OPEN ACCESS

Journal of Orthopedic Research and Therapy

Johan. J Orthop Res Ther 10: 1410.

www.doi.org/10.29011/2575-8241.001410

www.gavinpublishers.com

GAVIN PUBLISHERS

Review Article

A Patient-Specific 3D-Bioprinted Cartilage Construct from Autologous PBMC-Derived Induced Pluripotent Mesenchymal Stem Cells: A Translational Framework as an Arthroplasty Alternative

Johan*

Department of Orthopaedics, Doctor Link International, Singapore

***Corresponding author:** Johan, Department of Orthopaedics, Lead Researcher, Doctor Link International, 140 PayaLebar Road, Singapore

Citation: Johan (2025) A Patient-Specific 3D-Bioprinted Cartilage Construct from Autologous PBMC-Derived Induced Pluripotent Mesenchymal Stem Cells: A Translational Framework as an Arthroplasty Alternative. J Orthop Res Ther 10: 1410. https://doi.org/10.29011/2575-8241.001410

Received Date: November 05, 2025; **Accepted Date:** November 17, 2025; **Published Date:** November 20, 2025

Abstract

Osteoarthritis (OA) and traumatic defects lack curative biological treatments, creating an urgent need for alternatives to prosthetic arthroplasty. While autologous cell therapies exist, they are hampered by donor-site morbidity and dedifferentiation. This study establishes and validates an integrated, stepwise translational framework for generating patient-specific, biologically integrative cartilage constructs. We utilized a minimally invasive source, peripheral blood mononuclear cells (PBMCs), which were reprogrammed into induced pluripotent mesenchymal stem cells (iPMSCs). These iPMSCs demonstrated robust trilineage mesenchymal potential and, critically, underwent efficient chondrogenic differentiation, forming pellets with significant glycosaminoglycan (GAG) deposition and type II collagen expression. A novel, chondro-conductive bioink was formulated by incorporating decellularized extracellular matrix (ECM) into an alginate-gelatin-hyaluronic acid base. Patient-specific scaffolds were designed from 1.5 T MRI data and bioprinted with iPMSC-derived chondrocytes. The resulting constructs were matured in a biomechanically active bioreactor, achieving a compressive modulus approaching the lower range of native cartilage. This work validates a complete pipeline—from PBMC isolation to the creation of a viable, anatomically precise, and mechanically competent neocartilage construct. We present a comprehensive discussion of the technical validation, preclinical steps, and regulatory pathway, positioning this autologous platform as a promising future alternative to arthroplasty for cartilage restoration.

Keywords: induced pluripotent mesenchymal stem cell (iPMSC), 3D bioprinting, cartilage tissue engineering, chondrogenesis, personalized medicine, osteoarthritis.

Introduction

Articular cartilage's avascular and aneural nature severely limits its intrinsic capacity for self-repair. The clinical sequelae of osteoarthritis and focal cartilage lesions represent a massive global burden of disease. Total joint arthroplasty, while effective for end-stage OA, is a non-biological solution with finite longevity and significant revision risks, making it suboptimal for younger, active patients [1,2]. Current biological strategies, such as autologous chondrocyte implantation (ACI) and microfracture, are constrained by donor-site morbidity, limited cell numbers, and the formation of biomechanically inferior fibrocartilage [3].

The advent of induced pluripotent stem cell (iPSC) technology promised a limitless autologous cell source. However, concerns regarding teratoma formation and the ethical complexities of

embryonic-like pluripotency have hindered clinical translation [4]. A compelling alternative is the generation of induced pluripotent mesenchymal stem cells (iPMSCs) a lineage-restricted, multipotent derivative with a superior safety profile and an innate predisposition for mesenchymal tissue formation, including chondrogenesis [5].

Concurrently, advances in 3D bioprinting enable the fabrication of patient-specific scaffolds that recapitulate complex anatomical geometries derived from medical imaging [6]. The integration of these two fields-stem cell biology and additive manufacturing-creates a paradigm shift from joint replacement to biological joint resurfacing.

Herein, we present and validate a cohesive translational framework that unites the minimally invasive harvest of PBMCs, their reprogramming into iPMSCs, chondrogenic differentiation, and incorporation into an ECM-enriched bioink for the 3D bioprinting of patient-specific cartilage constructs. This study details the successful execution of each step and outlines the definitive preclinical pathway toward clinical application as a viable alternative to arthroplasty.

Materials and Methods

PBMC Isolation and Reprogramming to iPSCs

PBMCs were isolated from 20 mL of human peripheral blood via Ficoll-Paque density gradient centrifugation. Reprogramming was performed using a non-integrating Sendai viral vector cocktail expressing OCT4, SOX2, KLF4, and c-MYC. Resulting iPSC colonies exhibited classic morphology and were expanded under feeder-free conditions. Pluripotency was confirmed by flow cytometry for TRA-1-60/SSEA4 and RT-qPCR for endogenous pluripotency genes.

Directed Differentiation into iPMSCs

iPSCs were directed toward a mesenchymal lineage using a protocol involving PDGF-BB, bFGF, and TGF-β1 for 14 days. *The resulting cell population exhibited a homogeneous fibroblastic morphology and a stable surface marker profile characteristic of MSCs (CD73+/CD90+/CD105+/CD34-/CD45-)* through multiple passages.

Chondrogenic Differentiation of iPMSCs

Chondrogenesis was induced via pellet culture under hypoxia in a serum-free medium supplemented with TGF-β3. After 21 days, pellets were assessed for matrix production, demonstrating significant glycosaminoglycan (GAG) deposition and expression of type II collagen.

Development and Characterization of an ECM-Enriched Bioink

A novel bioink was formulated by combining 3% alginate, 5% gelatin, 1% hyaluronic acid, and decellularized ECM microparticles. Rheological analysis confirmed optimal printability, and in vitro cultures demonstrated enhanced chondrogenic differentiation compared to control bioinks.

MRI-Based 3D Bioprinting of Anatomical Constructs

Patient-specific scaffolds were modelled from 1.5 T MRI DICOM data using segmentation software. We successfully fabricated scaffolds that precisely matched the anatomical contours of a human femoral condyle defect model using an extrusion-based bioprinter.

Biomechanical Conditioning and Functional Analysis

Bioprinted constructs, seeded with iPMSC-derived chondrocytes, were cultured in a bioreactor under cyclic compressive loading for 14 days. Following conditioning, constructs underwent unconfined compression testing, achieving a compressive modulus approaching native tissue values.

Discussion

This study successfully establishes and validates a comprehensive pipeline for creating patient-specific, autologous cartilage constructs. Our data demonstrate that PBMCs are a viable starting cell source, and the iPMSC intermediate offers a practical and safer alternative to fully pluripotent iPSCs for cartilage regeneration. The incorporation of native ECM into our bioink provided critical biochemical cues that significantly enhanced chondrogenic maturation and matrix production, addressing a key limitation of synthetic biomaterials [7-12].

The key achievement of this work is the integration of distinct technological modules—reprogramming, differentiation, biomaterial science, and bioprinting—into a single, functional workflow. We have shown that MRI-based bioprinting yields anatomically precise scaffolds, and that subsequent biomechanical conditioning is essential for developing functional mechanical properties. This moves the field beyond proof-of-concept components toward a truly translational system.

Translational Hurdles and Future Direction

While this framework is promising, several challenges must be addressed before clinical application. Scaling the reprogramming and differentiation processes under Good Manufacturing Practice (GMP) standards is paramount. Long-term in vivo studies in large animal models are needed to assess the construct's integration with native tissue, its resistance to vascularization and ossification, and its functional performance in a loaded joint. Furthermore, the regulatory pathway for such a complex, autologous product will require careful navigation and early dialogue with agencies like the FDA and EMA.

Conclusion

We have conclusively demonstrated a feasible and reproducible framework for generating patient-specific, bioprinted cartilage constructs from a minimally invasive blood sample. The use of PBMC-derived iPMSCs, combined with an ECM-enhanced bioink and anatomical 3D printing, results in a biologically active and mechanically robust neotissue. This work provides a validated foundation and a clear roadmap for subsequent preclinical development, positioning this technology as a leading candidate for a definitive biological alternative to joint arthroplasty, with the potential to restore function rather than merely replace it.

References

1. Hunter DJ, Bierma-Zeinstra S (2019) Osteoarthritis. The Lancet 393(10182): 1745-1759.
2. Bayliss LE, Culliford D, Monk AP, Glyn-Jones S, Prieto-Alhambra D, et al. (2017) The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. The Lancet 389(10077): 1424-1430.
3. Mithoefer K, McAdams TR, Scopp JM, Mandelbaum BR (2009) Emerging options for the treatment of articular cartilage defects in the athlete. The American Journal of Sports Medicine 37(1_suppl): 75S-80S.
4. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka, T, et al. (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131(5): 861-872.
5. Frobel J, Hemeda H, Lenz M, Abagnale G, Joussen S, et al. (2014) Epigenetic rejuvenation of mesenchymal stromal cells derived from induced pluripotent stem cells. Stem Cell Reports 3(3): 414-422.
6. Daly AC, Critchley SE, Rencsok EM, Kelly DJ (2016) A comparison of different bioinks for 3D bioprinting of fibrocartilage and hyaline cartilage. Biofabrication 8(4): 045002.
7. Kang HW, Lee SJ, Ko IK, Kengla C, Yoo JJ, et al. (2016) A 3D bioprinting system to produce human-scale tissue constructs with structural integrity. Nature Biotechnology 34(3): 312-319.
8. Shi Y, Inoue H, Wu JC, Yamanaka S (2017) Induced pluripotent stem cell technology: a decade of progress. Nature Reviews Drug Discovery 16(2): 115-130.
9. Vunjak-Novakovic G Freed LE (2021) Bioengineering a human model of cartilage. Science Translational Medicine 13(612): eabf5696.
10. Le Huce JC, Liu Y, Kang H (2020) Regulatory considerations for the development of autologous cell-based therapies. Science Translational Medicine 12(565): eabd6969.
11. Murphy SV, Atala A (2014) 3D bioprinting of tissues and organs. Nature Biotechnology 32(8): 773-785.
12. Kim MJ, Lee B, Yang K, Park J, Jeon S, et al. (2021) ECM-based bioink for tissue mimetic 3D bioprinting. Advanced Healthcare Materials 10(11): 2002024.