International Journal of Pharmacology

Int. J. Pharmacol. **2025**; 21(8): 47419
https://doi.org/10.31083/IJP47419

Review

Pharmacology of Induced Artificial Platelets in Regenerative Medicine: Beyond Transfusion

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Academic Editor: Mehmet Ozaslan
Submitted: 16 October 2025 Revised: 7 November 2025 Accepted: 20 November 2025 Published: 19 December 2025

Abstract

Platelet-rich plasma has emerged as a widely used regenerative therapy across multiple medical specialties, yet fundamental quality-control and standardization challenges have limited the associated clinical evidence base. Induced pluripotent stem cell-derived artificial platelets represent a next-generation approach that addresses these limitations through standardized, scalable manufacturing under good manufacturing practice conditions. This review examines the pharmacological properties of induced pluripotent stem cell (iPSC)-derived artificial platelets, with an emphasis on the associated pharmacokinetics, pharmacodynamics, and safety profiles in regenerative medicine applications. Unlike donor-derived platelet concentrates, which exhibit substantial batch-to-batch variability in platelet counts, leukocyte content, and growth factor concentrations, iPSC-derived platforms enable precise control over product composition and functional characteristics. Moreover, preclinical studies have demonstrated therapeutic efficacy in osteoarthritis models by modulating anabolic and catabolic pathways, with emerging clinical data supporting acceptable safety profiles. The transition from transfusion-focused applications to regenerative medicine represents a paradigm shift in artificial platelet development, requiring novel pharmacological characterization frameworks distinct from traditional hematology endpoints. Therefore, manufacturing standardization, quantifiable pharmacokinetic parameters, and reproducible pharmacodynamic effects position iPSC-derived artificial platelets as promising candidates for regenerative applications, where current platelet-rich plasma therapies often yield inconsistent outcomes.

Keywords: induced pluripotent stem cells; blood platelets, artificial; regenerative medicine; pharmacokinetics; platelet-rich plasma

1. Introduction

Platelet-based therapeutics have transitioned from their historical role in hemostasis to become prominent interventions in regenerative medicine, driven by the recognition that platelets serve as rich reservoirs of bioactive molecules essential for tissue repair processes [1]. Platelet-rich plasma (PRP), defined as autologous blood plasma containing platelet concentrations exceeding baseline levels, has been adopted across orthopedics, dermatology, dentistry, and wound care based on the biological rationale that concentrated delivery of platelet-derived growth factors (PDGF), cytokines, and chemokines can accelerate healing cascades [1,2]. The alpha granules within platelets contain over 300 bioactive proteins, including platelet-derived growth factor, transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF), which collectively orchestrate cellular proliferation, angiogenesis, matrix synthesis, and immunomodulation [3].

Despite widespread clinical adoption, PRP therapies face fundamental challenges that compromise their therapeutic reliability and impede evidence-based clinical practice. Preparation protocols exhibit extraordinary heterogeneity across centrifugation parameters, anticoagulant selection, activation methods, and leukocyte inclusion criteria, resulting in final products with vastly different cellular and biochemical compositions [4–6]. This variability extends to inter-individual differences in baseline platelet function, with donor age, health status, medication use, and circadian rhythms significantly influencing the regenerative capacity of harvested platelets [6]. Systematic reviews consistently identify inadequate reporting of preparation details, platelet concentrations, and quality control measures in clinical trials, preventing meaningful cross-study comparisons and contributing to conflicting efficacy conclusions [7,8].

The advent of induced pluripotent stem cell technology has enabled development of artificial platelet platforms that circumvent donor dependency and intrinsic variability limitations [9]. Induced pluripotent stem cell (iPSC)-derived megakaryocytes can be expanded as immortalized cell lines through targeted transgene expression, creating renewable master cell banks capable of producing platelets under controlled conditions [10]. These engineered platforms offer standardized product attributes including defined platelet counts, reproducible growth factor content,

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and consistent functional characteristics across production batches. Furthermore, genetic manipulation capabilities allow for optimization of regenerative properties beyond what natural platelets achieve, including enhanced growth factor expression or extended circulation profiles [4].

The pharmacological characterization of iPSC-derived artificial platelets for regenerative applications requires frameworks distinct from traditional transfusion medicine endpoints. Rather than focusing solely on corrected count increments and hemostatic competence, regenerative pharmacology must assess biodistribution to target tissues, growth factor release kinetics, paracrine signaling effects on resident cell populations, and duration of biological activity following local administration. Initial clinical translation has focused on transfusion applications, with the landmark iPLAT1 (first-in-human clinical trial of iPSC-derived platelets as a phase 1 autologous transfusion) trial demonstrating safety of autologous iPSC-derived platelets in a patient with alloimmune transfusion refractoriness [11]. However, the regenerative medicine space represents a fundamentally different clinical context with distinct pharmacological requirements and regulatory considerations.

This review examines the pharmacological properties of iPSC-derived artificial platelets with emphasis on regenerative medicine applications, particularly osteoarthritis treatment where PRP evidence remains controversial. We analyze the quality control and standardization crisis affecting current PRP therapies, describe the fundamental manufacturing approaches for iPSC-derived platforms, characterize their pharmacokinetic and pharmacodynamic properties, review safety profiles from preclinical and early clinical studies, and discuss the developmental pathway exemplified by emerging clinical programs. The evidence synthesis reveals that standardized, characterizable artificial platelet products may address key limitations that have prevented PRP from achieving regulatory approval as defined pharmacological entities.

2. Platelet-Rich Plasma: Clinical Applications and Fundamental Limitations

Platelet-rich plasma has been investigated across numerous medical specialties based on the hypothesis that concentrated autologous growth factors can enhance tissue repair without the immunological complications associated with allogeneic biologics. Table 1 (Ref. [2,5,6,12–20]) summarizes the major clinical application areas, current evidence quality, key challenges encountered with conventional PRP, and potential advantages offered by standardized artificial platelet platforms.

In osteoarthritis (OA), which represents one of the most extensively studied PRP applications, meta-analyses reveal conflicting conclusions that reflect underlying heterogeneity in study design and product characteristics [5,12]. While some systematic reviews report modest improvements in pain and function scores compared to hyaluronic acid or placebo at six to twelve months, others demonstrate no significant differences or inconsistent effects across studies [13,21]. The RESTORE trial, a rigorously designed placebo-controlled study, found no significant benefit of PRP over saline injection for knee osteoarthritis at twelve months, directly challenging the treatment's efficacy assumptions [14]. This inconsistency extends across osteoarthritis severity grades, with early-stage disease potentially showing better responses but lacking definitive evidence for disease modification versus symptomatic relief [22].

The fundamental issue underlying PRP's inconsistent evidence base centers on preparation heterogeneity and insufficient product characterization. A systematic review of orthopedic clinical trials found that the majority failed to report basic parameters including platelet concentration, leukocyte content, activation status, or preparation protocol details sufficient for replication [7]. When reported, platelet concentrations ranged from 1.5-fold to over 9-fold increases above baseline, with some studies inadvertently creating platelet-poor preparations due to suboptimal centrifugation protocols [2]. Leukocyte content represents another critical variable, as these cells contribute pro-inflammatory mediators that may counteract regenerative effects in certain tissue environments, yet leukocyte-rich versus leukocyte-poor formulations show inconsistent comparative outcomes [23,24].

Growth factor quantification further illustrates the standardization problem. Studies measuring Platelet-Derived Growth Factor AB (PDGF-AB), TGF-β1, VEGF, and other key mediators in PRP preparations reveal enormous inter-individual variation, with coefficients of variation often exceeding 50% for specific factors [25,26]. This biological variability reflects donor-specific factors including age-related declines in platelet function, metabolic conditions affecting growth factor synthesis, and circadian rhythms influencing platelet activation status [27,28]. Activation methods also profoundly influence release kinetics, with calcium chloride, thrombin, collagen, or freeze-thaw cycles producing different temporal profiles of growth factor availability [29,30].

Temporal stability represents an additional challenge rarely addressed in clinical protocols. Growth factors released from activated platelets undergo rapid degradation, with half-lives ranging from minutes to hours depending on the specific protein and tissue environment [31]. Single-injection protocols therefore deliver a bolus of growth factors with limited sustained exposure, while multi-injection series increase variability by repeating preparation steps with potentially different outcomes each time. The lack of validated biomarkers for PRP potency compounds this issue, as clinicians cannot prospectively identify which preparations will prove therapeutically effective for individual patients.

Table 1. Clinical applications of platelet-rich plasma and potential advantages of artificial platelets.

Application area	Current PRP use and evidence quality	Key limitations of autologous PRP	Potential advantages of iPSC-derived artificial platelets	References
Knee osteoarthritis	Widely used off-label; conflicting evidence from meta-analyses showing modest benefit over HA at 6–12 months but inconsistent across studies; placebo-controlled trials show mixed results	Variable platelet concentrations (1.5–9× baseline); donor-dependent growth factor content varies >50% CV; lack of standardized protocols; inconsistent activation methods; rapid clearance requiring repeated injections	Standardized platelet counts and growth factor content across batches; reproducible manufacturing under GMP; quantifiable product specifications; potential for sustained-release formulations; lot-to-lot consistency enabling dose-response studies	[5,12–14]
Tendinopathy (rotator cuff, achilles, patellar)	Limited evidence of benefit over placebo; some studies show improvement at 3–6 months but not maintained long-term; heterogeneous study quality	Preparation variability affecting growth factor content; leukocyte inclusion inconsistently applied; optimal dosing undefined; inter-individual response variability	Defined growth factor profiles optimized for tendon healing; elimination of pro-inflammatory leukocytes if desired; standardized dosing enabling pharmacokinetic studies; reproducible composition for controlled trials	[15,16]
Wound healing (diabetic ulcers, chronic wounds)	Meta-analyses show improved healing rates and reduced healing time compared to conventional treatment; positive effects on venous and diabetic ulcers	Variable platelet activation affecting growth factor release; single-treatment bolus with limited sustained exposure; preparation sterility concerns in clinical settings	Pathogen-free manufacture eliminating contamination risk; potential controlled-release formulations prolonging growth factor exposure; standardized bioactive content; lyophilized formats enabling convenient application	[17,18]
Dental and maxillofacial surgery	Used for socket preservation, periodontal regeneration, implant procedures; studies show enhanced soft tissue healing and variable effects on bone regeneration	Inconsistent bone regeneration outcomes; preparation protocol heterogeneity; unclear optimal timing and dosing	Standardized osteogenic factor content; reproducible product composition; potential combination with bone scaffolds; quality-controlled manufacturing	[18,19]
Aesthetic dermatology (skin rejuvenation, hair restoration)	Increasingly popular for facial rejuvenation and androgenic alopecia; limited high-quality evidence but growing clinical use	Preparation technique significantly affects outcomes; optimal activation protocol unclear; patient-to-patient variability in response	Consistent growth factor concentrations; reproducible treatment protocols; potential for lyophilized formulations; standardized product specifications	[2,6]
Orthopedic surgery augmentation	Used to enhance bone graft healing, spinal fusion, fracture repair; evidence quality variable across applications	Donor-dependent healing capacity; inconsistent growth factor concentrations; variable platelet viability; preparation complexity in OR settings	Off-the-shelf availability; consistent bioactive content; GMP manufacturing quality; pathogen-free assurance	[20]

CV, coefficient of variation; GMP, good manufacturing practice; HA, hyaluronic acid; iPSC, induced pluripotent stem cell; OR, operating room; PRP, platelet-rich plasma.

Regulatory frameworks have responded to these quality concerns with caution. The United States Food and Drug Administration classifies autologous PRP as minimally manipulated tissue products exempt from biologics licensing when prepared by approved devices and administered during the same surgical procedure, but this regulatory flexibility comes with limited oversight of preparation standardization or outcome tracking [32]. The European Medicines Agency similarly treats autologous PRP as substantial manipulation requiring compliance with tissue engineering regulations, though enforcement varies across member states [33]. Neither framework addresses the fundamental scientific question of whether PRP represents a reproducible pharmacological entity with definable dose-response relationships and predictable clinical effects.

Professional society guidelines reflect this evidence uncertainty. The American Academy of Orthopaedic Surgeons assigned an "inconclusive" recommendation for PRP in knee osteoarthritis due to insufficient evidence quality and heterogeneous study results [34]. The Osteoarthritis Research Society International systematically reviewed PRP evidence and noted significant limitations including inadequate control groups, inconsistent preparation methods, and publication bias favoring positive results [35]. These organizations call for standardized reporting, rigorous placebo-controlled trials, and better product characterization before PRP can be recommended as evidence-based therapy.

The standardization crisis extends beyond osteoarthritis to all PRP application areas. In tendinopathy, systematic reviews demonstrate similar heterogeneity with some studies showing benefit while others fail to exceed placebo effects [15,16]. Wound healing applications report positive outcomes but lack standardized protocols for concentration, volume, or frequency of application [17]. Dental and maxillofacial surgery studies show promise for bone regeneration but with inadequate mechanistic understanding of dose-effect relationships [18]. This pattern of promising biological rationale undermined by inconsistent clinical evidence pervades the PRP literature across medical specialties.

Artificial platelet platforms derived from iPSCs offer potential solutions to these standardization challenges through manufacturing control and product consistency (Table 1). Unlike autologous preparations subject to donor variability, iPSC-derived platelets can be produced from characterized cell banks with reproducible cellular composition, growth factor content, and functional properties [10,36]. Quality control testing can quantify relevant biomarkers for each production batch, enabling lot-to-lot consistency monitoring. Cryopreservation and lyophilization approaches may extend product stability beyond the brief viability window of fresh PRP [37]. Most fundamentally, standardized products enable rigorous pharmacological characterization including dose-response relationships, pharmacokinetic parameters, and mechanism-based biomarkers that PRP's inherent variability precludes.

3. iPSC-Derived Artificial Platelets: Manufacturing Fundamentals

Cost considerations represent critical determinants of clinical viability, with current iPSC-derived cell therapy production costs approaching $1 million per dose for autologous products, though aggressive cost-reduction targets aim to decrease manufacturing costs to $30,000 per dose through automation and off-the-shelf allogeneic approaches [38]. The industry is actively pursuing "off-the-shelf" manufacturing strategies using Human Leukocyte Antigen (HLA)-homozygous or HLA-deficient iPSC lines to eliminate patient-specific production requirements, thereby enabling economy-of-scale production and inventory-based distribution models that substantially reduce per-dose costs [39,40]. Specialized bioreactor systems and 30-day production timelines require substantial capital investment, though standardized master cell bank approaches facilitate large-scale manufacturing once initial infrastructure is established [41].

The manufacturing of iPSC-derived artificial platelets for regenerative applications builds upon differentiation protocols developed initially for transfusion medicine but requires adaptation for scale, cost-effectiveness, and product specifications relevant to tissue repair rather than hemostasis. The fundamental process involves reprogramming somatic cells to pluripotency, directing differentiation through hematopoietic specification toward megakaryocyte lineages, and inducing platelet release through biophysical or biochemical stimulation [4,10].

iPSC generation typically employs integration-free reprogramming methods using Sendai virus or episomal vectors expressing Octamer-binding transcription factor 3/4 (OCT3/4), SRY (sex determining region Y)-box 2 (SOX2), Krüppel-like factor 4 (KLF4), and cellular Myelocytomatosis oncogene (c-MYC) to minimize genomic integration risks relevant for clinical products [42,43]. Master cell banks are established under good manufacturing practice conditions with extensive characterization including genomic integrity, pluripotency marker expression, differentiation capacity, and absence of adventitious agents [44]. For regenerative medicine applications where complete pathogen-free assurance is critical, xeno-free culture conditions eliminate animal-derived components that could introduce prions, viruses, or immunogenic proteins [45].

Megakaryocyte differentiation from iPSCs proceeds through hematopoietic progenitor intermediates, though multiple protocol variations achieve this goal through different lineage paths [9,46]. Protocols typically employ sequential cytokine exposures including stem cell factor (SCF), thrombopoietin (TPO), interleukin-3 (IL-3), IL-6, and IL-9 to drive hemogenic endothelium formation, emergence of Cluster of Differentiation 34 (CD34)-positive

hematopoietic progenitors, and megakaryocyte specification marked by CD41a and CD42b expression. Direct programming approaches overexpressing transcription factors including *GATA1*, *FLI1*, and *TAL1* can accelerate differentiation kinetics and improve megakaryocyte yields [4].

The critical innovation enabling scalable production involves establishment of immortalized megakaryocyte progenitor cell lines through controlled transgene expression [10]. Sequential introduction of c-MYC and BMI1 followed by B-cell lymphoma-extra large (Bcl-xL) under doxycycline-inducible promoters generates self-renewing megakaryocyte progenitors that can be expanded extensively while retaining platelet production capacity upon transgene withdrawal [10,47]. This approach creates renewable master cell banks analogous to those used in monoclonal antibody manufacturing, providing lot-to-lot consistency and eliminating the need to re-differentiate from iPSCs for each production batch. The immortalized cell lines can be cryopreserved and thawed on demand, facilitating manufacturing flexibility and inventory management.

Platelet production from megakaryocytes requires recapitulation of thrombopoiesis conditions that naturally occur in bone marrow sinusoidal vessels. Ito *et al*. [36] demonstrated through intravital microscopy that turbulent flow rather than laminar shear stress drives efficient platelet release, identifying specific turbulent energy and shear stress parameters necessary for optimal production. This discovery enabled development of large-scale bioreactor systems that generate clinical-scale platelet quantities approaching 10^{11} cells per batch through controlled turbulence rather than microfluidic or membrane-based approaches [36]. The bioreactor systems support production of soluble factors including Macrophage Migration Inhibitory Factor (MIF), Insulin-like Growth Factor Binding Protein 2 (IGFBP2), and N-arginine dibasic convertase (NRDC) that autonomously enhance platelet release, creating a self-augmenting production environment.

Several protocol adaptations optimize iPSC-derived artificial platelets specifically for regenerative applications versus transfusion. Growth factor content can be enhanced through controlled activation protocols or by engineering megakaryocyte cell lines to overexpress specific factors including PDGF, TGF-β, or VEGF [48]. Lyophilization approaches extend shelf life and enable distribution without cold chain requirements, critical for regenerative medicine where immediate availability is less pressing than for emergency transfusion [37]. Product formulations can incorporate excipients that enhance stability or prolong growth factor release kinetics following injection into target tissues.

4. Pharmacokinetics

The pharmacokinetic properties of iPSC-derived artificial platelets differ substantially from traditional small molecule or protein therapeutics, requiring adapted analytical approaches that account for cellular biodistribution, particle clearance mechanisms, and functional persistence distinct from molecular half-life. Initial characterization has focused primarily on systemic circulation following intravenous administration for transfusion applications, but local tissue kinetics following intra-articular or subcutaneous injection represent critical parameters for regenerative medicine applications.

Following intravenous administration in preclinical models, iPSC-derived artificial platelets demonstrate circulation kinetics that partially resemble but do not precisely match donor-derived platelets [11,47]. In mouse models, human iPSC-derived platelets achieve detectable circulating levels within one hour post-transfusion and persist for several hours, though quantitative recovery typically remains lower than would be expected for equivalent numbers of donor platelets [47]. The first-in-human iPLAT1 trial observed larger-sized platelets in circulation at two to six hours post-transfusion, suggesting delayed peak kinetics compared to the one-hour maximum typically seen with conventional platelet products [11]. Transient d-dimer elevations suggested some degree of platelet activation or clearance occurred during the early post-transfusion period, though no clinical thromboembolic events were observed [11].

Biodistribution studies following megakaryocyte infusion reveal preferential pulmonary localization with subsequent platelet release into systemic circulation [47,49]. This pattern suggests that mature megakaryocytes become trapped in pulmonary capillary beds where they undergo thrombopoiesis, though megakaryocytes themselves do not persist in lung tissue beyond initial distribution phases. Systematic tissue surveys at extended timepoints demonstrated absence of megakaryocytes in heart, spleen, bone marrow, and other organs, indicating that systemic biodistribution is limited and that cellular sequestration does not occur [47]. This favorable biodistribution profile alleviates tumorigenicity concerns that might arise from transplantation of immortalized cell lines.

Local administration kinetics relevant to regenerative applications remain incompletely characterized. Following intra-articular injection for osteoarthritis treatment, conventional PRP platelets undergo rapid clearance from synovial fluid with half-lives estimated at 12–24 hours based on radiolabeling studies [50]. Lymphatic drainage and synovial membrane uptake likely contribute to platelet removal from the joint space. Growth factors released from activated platelets diffuse through synovial fluid and may bind to extracellular matrix components, creating localized concentration gradients that persist longer than the platelets themselves. Whether iPSC-derived artificial platelets exhibit similar or distinct local kinetics requires direct investigation, as size differences, membrane composition variations, or activation state could influence retention time and clearance pathways.

Table 2. Pharmacokinetic properties: donor-derived platelets versus iPSC-derived artificial platelets.

Parameter	Donor-derived platelets	iPSC-derived artificial platelets	Clinical implications	References
Systemic circulation (IV administration)				
Initial detection time	Immediate detection post-transfusion	Detectable within 1 hour; potentially delayed peak at 2–6 hours	Differences may reflect size variations or activation state	[11,47]
Circulation half-life	3–5 days in healthy recipients	Incompletely characterized; flow cytometry suggests presence up to 7 hours; quantitative kinetics unclear	Limited circulation data; monitoring methods may fail to detect larger iPSC-platelets	[11]
Corrected count increment (1 h)	7000–13,000/μL per 10^{11} platelets transfused	Near-zero increment in iPLAT1 trial despite detectable platelets by flow cytometry	Suggests differences in circulation efficiency or analytical detection challenges	[11]
Biodistribution				
Primary localization	Circulating blood; margination to vascular endothelium	Initial circulation followed by distribution to lung, liver, spleen by imaging	Broader tissue distribution may influence regenerative applications	[11]
Pulmonary sequestration	Minimal for platelets; megakaryocytes show lung trapping	Megakaryocytes show predominant lung localization; platelets show systemic distribution	Megakaryocyte-based therapies differ from platelet product kinetics	[47,49]
Persistence in organs	Transient contact with vascular beds; no parenchymal persistence	No detection of megakaryocytes in heart, lung, spleen, or bone marrow at 14 days	Absence of cellular persistence reduces tumorigenicity concerns	[47]
Local administration (intra-articular)				
Joint space retention	12–24 hours estimated from radiolabeling studies (limited data)	No systematic characterization published	Critical parameter for regenerative efficacy; requires investigation	[50]
Synovial clearance	Lymphatic drainage and synovial membrane uptake	Presumed similar but uncharacterized	Local kinetics may differ based on size or surface properties	[50]
Clearance mechanisms				
Primary clearance pathway	Hepatic and splenic macrophages recognizing desialylated or senescent markers	Presumed similar mechanisms; direct characterization lacking	Understanding clearance may enable engineered extended circulation	[51,52]
Desialylation rate	Progressive β-galactose exposure over days triggering hepatocyte recognition	Unknown whether sialylation patterns differ from native platelets	Glycan structure differences could alter circulation time	[53]
Activation-dependent clearance	PS exposure and complement deposition accelerate removal	Activation state monitoring in vivo incomplete	Unintended activation reduces functional persistence	[51]

h, hour; iPSC, induced pluripotent stem cell; IV, intravenous; PS, phosphatidylserine.

Clearance mechanisms for iPSC-derived artificial platelets likely involve similar pathways described for native platelets, predominantly through hepatic and splenic macrophage recognition of senescent or activated platelet markers [51]. Platelets undergo progressive desialylation during circulation, exposing β-galactose and N-acetylglucosamine residues that serve as ligands for hepatocyte asialoglycoprotein receptors and macrophage galactose-type lectin, triggering rapid clearance [52,53]. The rate of desialylation may differ between iPSC-derived and donor platelets depending on sialyltransferase expression and glycan structure, though direct comparisons are limited. Activation-dependent clearance through phosphatidylserine (PS) exposure and complement deposition represents additional pathways that could differ between natural and artificial platelets.

Table 2 (Ref. [11,47,49–53]) summarizes available pharmacokinetic data comparing iPSC-derived artificial platelets with native donor-derived platelets, emphasizing that substantial knowledge gaps remain, particularly for local administration routes and biodistribution to non-vascular tissues relevant for regenerative applications.

5. Pharmacodynamics in Regenerative Applications

The pharmacodynamic effects of iPSC-derived artificial platelets in regenerative medicine applications derive from coordinated delivery of growth factors, cytokines, chemokines, and microRNAs that modulate cellular behaviors including proliferation, migration, differentiation, and matrix synthesis [54,55]. Unlike targeted biologics that engage specific receptor pathways, artificial platelets provide complex, polypharmacological stimulation that recapitulates aspects of normal wound healing cascades. Understanding the mechanisms through which concentrated platelets influence tissue repair requires analysis at multiple biological scales from molecular receptor engagement to tissue-level remodeling outcomes.

At the molecular level, key platelet-derived growth factors including PDGF, TGF-β, VEGF, fibroblast growth factor (FGF), Epidermal Growth Factor (EGF), and IGF-1 engage cognate receptors on target cell populations including chondrocytes, synoviocytes, osteoblasts, and mesenchymal stem cells present in injured tissues [1,56]. Platelet-Derived Growth Factor-BB (PDGF-BB) activates Platelet-Derived Growth Factor Receptor-beta (PDGFR-β) on mesenchymal cells, driving chemotaxis, proliferation, and matrix synthesis through PI3K/ Protein Kinase B (AKT) and MAPK/ERK signaling cascades [57]. TGF-β family members signal through SMA (Small worm phenotype) MAD (Mothers Against Decapentaplegic 2/3 (SMAD2/3) phosphorylation to promote chondrogenic differentiation and collagen type II expression while suppressing matrix metalloproteinase production [58]. VEGF stimulates angiogenesis through Vascular endothelial growth factor receptor 2 (VEGFR2) activation on endothelial cells, though excessive angiogenesis may prove deleterious in avascular tissues like articular cartilage [59]. IGF-1 enhances chondrocyte anabolic activity and inhibits apoptosis through IGF-1R engagement, complementing TGF-β effects [60].

The temporal coordination of growth factor signaling contributes critically to regenerative outcomes but remains incompletely controlled in current platelet-based therapies. Alpha granules contain pre-packaged growth factors released rapidly following platelet activation, creating high local concentrations that decline as factors diffuse away or undergo proteolytic degradation [54]. First-phase release occurs within minutes, while continued platelet activation may sustain factor release for several hours. Synthetic delivery systems that control release kinetics achieve superior tissue engineering outcomes compared to bolus growth factor administration, suggesting that artificial platelets incorporating sustained-release mechanisms could enhance regenerative efficacy [61].

Cytokine and chemokine content within platelets modulates inflammatory environments in ways that can promote or inhibit regeneration depending on context. IL-1β, Tumor necrosis factor-α (TNF-α), and IL-6 contribute to inflammatory cascades, while IL-4, IL-10, and IL-13 provide anti-inflammatory signals [62]. The balance between pro-inflammatory and regulatory mediators influences macrophage polarization toward M1 or M2 phenotypes, which exhibit distinct effects on tissue repair [63]. Leukocyte content in PRP preparations further modulates inflammatory profiles, though optimal leukocyte inclusion remains debated across different tissue contexts [23,24]. iPSC-derived artificial platelets enable control over inflammatory mediator content through cell line engineering or selective activation protocols.

Osteoarthritis represents a complex degenerative disease intrinsically linked to aging processes, necessitating concurrent investigation of senescence mechanisms, inflammatory aging (inflammaging), and age-related regenerative capacity decline alongside traditional cartilage pathology [40]. Pharmaceutical interventions targeting individual pathways have demonstrated limited efficacy in modifying disease progression, as OA pathogenesis involves multifactorial degradation of cartilage, subchondral bone remodeling, synovial inflammation, and biomechanical dysfunction that resist single-target therapeutic approaches [64]. Regenerative medicine strategies employing growth factor-rich biologics offer promise for addressing this therapeutic gap, yet definitive mechanistic frameworks delineating dominant pathway hierarchies, synergistic interactions, or antagonistic effects among PDGF, TGF-β, VEGF, and other mediators in osteoarthritic tissue microenvironments remain incompletely established, requiring systematic investigation across disease stages and patient phenotypes.

Table 3. Preclinical efficacy studies of iPSC-derived artificial platelets in regenerative applications.

Study model	Intervention details	Key findings	Mechanisms identified	References
IL-1β-damaged chondrocytes (*in vitro* OA model)	i-aPLP treatment of redifferentiated chondrocytes in alginate beads following IL-1β exposure	Increased mRNA expression of anabolic factors (aggrecan, collagen type II, SOX9); decreased catabolic enzymes (MMP1, MMP3, ADAMTS5); reduced inflammatory cytokines (IL-6, IL-8, IL-1β)	Shift from catabolic to anabolic balance; inhibition of NF-κB phosphorylation; increased ACAN and SOX9 protein expression; decreased MMP1 and MMP3	[40]
ACLT-induced rat OA model	Intra-articular administration of i-aPLP 8 weeks post-ACLT surgery	Improved weight-bearing on affected limb; enhanced proteoglycan content by safranin-O staining; reduced cartilage surface degradation; improved structural parameters	Disease-modifying effects in established OA; functional improvement and pain reduction; cartilage preservation	[40]
DMM-induced mouse OA model	Intra-articular administration of i-aPLP following DMM surgery	Similar improvements in cartilage structure and proteoglycan content; functional improvement	Reproducibility across species and OA induction methods; therapeutic window in chronic disease	[40]
Murine full-thickness wound model	Topical application of freeze-dried iPSC-derived megakaryocytes and platelets (iMPs)	Accelerated wound closure; enhanced angiogenesis; superior healing compared to autologous PRP	Growth factor content including FGF2 (absent in PRP); activation of vascular endothelial cells; promotion of neovascularization	[65]
Rat vertebral bone defect model	Freeze-dried iPSC-derived megakaryocytes and platelets combined with artificial bone material	Increased bone volume and density at 4 and 8 weeks; improved osteoid formation and mineralization	Osteogenic promotion through growth factor delivery; enhanced bone remodeling processes	[37]
Thrombocytopenic rabbit model (hemostasis)	IV transfusion of iPSC-derived platelets	Stable circulation 2–7 hours; 100% success in hemostasis tests; systemic distribution to lung, liver, spleen	Functional hemostatic competence; appropriate biodistribution patterns	[11]
HLA-sensitized mouse model	Transfusion of HLA-silenced iPSC-derived platelets into anti-HLA antibody-treated mice	No significant difference in platelet levels between treated and untreated mice; HLA-silenced platelets evade antibody-mediated clearance	Immune evasion through HLA class I knockdown enabling allogeneic use	[47]

ACLT, anterior cruciate ligament transection; DMM, destabilization of medial meniscus; FGF2, fibroblast growth factor 2; HLA, human leukocyte antigen; i-aPLP, induced artificial platelet-like particle; IL, interleukin; iMPs, iPSC-derived megakaryocytes and platelets; iPSC, induced pluripotent stem cell; IV, intravenous; MMP, matrix metalloproteinase; OA, osteoarthritis; PRP, platelet-rich plasma; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ACAN, Aggrecan; SOX, Sex-determining Region Y (SRY)-box 9.

Preclinical studies in osteoarthritis models provide the most extensive evidence for regenerative pharmacodynamics of iPSC-derived artificial platelets. Jeon *et al.* [40], demonstrated that induced artificial platelet-like particle (i-aPLP) treatment modulates key pathways implicated in cartilage degeneration using both *in vitro* and *in vivo* models. In IL-1β-damaged chondrocytes cultured in alginate beads to maintain differentiated phenotype, i-aPLP treatment significantly increased mRNA expression of anabolic factors including aggrecan, type II collagen, and SOX9, while reducing expression of catabolic enzymes including matrix metalloproteinase 1 (MMP1), MMP3, and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5). Inflammatory cytokines IL-6, IL-8, and IL-1β showed corresponding decreases following i-aPLP treatment. Protein-level analysis confirmed increased Aggrecan (ACAN) and SOX9 expression alongside decreased MMP1 and MMP3, with reduced nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) phosphorylation suggesting anti-inflammatory mechanism of action. These molecular changes indicate that i-aPLP treatment shifts the balance from catabolic, inflammatory processes toward anabolic, regenerative programs at the cellular level.

In vivo osteoarthritis models induced by anterior cruciate ligament transection (ACLT) with or without destabilization of medial meniscus confirmed i-aPLP therapeutic activity through multiple outcome measures [40]. Intra-articular administration of i-aPLP eight weeks following surgical OA induction improved weight-bearing capacity on the affected limb, indicating functional improvement and pain reduction. Histological analysis demonstrated enhanced proteoglycan content in articular cartilage as measured by safranin-O staining, reduced cartilage surface degradation, and improved structural parameters. These findings suggest that i-aPLP treatment can modify disease progression in established osteoarthritis rather than serving purely as symptomatic therapy. The therapeutic window extending from injury through chronic disease stages supports potential clinical utility across the osteoarthritis severity spectrum.

Growth factor quantification in iPSC-derived artificial platelets reveals concentrations of key regenerative mediators including PDGF-BB, TGF-β, EGF, VEGF, FGF2, and IGF-1 [65]. The presence of FGF2, which is absent or minimally present in conventional PRP, represents a potential advantage of iPSC-derived products, as FGF2 demonstrates potent effects on wound healing and angiogenesis [65]. Comparative studies show that iPSC-derived megakaryocyte-platelet preparations promote superior wound healing and angiogenesis compared to autologous PRP in murine models, suggesting that optimized growth factor profiles may enhance therapeutic efficacy beyond what conventional preparations achieve [65].

Osteogenic applications provide additional pharmacodynamic evidence for iPSC-derived platelet preparations. Lyophilized iPSC-derived megakaryocytes and platelets applied to vertebral bone defects in rat models enhanced bone formation and accelerated healing compared to artificial bone material alone [37]. Micro-CT analysis demonstrated increased bone volume and density at four and eight weeks post-implantation. Histological examination revealed improved osteoid formation and mineralization in groups receiving freeze-dried artificial platelets. These results indicate that regenerative effects extend beyond soft tissue applications to include hard tissue repair, expanding potential clinical indications.

Table 3 (Ref. [11,37,40,47,65]) summarizes preclinical efficacy studies across different regenerative medicine applications, highlighting the diverse mechanistic pathways through which iPSC-derived artificial platelets influence tissue repair processes.

6. Safety Profile

The safety profile of iPSC-derived artificial platelets represents a critical consideration for clinical translation, encompassing multiple dimensions including tumorigenicity risks from immortalized cell lines, immunogenicity concerns related to allogeneic administration, thrombotic complications from platelet activation, and infectious disease transmission possibilities. Preclinical safety assessment programs and early clinical data provide initial characterization of these risk domains, though long-term surveillance data remain limited.

Tumorigenicity assessment focuses primarily on the potential for immortalized megakaryocyte progenitor cells used in manufacturing to exhibit oncogenic transformation or persistence following product administration. The immortalization strategy employing c-MYC, BMI1, and B-Cell Lymphoma-extra Large (BCL-XL) introduces known oncogenes, necessitating stringent demonstration that final platelet products contain no residual progenitor cells capable of proliferation or tumor formation [10]. Flow cytometric purity analysis confirms that iPSC-derived platelet preparations contain predominantly CD41a/CD42b-positive, nucleus-negative particles lacking markers of undifferentiated cells or megakaryocyte progenitors [36]. Extended biodistribution studies in immunodeficient mice detected no evidence of megakaryocyte persistence or proliferation in any examined organs including lung, liver, spleen, or bone marrow up to 14 days post-administration [47].

The anucleate nature of mature platelets provides inherent safety advantages regarding proliferative capacity and tumor formation potential. Unlike nucleated cell therapies where residual undifferentiated cells could undergo uncontrolled expansion, platelets lack genomic machinery for replication and undergo apoptotic clearance within days following release [51]. Manufacturing specifications including maximum allowable percentages of nucleated cells, megakaryocyte content, and residual progenitor markers es-

tablish quantifiable safety margins. Quality control testing employs multiple orthogonal assays including tumorigenicity assessment in immunodeficient mice, clonogenic assays to detect proliferative capacity, and molecular analysis of transgene expression to confirm proper transgene silencing [11].

Immunogenicity represents a complex consideration influenced by product source, HLA matching status, and local tissue environment following administration. Autologous iPSC-derived products eliminate allogeneic immune recognition but require patient-specific manufacturing with associated time and cost implications [11]. Allogeneic approaches using HLA-homozygous iPSC lines or HLA-deficient cell lines through beta-2-microglobulin (*B2M*) knockout enable off-the-shelf availability while managing immune rejection risks [47,66]. HLA class I silencing reduces antibody-mediated rejection and T cell recognition while raising concerns about natural killer (NK) cell-mediated clearance, though compensatory mechanisms including HLA-E expression or NK inhibitory ligands may mitigate this risk [67].

For regenerative medicine applications involving local administration to immunoprivileged sites like joint spaces, immunogenicity concerns may differ from systemic transfusion contexts. Intra-articular injection of allogeneic biologics generally elicits limited systemic immune responses due to relative isolation from lymphatic drainage, though exceptions occur with repeated administration or in inflammatory environments. The transient presence of injected platelets lasting days rather than weeks may provide insufficient exposure duration for robust alloimmunization, particularly if patients receive single or limited repeat doses. Clinical protocols monitoring anti-HLA antibody development following artificial platelet administration will clarify practical immunogenicity risks in regenerative applications.

Comprehensive risk assessment extends beyond tumorigenicity and immunogenicity to encompass thrombotic complications, inflammatory cascade amplification, and long-term tissue integration consequences. Thrombotic risk requires quantitative monitoring of d-dimer, thrombin-antithrombin complexes, and platelet activation markers to establish safety margins, while excessive inflammatory response potential necessitates evaluation of cytokine release kinetics and macrophage polarization across relevant dose ranges [68]. Flow cytometric purity specifications must be validated against tumorigenicity assay sensitivity, with regulatory frameworks emphasizing multi-layered safety evaluation through immunodeficient mouse studies, clonogenic assays, and molecular transgene silencing confirmation [69]. Long-term consequences including ectopic calcification, fibrosis, or altered tissue mechanical properties require extended follow-up with advanced imaging to detect delayed effects not apparent in standard toxicology studies [70].

Thrombotic complications represent a theoretical concern given the inherent prothrombotic activity of platelets and their role in pathological thrombosis. iPSC-derived artificial platelets demonstrate functional competence in aggregation assays responding to physiological agonists including adenosine diphosphate (ADP), collagen, and thrombin, confirming their hemostatic capability [11,36]. However, the risk of unintended thrombosis must be assessed, particularly following systemic administration or in patients with pre-existing prothrombotic conditions. The iPLAT1 trial observed transient d-dimer elevation following the highest dose transfusion, suggesting some platelet activation or consumption occurred, though no clinical thromboembolic events developed and coagulation markers spontaneously normalized [11]. Local intra-articular administration for osteoarthritis treatment would theoretically pose minimal systemic thrombotic risk due to limited systemic exposure and rapid local clearance.

Infectious disease safety represents a fundamental advantage of iPSC-derived products manufactured under xeno-free, pathogen-controlled conditions. Unlike donor-derived blood products that carry inherent risks of viral transmission including hepatitis, human immunodeficiency virus (HIV), and emerging pathogens, iPSC manufacturing from characterized cell banks under Good Manufacturing Practice (GMP) conditions eliminates biological exposure risks. Extensive adventitious agent testing including sterility, mycoplasma, endotoxin, and viral screening at multiple manufacturing stages ensures product safety. This controlled manufacturing environment represents a significant safety advantage over autologous PRP prepared in clinical settings where contamination risks exist despite aseptic technique.

Preclinical toxicology assessment following Good Laboratory Practice (GLP) standards provides systematic safety characterization across multiple species and dose levels. Single-dose toxicity studies establish maximum tolerated doses and identify target organ toxicities, while repeated-dose studies evaluate cumulative toxicity and potential for sensitization or delayed adverse effects. Comprehensive histopathological examination of major organs, clinical chemistry panels, hematology parameters, and immunological assessments characterize safety margins above proposed therapeutic doses.

The first-in-human iPLAT1 trial provides initial clinical safety data, though the specific context of transfusion medicine for thrombocytopenia differs from regenerative applications. Three sequential dose escalations up to 1×10^{11} iPSC-derived platelets were administered without serious adverse events, allergic reactions, or clinically significant laboratory abnormalities during 12-month follow-up [11]. Vital signs remained stable, and no opportunistic infections, malignancies, or other long-term complications emerged. While these results support basic safety feasibility, the single-patient autologous design limits generaliza-

Table 4. Safety profile summary of iPSC-derived artificial platelets.

Safety domain	Assessment approach	Key findings	Residual uncertainties	References
Tumorigenicity	*In vitro* clonogenic assays; *in vivo* tumorigenicity studies in immunodeficient mice; flow cytometric purity analysis	No proliferative capacity detected in final platelet products; no tumor formation observed in extended mouse studies up to 6 months; <0.001% nucleated cell contamination	Long-term surveillance data in humans lacking; safety margins for acceptable progenitor cell contamination undefined	[10,47]
Cellular persistence	Biodistribution studies with histological examination of organs; molecular detection of human cells	No megakaryocyte persistence detected in lung, liver, spleen, bone marrow at 1 and 14 days post-administration	Local tissue persistence following intra-articular administration uncharacterized	[47]
Immunogenicity (autologous)	Clinical monitoring for allergic reactions; anti-platelet antibody testing	No allergic reactions or immune-mediated adverse events in iPLAT1 trial; no anti-platelet antibodies detected	Single-patient experience limits generalizability; repeat-dose immunogenicity unknown	[11]
Immunogenicity (allogeneic)	Preclinical studies in HLA-sensitized mouse models; HLA class I silencing efficacy testing	HLA-silenced iPSC-derived platelets evade anti-HLA antibody-mediated clearance in mice; >82% reduction in HLA class I expression	NK cell-mediated clearance potential incompletely characterized; human allogeneic experience absent	[47,66]
Thrombotic risk	D-dimer monitoring; clinical surveillance for thromboembolism; *in vitro* aggregation assays	Transient d-dimer elevation at highest dose in iPLAT1 without clinical thrombosis; normal aggregation responses to physiological agonists	Thrombotic potential following local high-dose administration uncertain; interaction with prothrombotic conditions unexplored	[11]
Infectious disease transmission	GMP manufacturing under xeno-free conditions; adventitious agent testing (sterility, mycoplasma, viral screening)	Negative results for all tested pathogens across multiple production batches	Emerging pathogen detection relies on known assays; prion testing approaches for cell-derived products evolving	[10]
Target organ toxicity	Preclinical GLP toxicology studies (planned); comprehensive histopathology; clinical chemistry; hematology	Non-GLP single-dose studies showed no overt toxicity; systematic GLP studies in progress	Species-specific toxicity patterns may not predict human effects; local tissue toxicity following intra-articular administration requires evaluation	[41]
Clinical safety (human data)	iPLAT1 trial: single patient, autologous product, 3 dose escalations up to 1×10^{11} platelets	No serious adverse events; stable vital signs; no infections, malignancies, or long-term complications at 12 months	Limited to transfusion context; regenerative applications in different patient populations and anatomical sites require dedicated assessment	[11]

GLP, good laboratory practice; GMP, good manufacturing practice; HLA, human leukocyte antigen; iPSC, induced pluripotent stem cell; NK, natural killer.

bility, and regenerative applications require dedicated safety assessment in appropriate patient populations and anatomical sites.

Table 4 (Ref. [10,11,41,47,66]) summarizes available preclinical and clinical safety data across relevant safety domains, emphasizing that comprehensive long-term surveillance remains necessary to fully characterize the safety profile of iPSC-derived artificial platelets in regenerative medicine applications.

7. Comparative Analysis With Emerging Regenerative Therapies

iPSC-derived artificial platelets represent one approach among several emerging technologies addressing PRP limitations. Mesenchymal stem cell-derived exosomes (MSC-Exos) have demonstrated consistent therapeutic benefits in preclinical osteoarthritis models through coordinated upregulation of collagen type II and aggrecan alongside downregulation of IL-1β, MMP-13, and TNF-α [71]. MSC-Exos offer advantages including non-immunogenic profiles, non-tumorigenic character, and superior storage stability enabling ambient distribution, while growth factor content remains substantially lower and less diverse than the 300+ bioactive proteins in platelet granules [72]. Critical limitations include large-scale production challenges, batch standardization difficulties due to donor-dependent variability, and undefined regulatory pathways complicating clinical translation [73].

Gene-edited platelet platforms enable precise functional modifications including HLA class I-null variants for universal transfusability and growth factor overexpression to amplify regenerative capacity [74]. Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9 (CRISPR/Cas9) technology has successfully produced platelets expressing rare antigen variants and enhanced functional properties unattainable through natural systems [39]. However, gene editing introduces regulatory complexity requiring comprehensive genomic characterization, extensive safety evaluation including long-term tumorigenicity monitoring, and specialized manufacturing infrastructure beyond conventional iPSC-platelet production [69]. Public acceptance and ethical considerations surrounding genetic modification, while less pronounced for anucleate platelets, represent additional translational barriers.

Standard iPSC-derived artificial platelets without genetic modification offer reproducible, characterized products suitable for widespread regenerative applications where standardization represents primary advantage over autologous PRP. MSC-exosomes excel in applications requiring minimal immunogenicity and maximum storage stability, particularly for repeat-dose protocols. Gene-edited platelets suit specialized applications requiring unique functional properties, including universal donor products for immunized patients or enhanced products with optimized growth factor profiles. The comparative landscape reveals that no single technology addresses all requirements, with iPSC-derived artificial platelets occupying a promising position offering substantial PRP improvements through standardization while avoiding complex gene editing or exosome purification challenges [75]. Combination approaches integrating multiple technologies may yield synergistic benefits, such as co-administration of MSC-exosomes with iPSC-platelets to enhance anti-inflammatory effects while maintaining growth factor delivery [76].

8. Case Study: Early Development of the Dewcell i-aPLP Program

A representative example of translational development for iPSC-derived artificial platelets in regenerative medicine is provided by the Dewcell Biotherapeutics i-aPLP program targeting osteoarthritis treatment. This program employs a proprietary en-aPLT platform to generate i-aPLP products under GMP conditions, with systematic preclinical characterization supporting regulatory authorization for Phase I clinical trials. The development pathway illustrates the strategic considerations, regulatory interactions, and clinical trial design principles relevant to advancing novel artificial platelet products from concept through early-phase human testing. Preclinical work characterized i-aPLP products through comparative analysis with donor-derived platelets, demonstrating similar structural features including alpha-granules and dense granules visible by transmission electron microscopy, expression of platelet-specific surface markers CD41a, CD42b, and CD61, and functional responses to ADP stimulation measured through procaspase activating compound (PAC-1) and CD62P expression. Growth factor content including Platelet-Derived Growth Factor-AA (PDGF-AA), EGF, and bFGF was quantified, with concentrations meeting predefined target product profile specifications. Efficacy assessment in IL-1β-induced *in vitro* OA models and surgical OA models induced by ACLT with or without destabilization of the medial meniscus (DMM) demonstrated favorable effects on relevant biomarkers and functional outcomes as detailed previously.

The Phase I clinical trial design employs a traditional 3 + 3 dose-escalation scheme across three cohorts receiving 3×10^9, 10×10^9, and 30×10^9 platelets via single intra-articular injection to the affected knee joint (Fig. 1). Primary endpoints focus on safety assessment including dose-limiting toxicity evaluation, adverse event monitoring, laboratory safety parameters, vital signs, and immunogenicity testing through anti-HLA and anti-platelet antibody measurement at scheduled intervals through 24 weeks. Secondary exploratory endpoints assess preliminary efficacy signals through patient-reported outcome measures including Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and

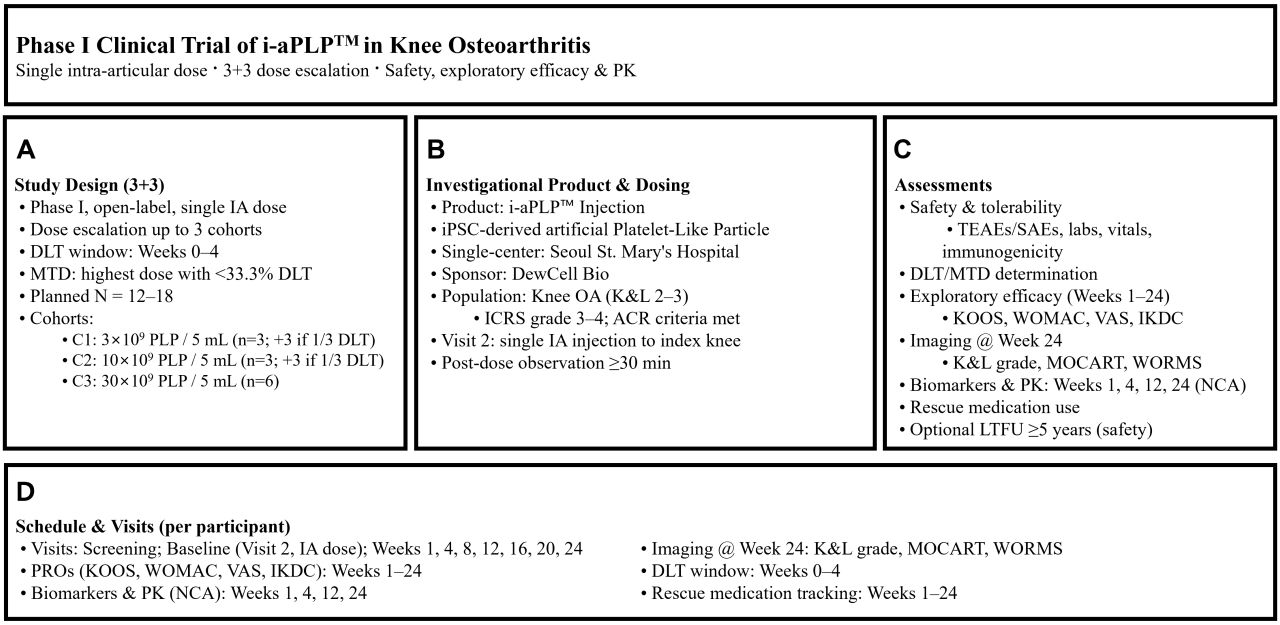

Fig. 1. Study design, dosing, and assessment overview for the Phase I clinical trial of i-aPLT™ in patients with knee osteoarthritis. (A) Study design schematic showing a 3 + 3 dose escalation format with three cohorts (3×10^9, 1×10^{10}, and 3×10^{10} PLP/5 mL). Participants receive a single intra-articular injection into the index knee, followed by dose-limiting toxicity (DLT) monitoring during Weeks 0–4. (B) Investigational product and dosing details, including iPSC-derived artificial platelet-like particles (i-aPLT™) manufactured under GMP conditions and administered at St. Mary's Hospital. (C) Key safety, tolerability, and exploratory efficacy assessments will be conducted over 24 weeks, including Treatment-Emergent Adverse Event (TEAEs)/ Serious Adverse Event (SAEs), laboratory and immunogenicity testing, patient-reported outcomes (Knee Injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS), International Knee Documentation Committee (IKDC)), and imaging evaluations (Kellgren–Lawrence, Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART), and Whole-Organ Magnetic Resonance Imaging Score (WORMS)). (D) The visit and evaluation schedule per participant will include baseline screening, serial biomarker/pharmacokinetic sampling (Weeks 1, 4, 12, and 24), imaging at Week 24, and optional long-term safety follow-up ($\geq$ 5 years).

Osteoarthritis Outcome Score (KOOS), visual analog scale (VAS) pain scores, and International Knee Documentation Committee (IKDC) functional assessments, alongside structural evaluation using Kellgren-Lawrence (K-L) radiographic grading, Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART MRI) scoring, and Whole-Organ Magnetic Resonance Imaging Score (WORMS) assessment. Biomarker analysis includes synovial fluid sampling for inflammatory mediators and cartilage degradation products. Pharmacokinetic assessment employs novel approaches including next-generation sequencing-based detection of iPSC-derived platelet-specific genetic signatures in blood and synovial fluid samples at defined timepoints following administration. Table 5 provides detailed trial design parameters including eligibility criteria, dose escalation rules, assessment schedules, and endpoint definitions.

9. Future Perspectives

The transition of iPSC-derived artificial platelets from transfusion medicine applications toward regenerative medicine represents an emerging frontier with substantial opportunity but requiring systematic investigation across multiple domains. Manufacturing scalability and cost reduction remain critical to achieving commercial viability, as current production costs substantially exceed donor-derived platelets despite offering quality and consistency advantages. Process optimization targeting increased platelet yield per megakaryocyte, reduced culture media costs through defined formulations, and automated manufacturing systems will prove essential for economic feasibility. Lyophilization or alternative stabilization approaches enabling ambient storage would eliminate cold chain requirements and extend product shelf life beyond the five to seven day limitation of liquid platelet products.

Product optimization for regenerative applications may diverge from transfusion-optimized formulations in multiple dimensions. Growth factor content could be enhanced through megakaryocyte cell line engineering to overexpress specific factors including PDGF, TGF-β, or VEGF based on target indication requirements. Controlled-release formulations incorporating hydrogel carriers, microspheres, or other delivery systems could extend growth

Table 5. Phase I clinical trial design for i-aPLP in knee osteoarthritis (dewcell biotherapeutics).

Trial design element	Specification	Rationale and details
Study design	Single-center, open-label, dose-escalation Phase I trial	Traditional 3 + 3 design for first-in-human safety assessment
Target population	Adults age ≥19 years with mild-moderate knee OA (K-L grade 2–3; ICRS grade 3–4)	Excludes severe OA (K-L grade 4) where cartilage loss precludes regenerative potential
Sample size	12–18 patients (3–6 per cohort depending on DLT occurrence)	Standard 3 + 3 escalation allows early termination if unacceptable toxicity
Dose levels	Cohort 1: 3×10^9 PLP/5 mL; Cohort 2: 10×10^9 PLP/5 mL; Cohort 3: 30×10^9 PLP/5 mL	Based on preclinical effective doses and donor PRP platelet concentrations (2.5×10^9/mL)
Administration route	Single intra-articular injection to index knee under ultrasound guidance	Minimizes systemic exposure for initial safety evaluation
Primary endpoints	Safety and tolerability: DLT frequency; adverse events (CTCAE v5.0 grading); laboratory abnormalities; vital signs; immunogenicity (anti-HLA, anti-platelet antibodies)	DLT defined as Grade ≥3 adverse drug reactions within 28 days excluding procedure-related local reactions
Secondary endpoints (efficacy signals)	WOMAC pain/function scores; KOOS subscales; 100-mm VAS pain; IKDC; K-L grade; MOCART MRI score; WORMS assessment; synovial biomarkers; rescue medication use	Comprehensive assessment balancing symptoms, function, and structure
PK/PD endpoints	Next-generation sequencing for iPSC-specific genetic signatures in blood/synovial fluid at 1 week, 4 weeks, 12 weeks, 24 weeks; synovial fluid growth factor levels	Novel approach using molecular tracking for cellular pharmacokinetics
Key inclusion criteria	BMI <30 kg/m^2; ≥12 weeks failed conservative therapy; VAS pain ≥50 mm; ACR clinical + radiographic OA criteria; stable medication regimen	Enriches for patients likely to complete trial; excludes confounding treatments
Key exclusion criteria	K-L grade 4 OA; Grade III ligament laxity; prior intra-articular injections within 12 weeks (HA) or 4 weeks (corticosteroids); inflammatory arthropathy; bleeding disorders; malignancy; HCV/HBV/HIV infection; immunosuppressant use	Minimizes safety risks and outcome confounders for first-in-human study
Dose escalation rules	0/3 DLTs → advance to next cohort; 1/3 DLTs → expand to 6, then decide; ≥2/3 or ≥2/6 DLTs → stop or de-escalate	BOIN or mTPI-2 designs considered but traditional 3 + 3 selected for transparency
Maximum tolerated dose	Highest dose level with DLT rate <33%	Informs Phase II dose selection
Assessment schedule	Screening, baseline, post-injection observation (30 min), weeks 1, 4, 8, 12, 16, 20, 24	Intensive early monitoring for safety; extended follow-up for efficacy signals
Long-term follow-up	Annual contact for 5 years monitoring for malignancy and serious delayed events if designated long-term follow-up product	Addresses theoretical tumorigenicity concerns from immortalized cell line manufacturing
Regulatory pathway	Korean MFDS approval under regenerative medicine regulations; IRB approval; GCP compliance	Aligns with Korean regulatory framework for advanced therapy medicinal products

ACR, American College of Rheumatology; BOIN, Bayesian optimal interval; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; GCP, good clinical practice; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HA, hyaluronic acid; HLA, human leukocyte antigen; i-aPLP, induced artificial platelet-like particle; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; IRB, institutional review board; K-L, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; MFDS, Ministry of Food and Drug Safety; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; mTPI-2, modified toxicity probability interval-2; OA, osteoarthritis; PD, pharmacodynamics; PK, pharmacokinetics; PLP, platelet-like particle; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; WORMS, Whole-Organ Magnetic Resonance Imaging Score; BMI, Body Mass Index.

factor exposure duration and improve tissue retention compared to suspension formulations subject to rapid clearance. Combination products integrating artificial platelets with hyaluronic acid, stem cells, or extracellular matrix scaffolds may achieve synergistic effects exceeding monotherapy outcomes.

Clinical development pathway optimization requires strategic indication selection balancing scientific rationale, unmet medical need, regulatory pathway feasibility, and commercial opportunity. Osteoarthritis represents a large market with controversial PRP evidence, suggesting that a standardized, well-characterized product demonstrating superiority over autologous PRP could achieve regulatory approval and clinical adoption. However, the chronic nature and slow progression of osteoarthritis necessitate long-term efficacy trials with structural and symptomatic endpoints, increasing development costs and timelines. Alternative indications including acute traumatic injuries, surgical augmentation, or wound healing may offer faster development pathways with more definitive endpoints, though potentially smaller commercial markets. Orphan designation opportunities exist for rare conditions where platelet-based therapy shows promise but donor platelet availability proves limiting.

Regulatory frameworks for iPSC-derived artificial platelets in regenerative medicine remain evolving, as existing guidance documents address primarily transfusion applications or cell therapy products rather than cell-derived particles with distinct characteristics. Engaging regulatory authorities early through scientific advice procedures or pre- Investigational New Drug Application (pre-IND) meetings clarifies expectations for nonclinical testing, manufacturing controls, clinical trial design, and approval standards. Demonstrating comparability to conventional PRP while establishing advantages in consistency, characterizability, and clinical outcomes will support regulatory differentiation. Long-term follow-up requirements for cell-derived products may necessitate registry systems tracking safety outcomes and product performance across expanded patient populations post-approval.

Combination product opportunities integrating artificial platelets with other regenerative technologies may accelerate clinical translation and enhance therapeutic efficacy. Mesenchymal stem cell therapies could be augmented with artificial platelets providing growth factor support enhancing engraftment and differentiation. Tissue engineering scaffolds seeded with artificial platelets may improve vascularization and cellular infiltration in construct integration. Gene therapy vectors delivered alongside artificial platelets could benefit from platelet-mediated anti-inflammatory effects and wound healing promotion. Such combination approaches require additional regulatory and development complexity but may address clinical needs inadequately served by monotherapies.

Market access strategies must consider reimbursement pathways for novel platelet-based regenerative products in health systems accustomed to PRP as physician-prepared, facility-billed procedures rather than manufactured pharmaceutical products. Demonstrating cost-effectiveness compared to surgical interventions like joint replacement or to repeated PRP injection series will prove essential for payer acceptance. Real-world evidence generation through registry studies documenting outcomes, healthcare utilization, and quality-of-life impacts can support value propositions beyond randomized trial efficacy data. Patient access programs and outcomes-based contracts may facilitate adoption during evidence accumulation phases.

The scientific foundation established through iPSC-derived platelet development for transfusion medicine provides substantial translational advantage for regenerative applications, though key knowledge gaps require focused investigation. Pharmacokinetic characterization following local administration to joints, subcutaneous tissues, or wound sites needs systematic study using appropriate analytical methods for cellular pharmacokinetics. Mechanistic understanding of how different growth factor profiles and concentrations influence specific tissue repair processes would enable rational product optimization. Biomarker development predicting therapeutic response could identify patient populations most likely to benefit and guide personalized medicine approaches. These foundational investigations position iPSC-derived artificial platelets as next-generation regenerative medicine products addressing critical standardization and quality limitations that have prevented conventional PRP from achieving its therapeutic potential.

10. Conclusion

Platelet-rich plasma has demonstrated biological potential in regenerative medicine but remains limited by fundamental standardization challenges, donor-dependent variability, and inconsistent clinical outcomes that prevent regulatory approval as defined pharmacological entities. iPSC-derived artificial platelets address these critical limitations through controlled manufacturing under GMP conditions, enabling reproducible platelet counts, quantifiable growth factor content, and consistent functional characteristics across production batches. Preclinical evidence demonstrates therapeutic efficacy in osteoarthritis models through modulation of anabolic and catabolic pathways, while early clinical data support acceptable safety profiles without tumorigenicity or serious adverse events. The transition from transfusion-focused applications to regenerative medicine requires novel pharmacological characterization frameworks encompassing local tissue pharmacokinetics, mechanistic biomarkers, and long-term structural outcomes. Although challenges remain in manufacturing scalability, cost reduction, and regulatory pathway optimization, standardized iPSC-derived artificial platelet products

represent a promising next-generation approach that may establish platelet-based therapeutics as evidence-based regenerative medicine interventions where conventional PRP has failed to achieve consistent clinical validation.

Author Contributions

SH contributed to the conceptualization of the research, secured funding acquisition, managed project administration, wrote the original draft of the manuscript, and provided supervision throughout the study. KC was responsible for data curation, formal analysis, visualization of the results, and validation of the findings. CK and HJJ provided essential resources and contributed to the development of methodologies for iPSC-derived artificial platelet production and characterization. All authors have reviewed and approved the final version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

All authors of the manuscript are immensely grateful to Man Soo Kim, M.D., Ph.D., Department of Orthopedics, College of Medicine, Seoul St. Mary's Hospital for his invaluable support in inaugurating the clinical study of iPSC-derived artificial platelet.

Funding

This study was supported by the Korean Fund for Regenerative Medicine (KFRM) grant funded by the Korean government (the Ministry of Science and ICT, the Ministry of Health & Welfare: Code: KFRM 23C0104L1).

Conflict of Interest

Chihwa Kim and Hyo-Jin Jeon are employees of Dewcell Inc, Seongnam, Republic of Korea. The other authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

The authors used ChatGpt and Claude in order to check spell and grammar during manuscript preparation. After using this large language model service, the authors prudently screened and edited the paragraph as needed and took full responsibility for the content of the publication.

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