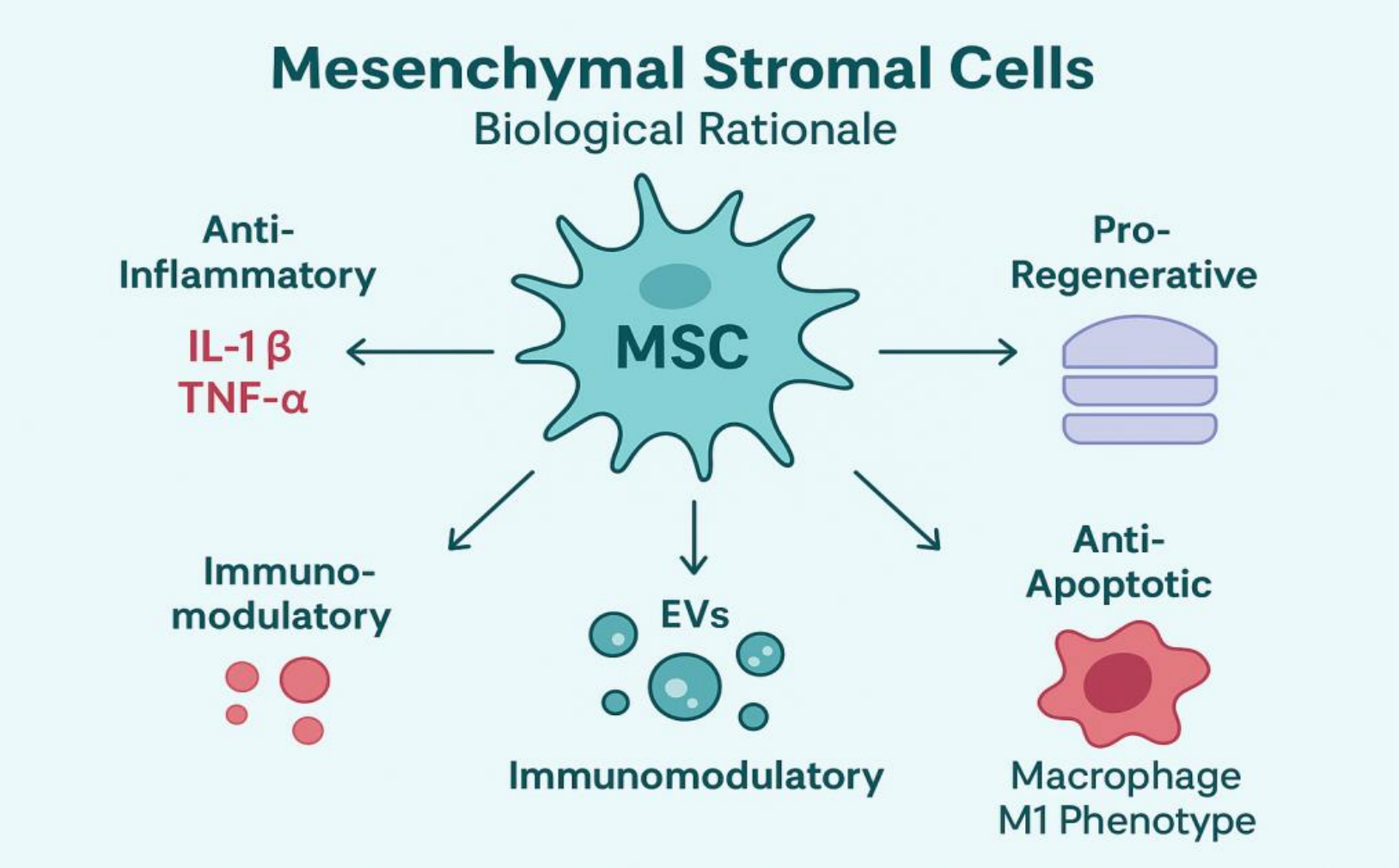
	PRF Intervention Design	Main Clinical Outcome	Reference
Review	Mention of PRF as a bioactive adjunct option in reconstructive surgery for HA	**No RCTs or independent intra-articular PRF injections reported**	(HA & regenerative surgery) 2013–2024

Number of Patients (Joints)	Type / Grade of Arthropathy	PRF Intervention Design	Main Clinical Outcome	Reference
5 patients (5 ankles)	Hemophilic ankle arthropathy with : 1. osteochondral lesions 2. (non ankylosed HA; exact grade not reported)	**One-step arthroscopic repair combined with bone marrow–derived cell transplantation (MSC-rich)**	**1. Significant improvement in function (AOFAS)** **2. Pain reduction** **3. MRI evidence of lesion filling** **4. No PRF-related complications**	Buda R. Cartilage. 2013
5 patients	Hemophilic ankle arthropathy with osteochondral lesion	**Use of PRF scaffold/membrane as a biological matrix and growth factor source alongside BMDCT**	**1. Sustained improvement in joint function** **2. Clinical symptoms** **3. Mid-term follow-up; PRF reported as safe and feasible**	Buda R. Cartilage. 2015



Mesenchymal Stem Cells (MSCs) & MSC derived Exosome (Evs)

Mesenchymal Stem Cells (MSCs)



Front Bioeng Biotechnol . 2025 Apr 24:13:1591400

Clinical Translation Challenges

MSC/EV Standardization:

- Variability in donor
- Culture conditions
- Isolation methods

Dosing & Delivery:

- IA vs IV, frequency, concentration,
- Early vs established HA

Manufacturing & GMP:

- Large-scale production, cost, stability, product consistency

Regulatory Pathways:

- Undefined frameworks for cell-free biologics (EV-based therapies)

Chronological list of studies regarding the application of MSCs in patients with knee OA.

Type of therapy	Publication Year	Study type	Patient population	Study design	Follow-up	Outcome
Stem cell therapy	2013	Double blinded controlled trial	40	Autologous Ad-MSCs	6 months	Similar effectiveness in pain score compared to placebo
	2014	Double-blinded controlled trial	46	BM-MSCs	12, 24 and 36 weeks	Significant clinical improvement after MSC treatment
	2014	Double-blinded controlled trial	55	Allogenic MSCs	12 months	Meniscus regeneration and improved pain
	2014	Clinical trial	18	Ad-MSCs	6 months	Safety; Improved WOMAC score; decreased cartilage defect
	2015	Double-blinded controlled trial	30	Allogenic BM-MSC	12 months	Significant improvements in functional indices; more convenient than autologous MSCs
	2016	Clinical trial	60	BM-MSCs	1, 3, 6, 12 months	Reduced pain in patients and repaired damaged cartilage
	2016	Phase I/II multicenter randomized clinical trial	30	Autologous BM-MSCs	12 months	Safety, clinical and functional improvement
	2016	Phase I Dose-Escalation Trial	18	Ad-MSCs	6 months	Safety; Significant improvements in pain and function

SVF: stromal vascular fraction; PRP: platelet-rich plasma; HA: hyaluronic acid; MRI: magnetic resonance imaging; VAS: visual analog scale; ECM: extracellular matrix; MSC: mesenchymal stem cell; ADSC: adipose-derived stem cell; WOMAC: Western Ontario and McMaster Universities osteoarthritis; FRI: functional rating index; ROM: range of motion; BM: bone-marrow; MP: methyl prednisone.

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MSC / MSC-containing therapies in joint regeneration in hemophilic arthropathy.

Number of Patients (Joints)	Type / Grade of Arthropathy	MSC-Based Intervention Design	Main Clinical Outcome	Reference
Review	Mild–moderate HA	**1. MSC-rich/BMAC approaches (scattered clinical reports)**	**1. Symptom improvement** **2. imited evidence** **3. RCTs needed**	Front Bioeng Biotechnol. 2024;13:1684096

Number of Patients (Joints)	Type / Grade of Arthropathy	MSC-Based Intervention Design	Main Clinical Outcome	Reference
5 patients (5 ankles)	Hemophilic ankle arthropathy with osteochondral lesions (exact grade not specified; non-ankylosed HA)	1. One-step arthroscopic bone marrow–derived cell transplantation (BMDCT) 2. Plus scaffold 3. Plus PRF (MSC-rich product)	1. Improvement in pain and joint function 2. Better clinical scores and MRI findings at mid-term follow-up	Buda R. Cartilage. 2013;4(3):218–226.
5 patients	Hemophilic ankle arthropathy with osteochondral lesion	1. One-step BMDCT (bone marrow–derived MSC-rich cells)	1. Improved ankle function 2. Reduced symptoms 3. No serious adverse events	Buda R. Cartilage. 2015;6(3):150–155.

Arthropathy Grade	MSCs Dose per Injection	Approximate Number of Injections
Grade 1 & 2	(1 ×106 to 1× 107)	1–2 injections
Grade 3 & 4	(1× 107 to 1× 108)	2–3 injections or more

MSCs have shown **pain reduction, functional improvement**, and possible chondro-protection, although evidence is still limited to small series and case reports.

Exosome / Extracellular Vesicles (MSC-Evs)

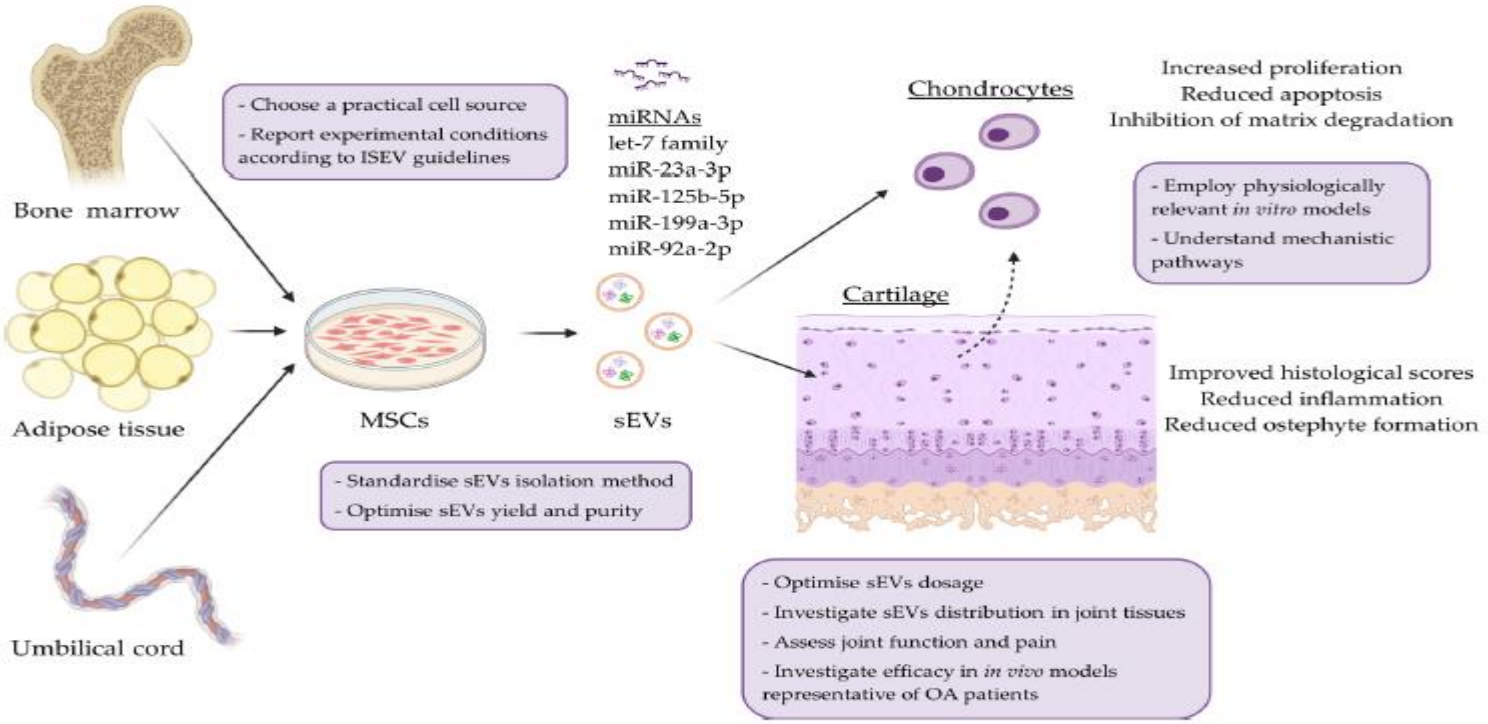

Diagram showing the main effects of MSC-derived sEVs on chondrocytes and cartilage, the most abundant miRNAs across different MSC sources, and recommendations for future research

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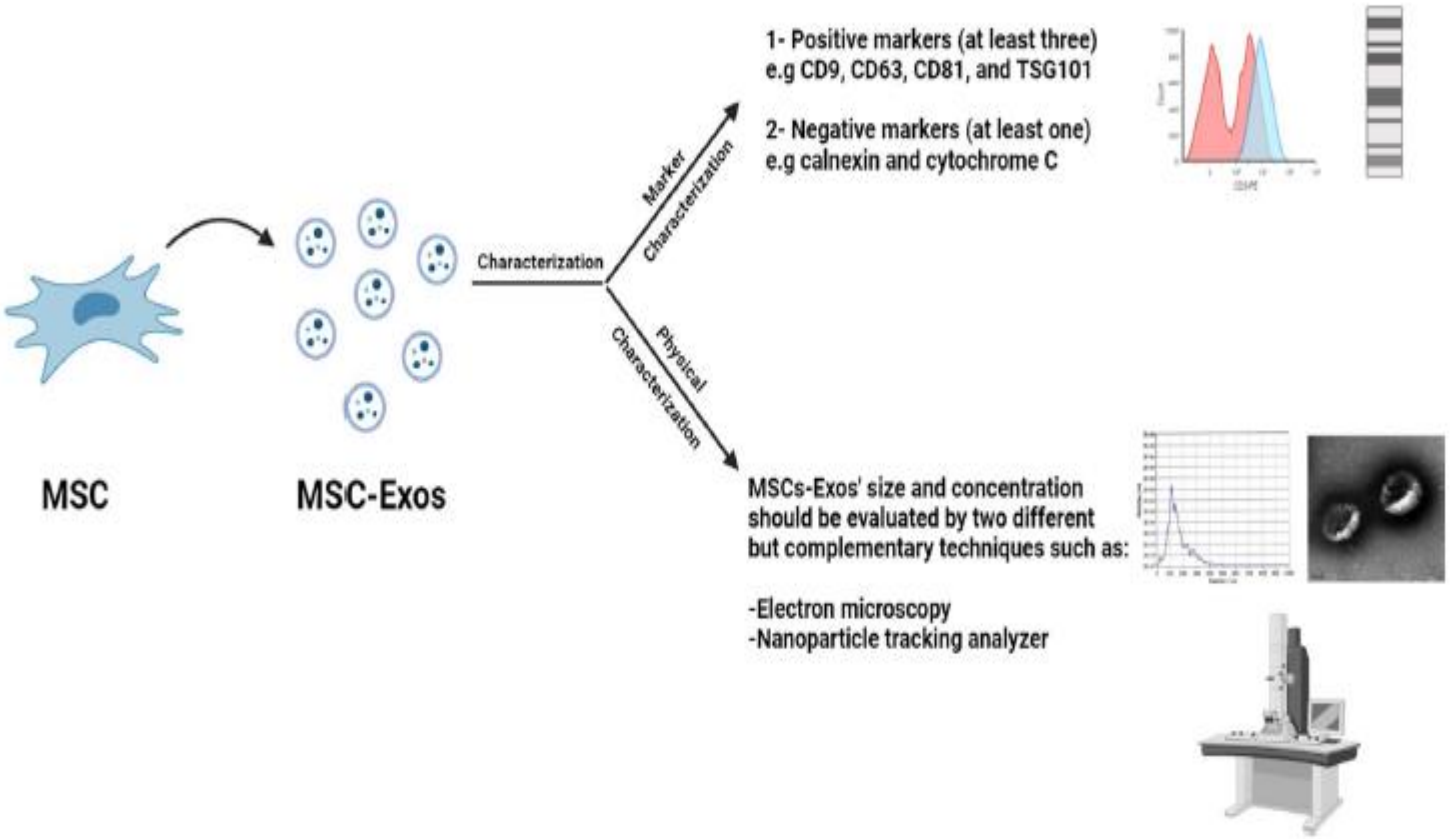

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Comparison Axis	MSC-Derived Exosomes (EVs)	Challenges
Type of Therapy	**1. Cell-free** **2. biological product containing miRNA, proteins, and growth factors**	**Preclinical phase and early clinical trials**
Main Mechanism	**1. Anti-inflammatory: ↓ IL-1β, TNF-α, IL-6** **2. Reduction of MMPs** **3. Stimulation of cartilage ECM synthesis**	**Exact mechanism in human hemophilic arthropathy (HA) still requires further study**
Safety	**1. No live cell injection** **2. No risk of tumorigenesis** **3. Lower risk of embolism**	**Effective dosing remains a challenge**
Practical Aspects	**1. Off-the-shelf** **2. Can be frozen and stored; scalable production**	**Requires GMP infrastructure for large-scale manufacturing and quality control**
Immunology	**Lower immunogenicity compared to whole MSCs**	**Potential immune response against EV surface proteins still needs monitoring**
Comparison with Standard Therapy	**Direct targeting of cartilage regeneration and modulation of joint microenvironment**	**EVs not yet established in guidelines**

TABLE 2 Summary of animal studies reported the roles of MSC-EVs in cartilage repair.

MSC-EVs type	*In vitro* model	*In vivo* model	Animal model species	Processing method	Effects	References
Equine BMSC -EVs	eACs were co-cultured with EVs	None	None	The expression of healthy cartilage/OA and proliferation markers was evaluated in eACs (monolayers or organoids).	Compared with the equine BM-MSCs, equine BM-MSC-EVs can affect the phenotype of eACs more obviously and increase the expression of chondrocyte functional markers and cell migration more effectively, thus potentially slowing the progression of OA.	Contentin et al. (2022)
BMSC -EXOs	The chondrocytes isolated from the OA rats were co-cultured with EXOs	ACLT- induced OA model	Rat	BMSC-EXOs after LIPUS stimulation can exert an effect on the biological function of OA chondrocytes *in vitro* and a protective effect on cartilage injury *in vivo*.	LIPUS can enhances the repair effect of MSCs on OA cartilage, and its underlying mechanism is related to increased autophagy-mediated exosome release.	Xia et al. (2022)
UC-MSCs-EXOs	Chondrocytes were co-cultured with EXOs	Cartilage defect model	Rat	Effect of UC-MSCs-EXOs in mechanical environment of RCCS on the biological function of chondrocytes was investigated.	The mechanical stimulation can increase the yield of exosomes and its biological function in the repair of cartilage defects.	Yan et al. (2020)
hAD-MSCs-EVs	Hypoxia-preconditioned AD-MSCs-EVs co-cultured with BM-MSCs and chondrocytes, respectively	Cartilage defect model	Rat	Investigation of whether hypoxia preconditioned AD-MSCs-EVs affect BM-MSCs and chondrocytes *in vitro* and cartilage repair *in vivo* compared to normal.	A modified gelatin matrix/3D-printed ECM scaffold - based ApoEVs delivery system with hypoxic preconditioning boosts MSC - ApoEVs' function and cartilage repair.	Ding et al. (2024)
hSM-MSC-EVs	IL-1β induced OA SW1353 were co-cultured with EVs	Both the medial collateral ligament and the medial meniscus were completely transected	Rat	Effects of SM-MSC-EVs containing miR-26a-5p on biological function of OA SW1353, inflammation *in vitro* and their action mechanisms and repair effect on OA were explored *in vitro* and *in vivo*.	SM-MSC-EVs can transfer miR-26a-5p into chondrocytes to upregulate miR-26a-5p and inhibit PTEN, thereby inhibiting apoptosis and inflammation and ameliorating cartilage injury in OA.	Lu et al. (2021b)
hMSCs -EXOs	OA chondrocytes induced by IL-1β was co-cultured with EXOs	DMM and ACLT-induced OA model	Rat	The *in vitro* and *in vivo* exploration of hMSCs-EXOs with miR-199a-3p on OA chondrocytes' function, mechanism, and repair effect.	hMSCs-EXOs can partially alleviate the pathological severity degree through the miR-199a-3p-mediated mTOR-autophagy pathway in animal OA model.	Zhao et al. (2023)
hUMSC -EXOs	EVs were co-cultured with BMSCs, chondrocytes and macrophages	Osteochondral defect model	Rabbit & Rat	Weather MSC-EXOs can enhance the reparative effect of ACECM scaffold and its underlying mechanism were explored.	In rabbit and rat models, hWJ-MSC-Exos enhance ACECM scaffold effect and promote osteochondral regeneration and regulate joint microenvironment.	Jiang et al. (2021)
BMSCs -EVs	Chondrogenic potentials and matrix formation of EVs derived respectively from naïve MSC, chondrogenically primed MSCs, chondrocytes, and co-cultures of chondrocytes plus MSCs at different ratios were evaluated *in vitro*	MIA-induced OA model	Rat	The chondrogenic potential of the EVs was investigated.	EVs derived from a higher ratio of chondrocytes to BM-MSCs have a better chondrogenic effect in the treatment of osteochondritis.	Hosseinzadeh et al. (2023)
hWJ-MSC-EVs		Osteochondral defect model	Rabbit	*In vitro*, hWJ-MSC-EVs co-cultured with hBM-	hWJ-MSC-EVs can promote cartilage	Chen et al. (2024)

Producing cells	*Animal model*			Disease model	Administration route	Treatment	Outcomes
	Strain/Sp	Sex	Age				
UCMSCs (human)	SD Rat	-	8 weeks	Monoiodoacetate	Intraarticular	10^8 EVs/10 µL PBS **Once a week/4 weeks (1 week after MIA)** No further follow-up	Reduced Mankin score* No changes in articular space width No changes in subchondral bone (BVF)
SMSCs (human)	SD Rat	Male	10 weeks	DMM (ACLT + MCL transection)	Intraarticular	3×10^9 EVs/30 µL PBS **Once a week/3 weeks (1 week after surgery)** Follow-up: 1 week	Reduced Mankin score* Reduced inflammatory cytokines [ELISA] Reduced apoptosis
BMSCs (human)	SD Rat	Male	10 weeks	Collagenase-induced OA	Intraarticular	400 µg EVs/mL **1 week after CIOA** Follow-up: 6 weeks	Reduced OARSI/Mankin score*
BMSCs (rat)	SD Rat	Female	7–8 weeks	DMM (ACLT + medial meniscectomy)	Intraarticular	200 µg EVs/200 µL PBS **4 weeks after surgery** Follow-up: 4 weeks	Reduced OARSI score Reduced osteophyte score Increased COL2 [IHQ/WB]
UCMSCs (human)	SD Rat	Male	8 weeks	DMM (ACLT)	Intraarticular	30 µg EVs/200 µL PBS **Once a week/4 weeks (1 week after surgery)** Follow-up: 4 weeks	Reduced OARSI score* Increased COL2 [IHQ]
SMSCs (human)	SD Rat	Male	12 weeks	DMM (ACLT + medial meniscectomy)	Intraarticular	2×10^{10} EVs/200 µl in hydrogel **Every 4 weeks (x6)** No further follow-up	Regenerated tissue with disorganized arrangement and poor in proteoglycans
ADSCs (human)	SD Rat	Male	8 weeks	Monoiodoacetate	Intraarticular	10^8 EVs/30 µl PBS **Subacute: Once a week/21 days (1 week after surgery)** **Chronic: Twice a week/40 days (2 weeks after surgery)** No further follow-up	Reduced Modified Mankin score (modest reduction in the chronic model)

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Producing cells	*Animal model* Strain/Sp	Sex	Age	Disease model	Administration route	Treatment	Outcomes
ADSCs (rat)	SD Rat	Male	8 weeks	Osteochondral defect	Implantation into cartilage defect	7.5×10^9 EVs/10 µl gel **(during surgery)** Follow-up: 4–8 weeks	Increased ICRS score* Increased collagen organization Reduced apoptosis Increased BVF and BMD
BMSCs (human)	SD Rat	Female	4 weeks	DMM (ACLT + medial meniscectomy)	Intraarticular	50–100 µg EVs/100 µL PBS **4 weeks after surgery** Follow-up: 4 weeks	Reduced Modified OARSI score* Increased COL2 [IHQ]
BMSCs (rabbit)	Wistar Rat	Male	8 weeks	Monoiodoacetate	Intraarticular	50 µg EVs/50 µl PBS **Once a week/4 weeks (3 weeks after MIA)** Follow-up: 8 weeks	Increased stride and step length, reduced toe-out angle and gait irregularity Reduced Mankin score* Reduced radiological score Increased COL2 [IHQ]
BMSCs (rabbit)	Wistar Rat	Male	8 weeks	Monoiodoacetate	Intraarticular	100 µg EVs/50 µl PBS **Once a week/4 weeks (3 weeks after surgery)** Follow-up: 12 weeks	Reduced irregularity in gait Reduced histological score* (2D only) Reduced radiological score (2D only)
BMSCs (human)	Wistar-Han Rat	Male	24 weeks	Groove surgery + metabolic dysregulation (Metabolic OA)	Intraarticular	7.77×10^7 EVs/25 µl PBS **Every 5 days/20 days (x5) (8 days after surgery)** Follow-up: 8 weeks	No changes in pain No changes in histology No changes in osteophytes/ subchondral bone Reduced systemic inflammation [ELISA]

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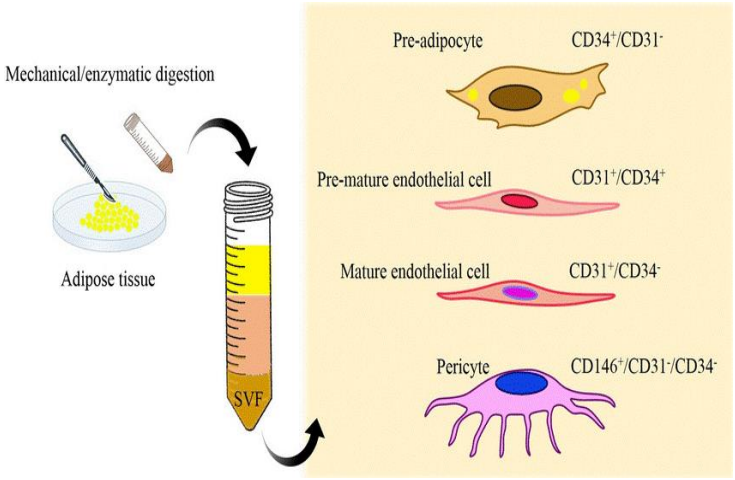
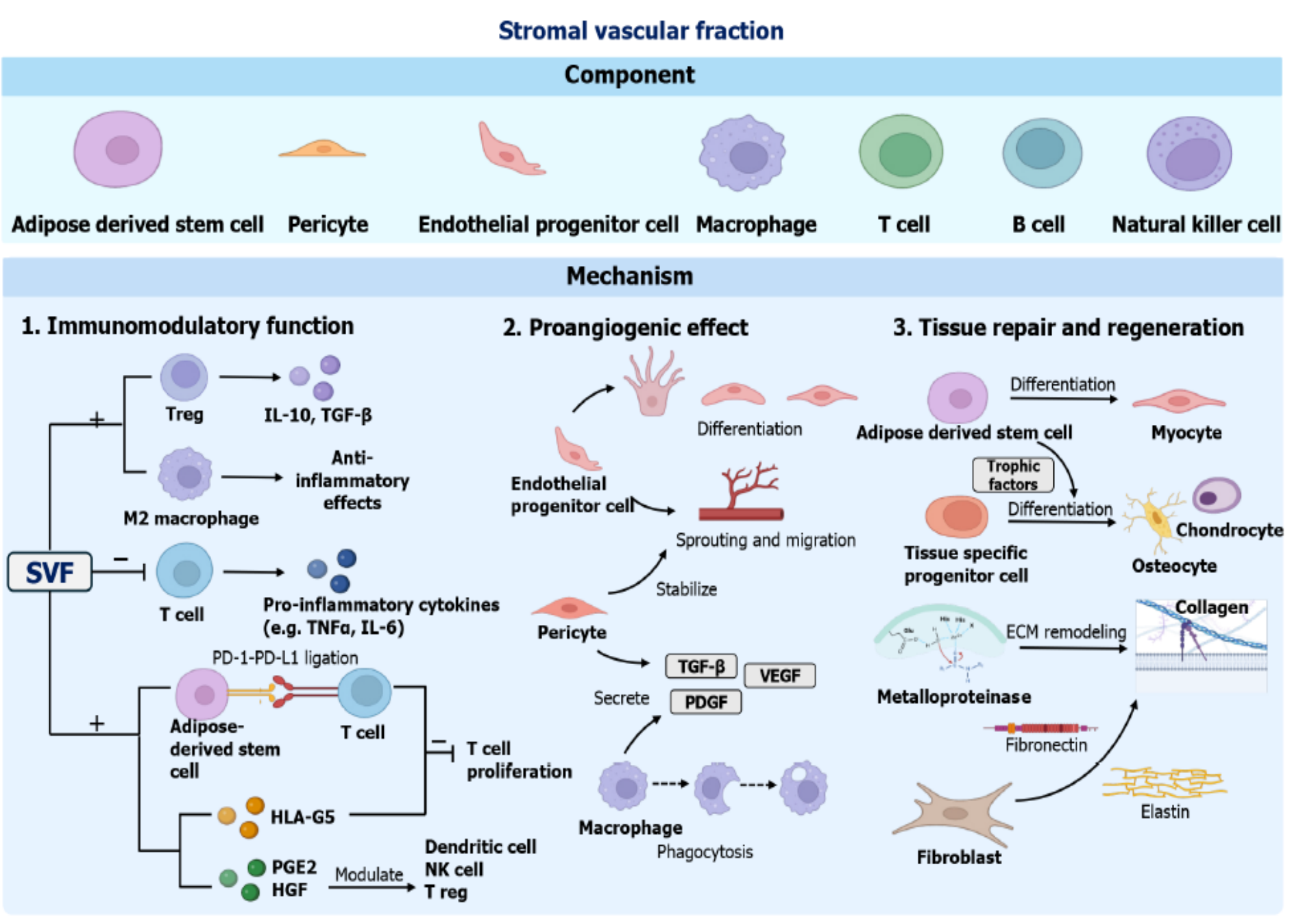


Stromal vascular fraction (SVF)



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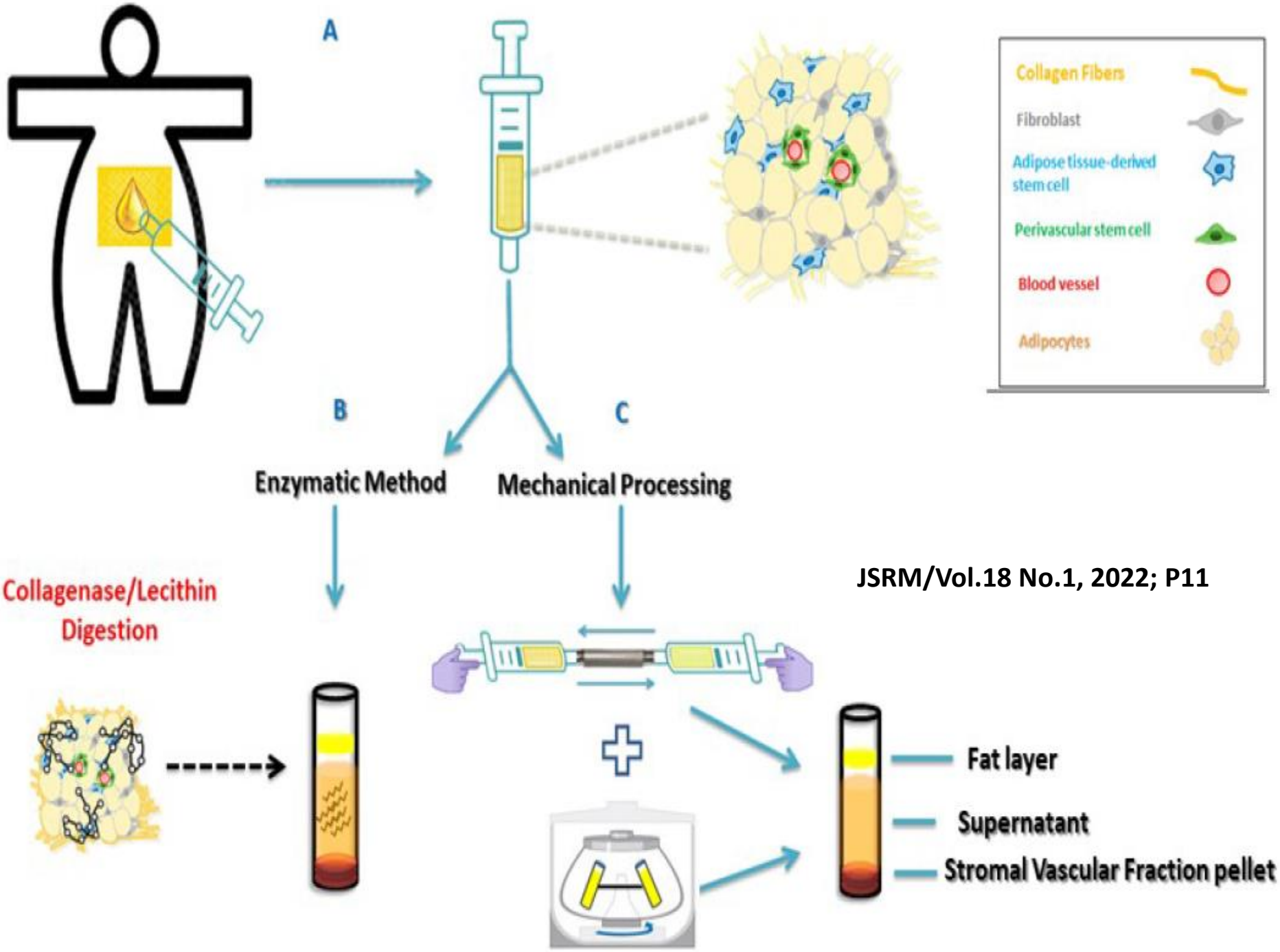

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Author(s) (Year)	Study Type	Sample Size	Key Findings	Conclusion	Complications
Onoi et al. [11] (2023)	prospective case series	42	Safety of autologous SVF	SVF cell injections in the hip joint showed good short-term clinical efficacy for reducing hip OA symptoms.	no
Kim et al. [12] (2023)	retrospective	43	Cartilage repair was evaluated based on the Magnetic Resonance Observation of Cartilage Repair Tissue scoring system, using the magnetic resonance imaging from the 12-month follow-up	SVF implantation improved pain and cartilage regeneration for patients with knee osteoarthritis. The cartilage lesion size and the number of SVF cells significantly influenced the postoperative outcomes.	no
Zhang et al. [13] (2022)	retrospective, randomized controlled clinical trial	126	The VAS and WOMAC scores in the SVF group were significantly better than those in the hyaluronic acid group during the 5-year follow-up after treatment.	Up to 5 years after autologous SVF treatment, acceptable clinical state was present for approximately 60% of patients with less cartilage volume loss. In addition, the high severity of BML and high BMI increased the risk of clinical failure. Intra-articular injections of SVF do not improve subchondral BML.	no
Kwon et al. [14] (2023)	prospective	20	The 6-month follow-up following scar revision surgery revealed better results after treatment with SVF than those in the control group.	Although more research is needed, autologous SVF is a valuable source of regenerative medicine that can be swiftly and inexpensively prepared from human fat tissue.	no
Garza et al. [15] (2021)	prospective double-blinded randomized trial	39	The median percentage change in WOMAC score at 6 months after injection for the high-dose, low-dose, and placebo groups was 83.9%, 51.5%, and 25.0%, respectively. The high- and low-dose groups had statistically significant changes in WOMAC scores when compared with the placebo group (high dose, $p = 0.04$; low dose, $p = 0.02$). The improvements were dose-dependent.	Intra-articular SVF injections can significantly decrease knee OA symptoms and pain for at least 12 months. The efficacy and safety demonstrated in this placebo-controlled trial support its implementation as a treatment option for symptomatic knee OA. Magnetic resonance image review revealed no changes in cartilage thickness after treatment.	no
Rodriguez-Merchan et al. [16] (2022)	literature review	28	Intra-articular injection of SVF seems to be a safe and efficacious method for managing knee osteoarthritis (OA). Platelet-rich plasma (PRP) and SVF are safe and effective management for intractable Achilles tendinopathy in humans, although subjects treated with SVF recover earlier.	The SVF can safely be used to treat diabetic subjects suffering from chronic foot ulcers. Experimental studies indicate that SVF could be a new option to osseous regeneration.	no

Author(s) (Year)	Study Type	Sample Size	Key Findings	Conclusion	Complications
Perdomo-Pantoja et al. [17] (2021)	prospective	36	The aim of this study was to compare the efficacy of freshly isolated adipose tissue-derived stromal vascular fraction (A-SVF) cells and bone marrow cells (BMCs) in achieving spinal fusion on rat models.	SVF cells yielded a comparable fusion mass volume and radiographic rate of fusion to BMCs when combined with a clinical-grade bone graft substitute. These results suggest the feasibility of using freshly isolated A-SVF cells in spinal fusion procedures.	no
Choi et al. [18] (2020)	prospective	10	Two polyetheretherketone (PEEK) cages were inserted into the intervertebral space following the complete removal of the intervertebral disc. The PEEK cage (SVF group) on the right side of the patient was filled with β-TCP in combination with SVF, and the cage on the left side (control group) was filled with β-TCP alone. Fusion rate and cage subsidence were assessed by lumbar spine X-ray and CT at 6 and 12 months postoperatively. At the 6-month follow-up, 54.5% of the SVF group (right-sided cages) and 18.2% of the control group (left-sided cages) had radiologic evidence of bone fusion ($p = 0.151$).	The 12-month fusion rate of the right-sided cages was 100%, while that of the left-sided cages was 91.6% ($p = 0.755$). Cage subsidence was not observed. Perioperative combined use of SVF with β-TCP is feasible and safe in patients who require spinal fusion surgery, and it has the potential to increase the early bone fusion rate following spinal fusion surgery.	no
Rowe et al. [19] (2023)	prospective	344	Mesenteric windows from old rats were isolated following exteriorization-induced (EI) hypoxic injury and intravenous injection of one of four cell therapies: (1) SVF from young or (2) old donors, (3) SVF from old donors depleted of or (4) enriched for T cells. Advancing age increased the SVF T-cell population but reduced revascularization following injury.	SVF represents a heterogeneous cell population shown to increase angiogenic regeneration in the researchers' novel aged mesenteric injury model. This study provides others with a new tool for tracking vascular remodeling and can be used in conjunction with study of cell therapies or drugs in a setting of advanced age. Furthermore, the researchers show how the age of the donor should be considered not only for cellular differences but functionality as a vascular therapeutic. Age-related changes to cell dynamics and function in providing therapeutic gains—that is, the secretion of anti-inflammatory cytokines, increasing sensitivity to VEGF, increasing the migration and engraftment potential of injected cells, and endothelial cell division.	no

Author(s) (Year)	Study Type	Sample Size	Key Findings	Conclusion	Complications
Brian et al. [20] (2020)	retrospective	350	Seven days after SVF cell therapy, 45.2% of subjects experienced improved pain levels and mobility. Three, six, and twelve months after therapy, improvement in pain levels reached 75.3%, 84.4%, and 84.9%, and improvement in mobility reached 75.2%, 84.4%, and 84.9%.	The treatment demonstrated a strong safety profile with no severe adverse events or complications reported. The results of the study are showing that SVF cell therapy was more effective in subjects with arthritis stage III compared to arthritis stages I, II, and IV.	no
Moon et al. [21] (2019)	retrospective	77	In the upper two-third and lower one-third zones, except for the ala, no statistically significant differences were found in any parameters. In the alar zone, statistically significant differences were detected in 10 of 21 POSAS parameters.	To cover nasal defects, the tissue-engineered dermis graft may be superior to the artificial dermis graft regarding scar quality at the ala. However, there were no significant differences in other zones.	no
Zimmermann et al. [22] (2018)	retrospective	10	In the transposition group, sustained pain reduction was not observed after an initial significant reduction 2 months post-surgery, resulting in pain relapse at 36 months and pain comparable to the preoperative assessment. In the graft group, some degree of pain reduction was observed at 2 months after the surgery and proved to be constant in the long-term outcome, although not statistically significant compared to preoperative levels.	Both SVF-enriched fat grafting and intramuscular transposition failed to prove statistically significant pain reduction in treating symptomatic neuromas of peripheral nerves.	no
Calcagni et al. [23] (2018)	retrospective	5	Pain reduction observed at 2 months after surgery was constant over time, though not statistically significant compared to preoperative levels.	SVF-enriched fat grafting represents another alternative to numerous available treatments of painful end-neuromas of the SBRN. The researchers' preliminary results could not show any significant difference in pain reduction following SVF-enriched fat grafting. Further larger trials are required in order to evaluate the therapeutic potential of SVF-enriched fat grafting.	no

Research A

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Stromal

Abstract

Objective: Stromal vas

that is associated with

non-randomized study

Methods: A total of 1

joints. A total of 1856

17.2 months) for safety

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Results: No serious sid

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Conclusion: Here we

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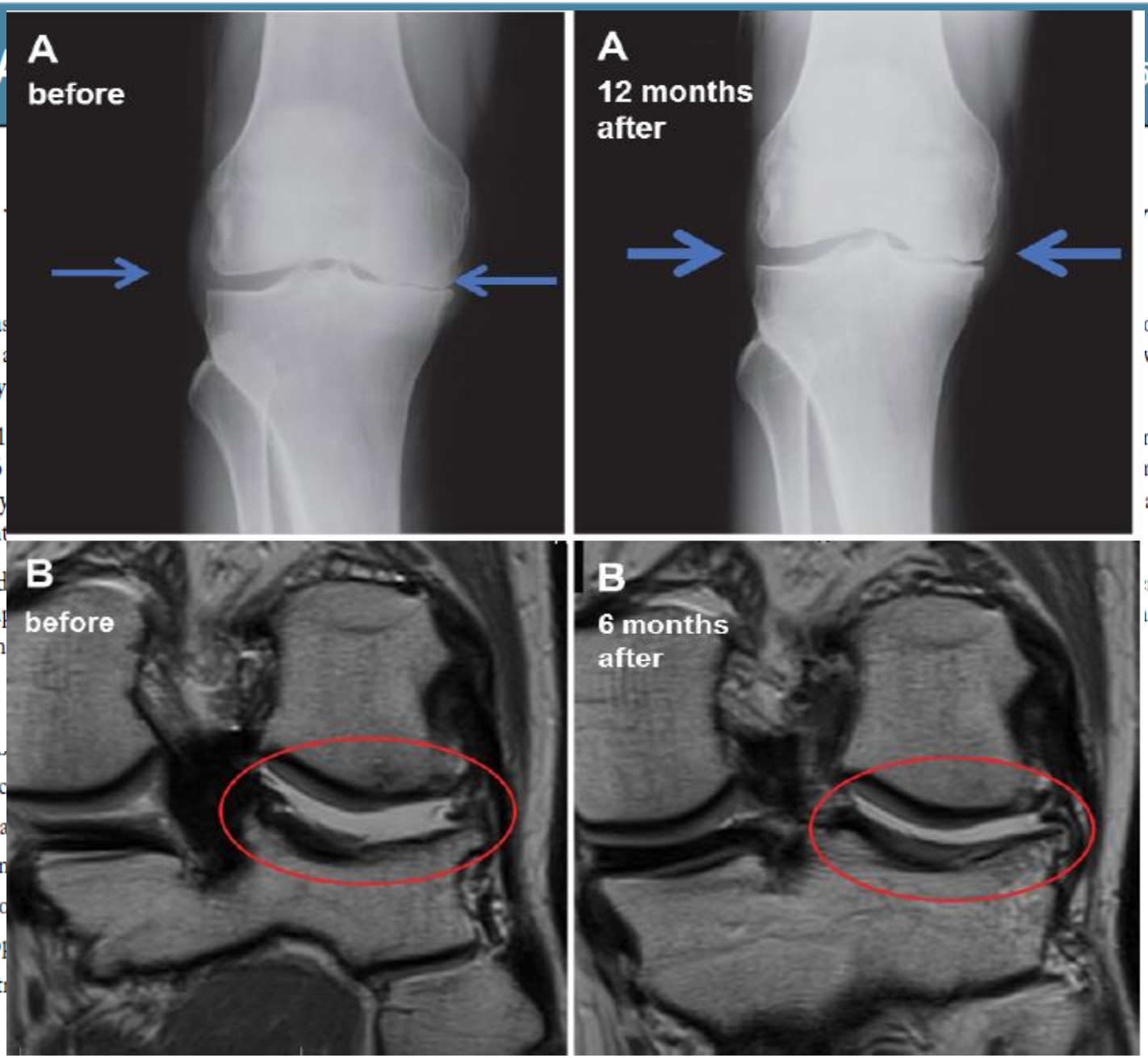
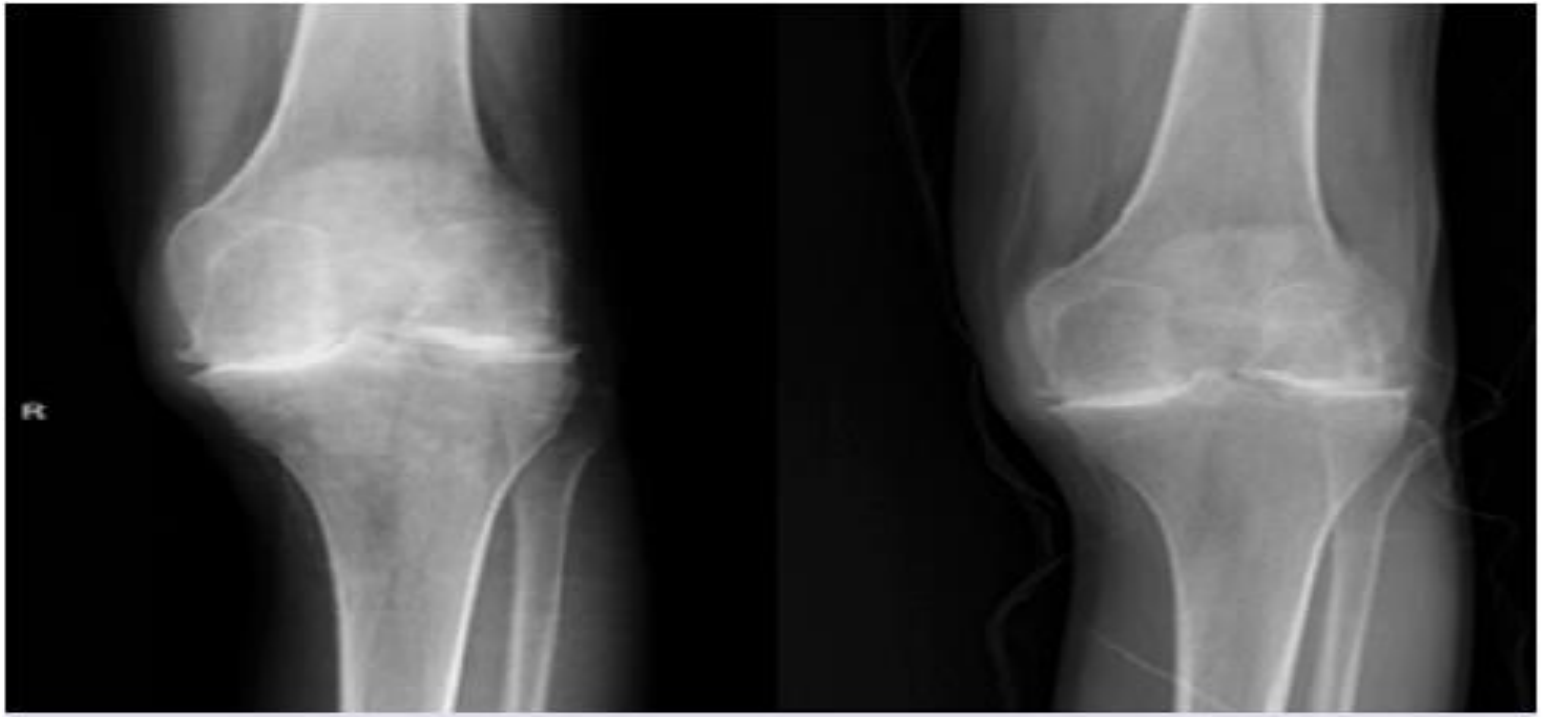


SVF Therapy in Hemophilic Arthropathy

Intra-articular SVF

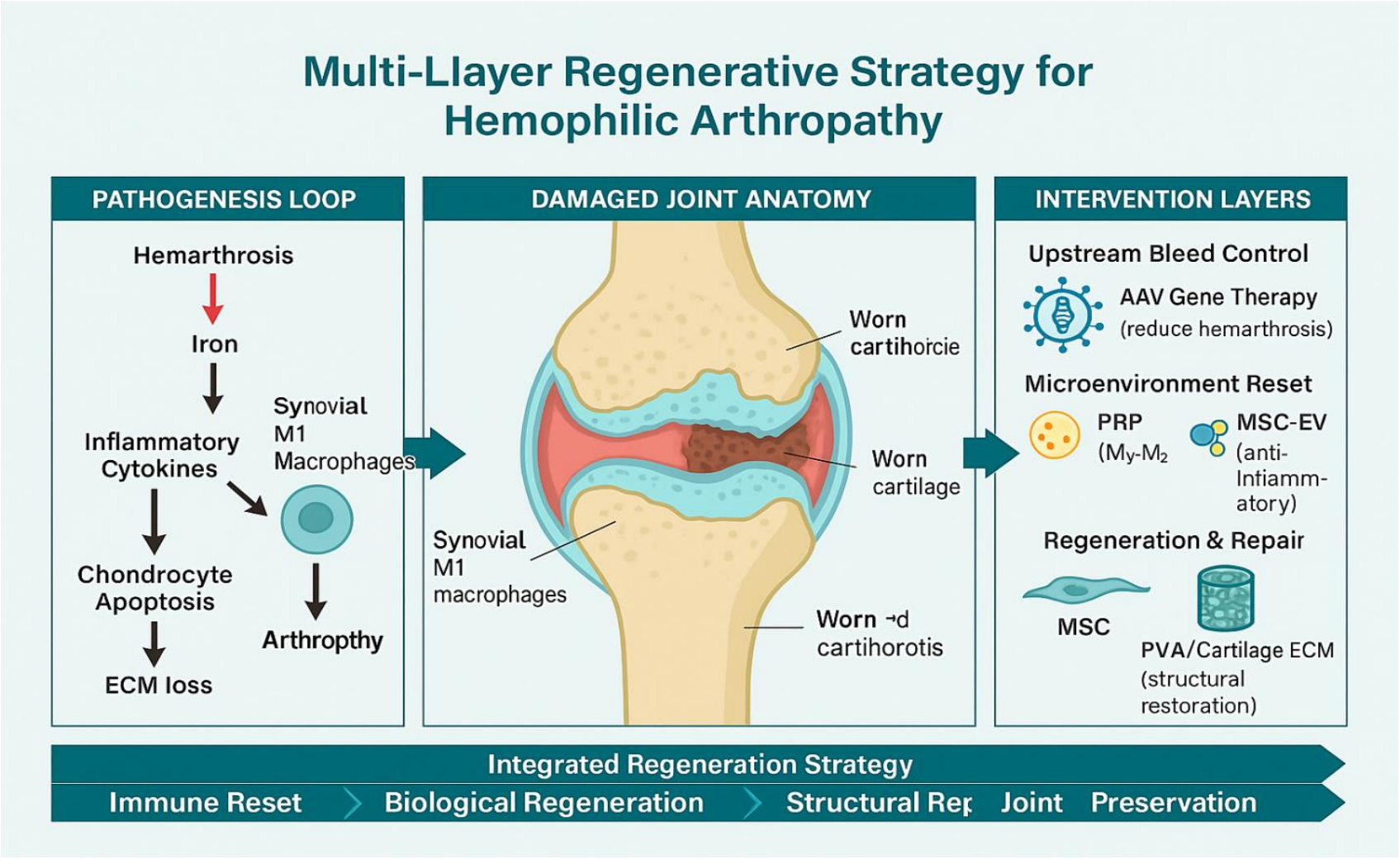


Right knee X-ray image at baseline and 1 year post-injection.

Agri 2025;37(1):62–65

Number of Patients (Joints)	Type / Grade of Arthropathy	MSC-Based Intervention Design	Main Clinical Outcome	Short Reference
1 patient (knee)	Hemophilia B; grade 4 hemophilic knee arthrosis	**1. Intra-articular injection of adipose-derived SVF**	**1. Significant pain reduction (WOMAC)** **2. Improved walking performance (6MWD)** **3. Improved MOCART scores on MRI at 1-year follow-up**	Güner D. Agri. 2025;37(1):62–65. PMID: 40767157

Multi-Modal Regenerative Strategy



Chronological list of studies regarding the application of SVF, PRP and MSCs in patients with knee OA.

Type of therapy	Publication Year	Study type	Patient population	Study design	Follow-up	Outcome
SVF therapy	2011	Case-series	3 women 1 man	ADSC HA PRP Calcium chloride	3 months	Positive changes in MRI; Improvements in pain, physical therapy outcomes and functional status
	2012	Therapeutic case-control level III	25	SVF + PRP	12 months	Improved Lysholm, Tegner and VAS scores; no adverse side effects
	2013	Case-series	18	SVF + PRP	24.3 months	Improved WOMAC, Lysholm, VAS and whole-organ MRI scores
	2013	Retrospective cohort study	91	SVF + PRP	26.62 ± 0.32 months	SVF is safe; no tumor formation; self-limited tendonitis and swelling
	2014	Case-series	21	SVF + PRP	8.5 months	Improved joint function; Decreased pain score; Increased Lysholm score; Improved MRI findings; No serious side effects
	2015	Comparative study	30	SVF	3, 12, 24 months	Improved clinical outcomes after 2-year follow-up
	2015	Case-series	30	SVF + PRP	24 months	Improved clinical results and cartilage status under second-look arthroscopic analysis
	2015	Multi-center case-control study	1114	SVF	17.2 months	Improved pain score and functional status
	2016	Case report	3	SVF + PRP + HA + ECM	3.5 months	Improved FRI, ROM and VAS
	2016	Case report	6	SVF	12 months	Improved pain, functional status; no MRI evidence of cartilage regeneration
	2017	Clinical trial	10	SVF + PRP	3 months	Reduced WOMAC score; Improved cartilage thickness; safety of treatment

SVF: stromal vascular fraction; PRP: platelet-rich plasma; HA: hyaluronic acid; MRI: magnetic resonance imaging; VAS: visual analog scale; ECM: extracellular matrix; MSC: mesenchymal stem cell; ADSC: adipose-derived stem cell; WOMAC: Western Ontario and McMaster Universities osteoarthritis; FRI: functional rating index; ROM: range of motion; BM: bone-marrow; MP: methyl prednisone.

ARTIFICIAL CELLS, NANOMEDICINE, AND BIOTECHNOLOGY 2019, VOL. 47, NO. 1, 882–890

Future Directions

- **RCT design**
- **Multi Modal Strategy**
- **Precision Immune Profiling:**
  - Single-cell RNA seq & special profiling of synovial macrophages and fibroblasts
- **Smart Sustained-Release Scaffolds:**
  - PVA/ECM scaffolds embedded with MSC-EVs for controlled local delivery

THANKS

Any questions?

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