



REVIEW

The Progress of Cartilage and Bone Related Organoid-on-a-Chip: Construction Strategies, Current Models, and Perspectives

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ABSTRACT: Bone and cartilage disorders, including osteoarthritis and osteoporosis, represent a leading cause of global disability and place an increasing burden on healthcare systems. Flat monolayer cultures cannot reproduce the spatial organization, cell–matrix contacts, or the mechanical and chemical milieu that define living musculoskeletal tissue, while animal models are constrained by interspecies differences. Organoid and organ-on-a-chip technologies provide biomimetic three-dimensional platforms that replicate tissue-specific architecture and permit precise control of mechanical loading, fluid perfusion, and real-time metabolic monitoring. This review summarizes recent progress in cartilage and bone organoid construction, encompassing cell sources, biomaterials, and culture strategies, and discusses the engineering of cartilage/bone organ-on-a-chip systems, including microfluidic design, physical stimulation, and biosensing. The review also covers monoculture and multi-tissue chip designs—specifically osteochondral and vascularized marrow systems—and discusses outstanding hurdles in scaffold design, co-culture methods, organoid-chip coupling, protocol standardization, and bench-to-bedside translation. Taken together, these engineering advances are poised to improve preclinical disease models, accelerate therapeutic discovery, and guide future cell-based repair strategies.

KEYWORDS: Cartilage; bone; organoid; organ-on-a-chip; microfluidics; tissue engineering

1 Introduction

Bone and cartilage are the most essential tissues in the human motor system, providing structural protection, mechanical support, hematopoiesis, and maintenance of mineral ion homeostasis.

Trabecular bone undergoes continuous turnover through the coupled activities of osteoblasts, which deposit new matrix, and osteoclasts, which resorb old tissue. Osteocytes embedded within the mineralized matrix coordinate this balance by releasing local signaling factors [1–3]. When this balance is disturbed, metabolic bone disorders such as osteoporosis can develop [4–6]. After menopause, the decline in circulating estrogen shifts the bone turnover balance toward net loss, as osteoclast activity outpaces osteoblast-driven matrix synthesis [6,7]. In elderly men, impaired bone formation predominates [8–12].

Current pharmacological strategies—bisphosphonates and teriparatide—exhibit significant side effects, including osteonecrosis of the jaw and atypical femoral fractures, showing the need for safer, mechanism-based therapies [13]. Because cartilage contains no blood vessels or nerves, its ability to heal after injury is inherently poor. Chondrocytes are metabolically quiescent, and the dense extracellular matrix impedes

cellular infiltration [14,15]. Osteoarthritis (OA)—described by progressive cartilage degradation—remains incurable, with clinical management focused on symptomatic relief and end-stage joint replacement [5,16–31].

Musculoskeletal conditions rank among the top contributors to worldwide disability. The 2021 Global Burden of Disease analysis estimated that more than 600 million people live with osteoarthritis [16,32,33]. Fragility fractures from osteoporosis impose a comparable burden: among Americans over 50, roughly one in two women and one in five men will sustain such a fracture in their remaining years, and the direct medical costs are forecast to exceed \$25 billion annually by 2025 [4,6,34,35].

Traditional two-dimensional cell culture systems cannot replicate the three-dimensional architecture, cell–matrix interactions, and spatiotemporal signaling dynamics of native bone and cartilage tissues. Animal models, while indispensable, are constrained by interspecies physiological differences, prohibitive costs, and ethical concerns. Advances in micro- and nanofabrication have enabled the development of biomimetic 3D culture platforms, including organoids and organ-on-a-chip systems. Organoids replicate the architectural and functional complexity of target tissues through stem cell self-assembly. Microfluidic chip systems combine continuous medium exchange, programmable mechanical loading, and defined tissue boundaries within a single device. Merging organoid self-assembly with chip-based perfusion and sensing opens the door to tightly controlled, scalable tissue models that were previously unattainable. This review focuses on bone and cartilage organoid-on-a-chip systems [36–46] (Fig. 1). Representative platforms are summarized in Table 1.

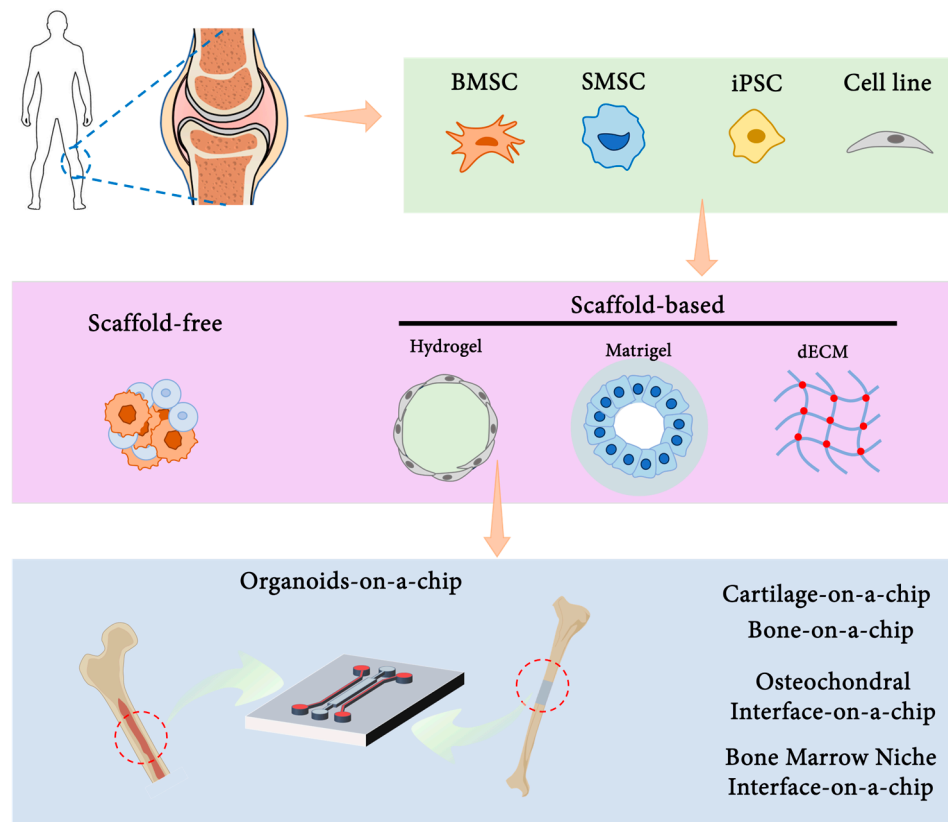


Figure 1: Schematic description of the motor-system related organoid-on-a-chip.

Table 1: Representative cartilage/bone organoid and organ-on-a-chip platforms.

Study [Ref.]	System Type	Cell Source	Scaffold/Material	Stimulation	Key Read-out/Application
Chen et al. [47]	Cartilage organoid	BMSC	Scaffold-free self-assembly	Static	Gradient osteochondral regeneration
Abraham et al. [48]	Skeletal organoid	Pediatric joint cells	Matrigel	Static	Disease modeling; drug testing
Miao et al. [49]	Cartilage organoid	BMSC + SOX9-EV	Decellularized cartilage ECM	Cyclic compression	Cartilage rejuvenation; OA-on-chip
Park et al. [50]	Bone organoid	Osteoblast–osteoclast	Demineralized bone paper	Static	Bone remodeling cycle
Wang et al. [51]	Bone organoid	BMSC	Hydroxyapatite composite	Perfusion	Large-scale self-mineralization
Occhetta et al. [52]	Cartilage chip	Chondrocytes	Cartilage-on-chip construct	Hyperphysiological compression	OA catabolic response modeling
Li et al. [53]	Mini joint chip	Human MSCs	Osteochondral + reactive compartments	IL-1 β stimulation	Joint inflammation modeling; drug testing
Dornhof et al. [54]	Bone chip + biosensor	3D bone cell culture	Sensor-integrated chip	Perfusion	Real-time O ₂ /lactate/glucose monitoring
Stelzer et al. [43]	Bone + marrow chip	Autologous primary cells	3D bone/marrow construct	Perfusion	Long-term bone remodeling
Tuerlings et al. [55]	Osteochondral chip	Chondrocytes + osteoblasts	Fibrous PCL matrix	Interface co-culture	Osteochondral interface modeling
Torisawa et al. [56]	Bone marrow chip	Engineered bone + marrow	Bone in microfluidic device	Continuous perfusion	Hematopoietic niche physiology
Glaser et al. [57]	Vascularized marrow chip	Marrow + vascular cells	Organ-on-chip construct	Flow	Vascularized bone marrow niches

2 Methodological Foundations of Cartilage/Bone Organoid Construction

Building cartilage and bone organoids requires three deliberate choices: which cells to start with, what scaffold to provide, and how to condition the culture environment. Unlike organoids derived from soft tissues, bone and cartilage makes must accommodate mineralized matrix deposition, load-bearing mechanical function, and—in the case of cartilage—maintenance of an avascular and hypoxic niche [58–60].

For clarity, we define organoids as self-organized, three-dimensional tissue constructs generated from stem cells, progenitor cells, or primary tissue-resident cells that recapitulate key aspects of the architecture, cellular composition, and function of their native tissue through cell-intrinsic developmental programs, typically without a preformed scaffold dictating tissue shape. This definition distinguishes organoids from spheroids and simple cell aggregates, which arise from passive cell clustering and lack organized, tissue-specific architecture and lineage hierarchy; and from engineered 3D tissue constructs, whose geometry and composition are externally imposed by scaffolds or bioprinting rather than generated by self-organization. Along this continuum, organ-on-a-chip systems are microfluidic culture platforms that reproduce organ-level physiological cues—perfusion, mechanical loading, and tissue interfaces—but

generally rely on externally structured tissues, whereas organoid-on-a-chip platforms combine the self-organized 3D architecture of organoids with the dynamic, controllable microenvironment of chips, and therefore occupy the most biomimetic end of the spectrum.

2.1 Cell Sources and Differentiation Strategies

Current approaches use mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), primary cells, and immortalized lines [61,62]. Among tissue-resident MSCs, bone marrow-derived MSCs (BMSCs) remain the gold standard for bone organoid engineering from their robust osteogenic potential and established clinical track record [63–69]. Xie et al. showed that BMSC-laden hydrogel microspheres, when directed through chondrogenic differentiation, formed bony callus organoids that faithfully simulated the endochondral ossification process observed in native fracture healing [70]. Expanding this principle, Chen et al. showed that single BMSC-derived cartilage organoids could be patterned to make gradient varied osteochondral tissue by leveraging the native vascular microenvironment, showing that a single cell source, when exposed to controlled differentiation cues, can recreate the zonal organization of native osteochondral interfaces [47] (Fig. 2A).

MSCs harvested from synovial tissue exhibit strong chondrogenic commitment and maintain their phenotype during expansion, making them attractive for cartilage organoid work. Sun et al. made three-dimensional cultured SMSC organoids that, upon *in vivo* transplantation, made ectopic cartilage tissue and controlled the miR-138/FOXC1/HIF signaling axis. This study established SMSCs as a robust source for cartilage organoid construction and showed a mechanistic link between synovial MSCs and hypoxia-responsive pathways. In a subsequent investigation, the same group identified aging markers in patients with osteochondral defects and made an aging-targeted miR-24/SMSC organoid hydrogel that repaired cartilage defects through restoration of chondrocyte homeostasis [71,72].

iPSC technology has expanded the cell source repertoire, offering unlimited quantities of patient-specific cells. Abe et al. achieved a landmark demonstration by transplanting allogeneic iPSC-derived cartilage organoids into knee cartilage defect models in cynomolgus monkeys, observing survival, integration, and differentiation into articular cartilage at the defect site [61]. Rodríguez Ruiz et al. further generated distinct cartilage and bone organoids directly from human iPSCs, showing that osteoprotegerin mutations drive cartilage fibrosis while enhancing bone mineralization, recapitulating bidirectional osteochondral dysregulation in the organoids [73]. iPSC-derived organoids, however, demand lengthy, multi-step differentiation protocols and carry the residual hazard of undifferentiated pluripotent cells, so extensive quality-assurance testing is mandatory before any therapeutic use.

Immortalized cell lines like MC3T3-E1 pre-osteoblasts and RAW 264.7 macrophages have proven invaluable for proof-of-concept bone organoid models. Fuller et al. established a three-dimensional bone organoid model using these murine cell lines that simulated bone mineralization and the dynamic balance between formation and resorption [62] (Fig. 2B).

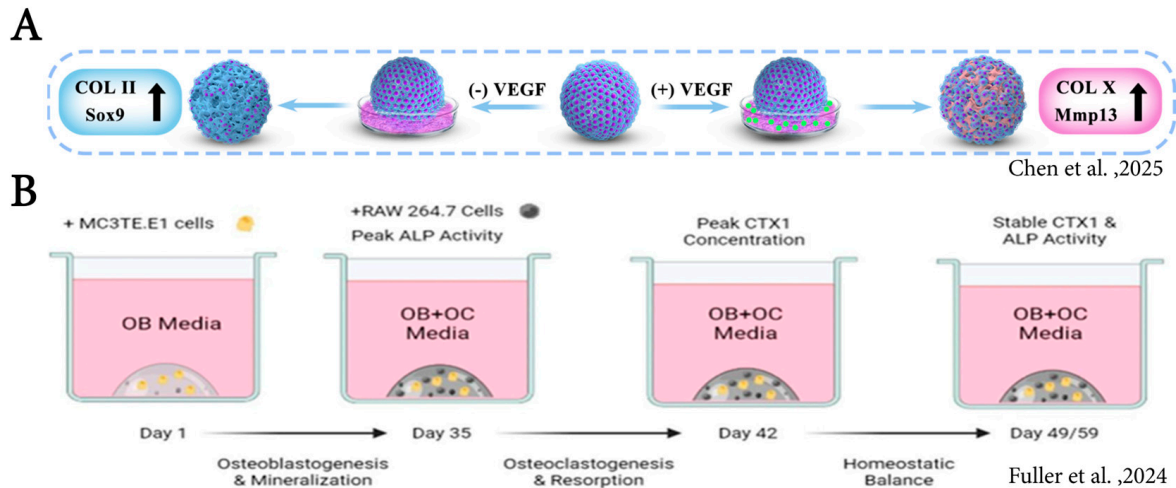


Figure 2: Different cell sources. (A) Single BMSC-derived cartilage organoids could be patterned to make gradient varied osteochondral tissue by leveraging the native vascular microenvironment; (B) A three-dimensional bone organoid model using these murine cell lines that simulated bone mineralization and the dynamic balance between formation and resorption. Panels (A,B) are reprinted with permission from Chen et al., 2025 [47] (Copyright 2025, BMC) and Fuller et al., 2024 [62] (Copyright 2024, MDPI), respectively.

2.2 Biomaterials and Scaffold Systems

Scaffold selection differs for bone (mineralized, stiff) and cartilage (avascular, soft, hypoxic). Biologically derived hydrogels continue to serve as common scaffold substrates. Matrigel has served as a supportive matrix for numerous organoid systems from its rich complement of laminin, collagen IV, and growth factors. Abraham and colleagues employed Matrigel to promote the self-organization of skeletal organoids derived from pediatric joint cells. Matrigel suffers from significant batch-to-batch variability, insufficient mechanical strength for load-bearing applications, xenogeneic origin introducing immunogenicity risks, and undefined composition that precludes precise mechanistic interrogation [48].

Type I and type II collagen hydrogels offer a more defined alternative while keeping native cell-adhesive ligands. Roshanbinfar et al. made a shrink-resistant collagen-hyaluronan composite hydrogel that improved cartilage tissue engineering applications, with the inclusion of hyaluronan proving essential for preserving chondrocyte phenotype and promoting proteoglycan synthesis [74] (Fig. 3A). Silk fibroin offers tunable degradation rates, exceptional mechanical strength, and minimal inflammatory response. As reviewed by Shen et al., microfluidic RGD-modified silk fibroin-DNA hydrogel microspheres hold promise as a scaffold material for cartilage organoids [75].

Chemically synthesized hydrogel networks allow researchers to tune stiffness, functional group density, and degradation kinetics with high precision. Gelatin methacryloyl (GelMA) has become a versatile synthetic-natural hybrid hydrogel, combining the cell-adhesive and MMP-degradable properties of gelatin with photocrosslinking capacity. Wang et al. engineered a composite bioink based on gelatin methacrylate, sodium alginate methacrylate, and hydroxyapatite (GelMA/AlgMA/HAP) for three-dimensional bioprinting of bone organoids [51].

Decellularized ECM offers a tissue-specific approach that retains the native biochemical makeup and structural organization of the source tissue [76]. Pati and colleagues reported that cartilage dECM bioinks enhanced chondrogenic differentiation and cell survival relative to synthetic alternatives [77] (Fig. 3B). Park et al. prepared demineralized bone paper (DBP) and made a trabecular bone organoid model that

recreated the bone remodeling cycle, showing the spatiotemporal distribution of regulatory molecules and the impact of cell-cell contacts on local bone remodeling [50] (Fig. 3C).

The different material requirements for bone and cartilage organoids reflect different physiological niches. Bone organoids demand scaffolds with osteoconductive and osteoinductive properties, mechanical stiffness sufficient to promote osteogenic mechanotransduction, and capacity for biological mineralization. Cartilage organoids require relatively soft, hydrated, and viscoelastic matrices that approximate the low elastic modulus of native cartilage, while permitting maintenance of hypoxic conditions and supporting the synthesis of a dense, type II collagen-rich ECM.

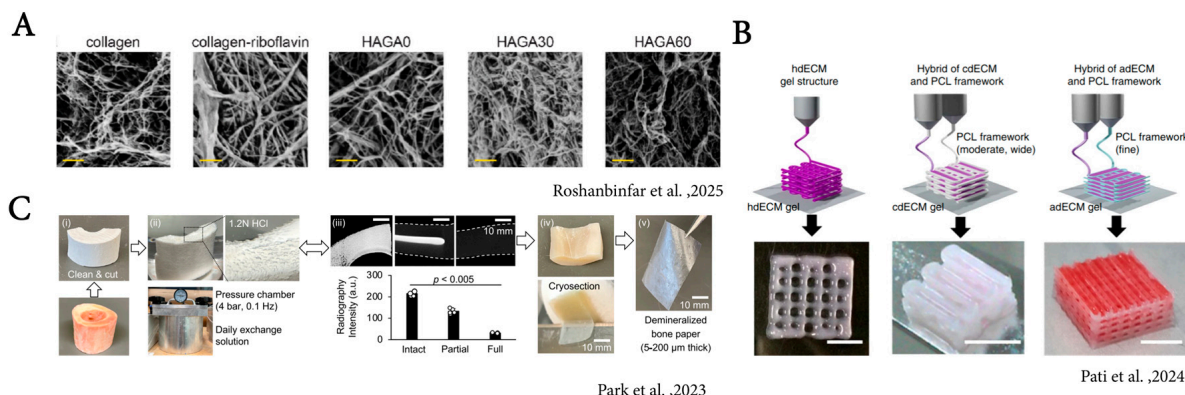


Figure 3: Biomaterials and scaffold. (A) A shrink-resistant collagen-hyaluronan composite hydrogel that improved cartilage tissue engineering applications. Scale bars: 100 μm ; (B) Cartilage dECM bioinks improved chondrogenic differentiation and viability compared to synthetic scaffolds; (C) Preparation of demineralized bone paper (DBP) and reconstruction of the bone remodeling cycle: (i) cleaning and cutting of bone slices; (ii) partial demineralization with 1.2 N HCl in a pressure chamber (4 bar, 0.1 Hz) with daily solution exchange; (iii) radiographic assessment of the demineralization extent (intact, partial, or full); (iv) cryosectioning of the demineralized bone; and (v) demineralized bone paper (5–200 μm thick) used as the culture substrate for the trabecular bone organoid model. Panels (A–C) are reprinted with permission from Roshanbinfar et al., 2025 [74] (Copyright 2025, Elsevier), Pati et al., 2024 [77] (Copyright 2024, Springer Nature) and Park et al., 2023 [50] (Copyright 2023, Springer Nature), respectively.

2.3 Culture Systems and Microenvironmental Modulation

Culture conditions also influence differentiation and maturation. Static suspension culture systems—including high-density micromass, pellet culture, and ultra-low attachment plate formats—show the simplest approach for cartilage/bone organoid generation. O'Connor et al. used iPSCs to culture micro-blocks without scaffolds in a cartilage formation medium, making bone-cartilage organoids with a cartilage core and a mineralized outer layer [78].

Dynamic perfusion culture systems address these limitations by providing continuous medium perfusion that improves nutrient delivery, waste removal, and mechanical stimulation. Yamada et al. showed that bone marrow stem cells cultured in a perfusion bioreactor exhibited a unique osteogenic profile dependent on Rho-ROCK-mediated contractility, highlighting how fluid flow can directly influence lineage commitment through mechanotransduction pathways [40] (Fig. 4A).

Growth factors are essential for directed differentiation. Oxygen tension is a key design parameter for cartilage organoids. Because adult articular cartilage lacks blood vessels, oxygen levels fall sharply from the joint surface (roughly 6–10%) to the tidemark region (as low as 1–2%), and hypoxia-inducible factor (HIF) pathways mediate cellular adaptation to these gradients [15,79,80]. Jain et al. showed that hypoxia

promoted SOX9, COL2A1, and ACAN protein expression in chondrocytes, hyperoxic conditions elevated matrix metalloproteinase-13 production [81].

Scaffold-free self-assembly approaches use the intrinsic capacity of cells to organize into tissue-like structures through cell-cell adhesion and ECM secretion. Tam et al. showed that human pluripotent stem cells could be directed to form cartilaginous organoids through self-assembly in suspension culture, with subsequent hypertrophic priming enabling bridging of essential-size long bone defects in immunocompromised mice [82] (Fig. 4B).

Accordingly, the methodological foundations of cartilage/bone organoid construction demand targeted, application-driven choices at every level of the engineering pipeline. The choice of cells, scaffolds, and culture parameters should be tailored to the experimental goal, be it mimicking cartilage breakdown, investigating bone turnover, or designing grafts for osteochondral lesions.

Several cross-cutting patterns emerge from the comparative assessment above. For disease modeling, iPSC- and patient-derived sources are preferable because they preserve disease-associated genotypes and enable patient-specific drug testing, whereas for regenerative applications, BMSCs and SMSCs currently offer the most practical balance of potency, scalability, and regulatory precedent. Regarding functional maturity, genuine long-term bone remodeling—coupled osteoclast resorption and osteoblast matrix formation sustained over extended culture—has been demonstrated only in a small subset of platforms, notably perfused bone and bone marrow chips and demineralized-bone-paper organoids [50]; most other bone models have reported osteogenic markers and mineral deposition without evidence of resorption-formation coupling. Similarly, most cartilage organoid studies remain at the level of matrix deposition and chondrogenic marker expression, while load-bearing function and long-term phenotypic stability are seldom demonstrated. We therefore urge readers to interpret marker-level outcomes as indications of developmental potential rather than proof of functional tissue equivalence. The advantages, limitations, and best-suited applications of these cell sources are compared in Table 2.

Table 2: Comparison of cell sources for cartilage/bone organoid engineering.

Cell Source	Advantages	Limitations	Best-Suited Application
BMSCs	Robust osteo/chondrogenic potential; clinical track record	Donor variability; limited lifespan	Regenerative applications; bone organoids
SMSCs	Strong chondrogenic commitment; phenotypic stability	Limited supply; site-specific harvest	Cartilage organoids; cartilage repair
iPSCs/hPSCs	Unlimited expansion; patient-specific; scalable	Lengthy differentiation; pluripotency risk	Disease modeling; drug screening
Primary cells	Most native phenotype; clinical relevance	Scarce supply; dedifferentiation	Mechanistic and validation studies
Immortalized lines	Reproducible; low cost; easy handling	Transformed phenotype; low fidelity	Proof-of-concept; high-throughput screening

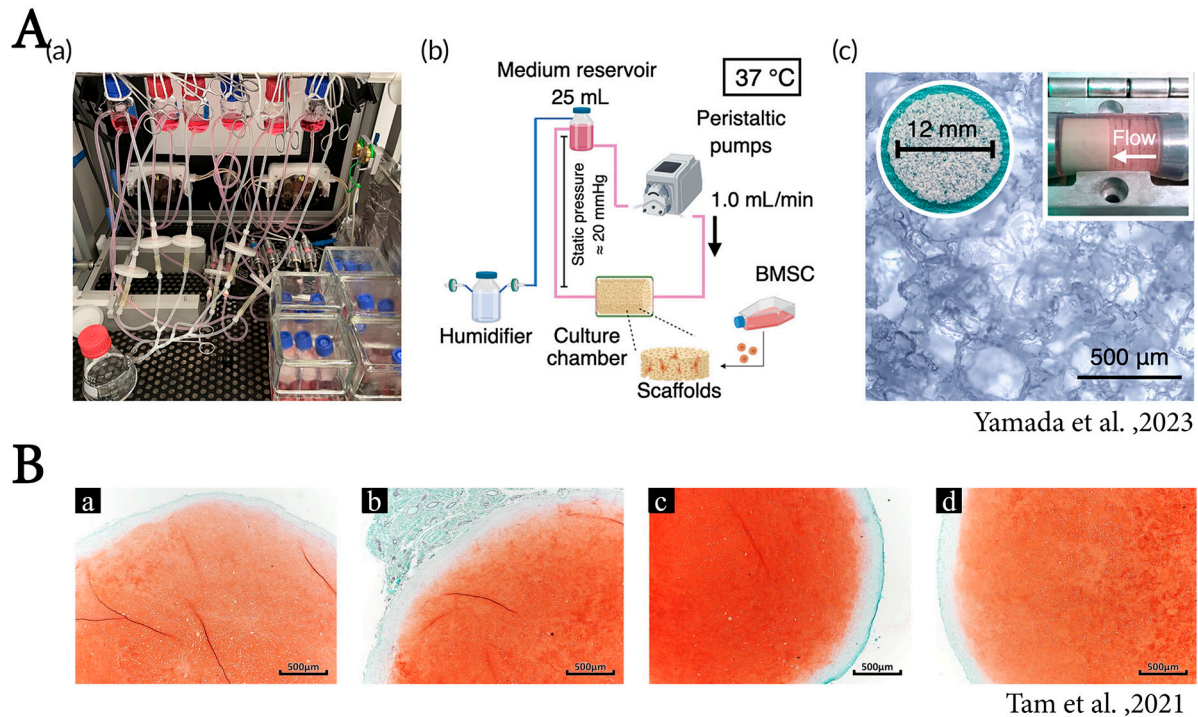


Figure 4: Culture systems. (A) Perfusion culture of bone marrow stem cells: (a) photograph of the multi-chamber perfusion bioreactor system; (b) schematic of the perfusion circuit, showing the medium reservoir (25 mL, 37°C), peristaltic pumps (1.0 mL/min, static pressure ≈ 20 mmHg), humidifier, and the culture chamber loaded with scaffolds seeded with BMSCs; and (c) macroscopic view of the scaffold (12 mm in diameter) and the flow-through culture chamber; (B) Ectopic implantation of human-induced pluripotent-derived organoids. Chondrogenic organoids remained cartilaginous following BMP4 (a), BIO (b), T3 (c) and BBT3 (d) treatment and ectopic implantation. Panels (A,B) are adapted and reprinted with permission from Yamada et al., 2023 [40] (Copyright 2023, Wiley) and Tam et al., 2021 [82] (Copyright 2021, BMC), respectively.

3 Methodological Foundations of Cartilage/Bone Organ-on-a-Chip Engineering

Chip platforms integrate microfluidics, biosensors, and mechanical stimulation. For bone and cartilage, chip design is critical for biological fidelity [54].

3.1 Microfluidic Device Design and Fabrication

The physical architecture of cartilage/bone chips is dictated by the unique structural, mechanical, and metabolic requirements of bone and cartilage tissues. Unlike many parenchymal organ models that can be accommodated within simple single-chamber layouts, cartilage/bone chip systems must replicate load-bearing interfaces, establish distinct oxygen and nutrient regimes, and permit the application of relevant mechanical forces. PDMS exhibits high permeability to small hydrophobic molecules, including many steroid hormones and lipophilic signaling compounds that are pharmacologically relevant to bone and cartilage biology [39]. This absorptive property can alter the effective concentration of administered compounds within the culture chamber, introducing uncontrolled variability into drug screening experiments.

The emergence of high-resolution additive manufacturing technologies has expanded the design space for cartilage/bone chip architectures. Tang et al. used ceramic stereolithography to prepare hydroxyapatite substrates with precise microchannel architectures, then made hybrid HA-PDMS microfluidic chips that

supported osteoblast culture, matrix mineralization, and drug screening in an environment combining the biological fidelity of a bone-mimetic substrate with the microfluidic functionality of PDMS [83] (Fig. 5A).

Microfluidic systems improve the physiological relevance of osteochondral organoids by establishing discrete yet fluidically connected compartments that simulate the hypoxic cartilage zone and the normoxic bone zone [27,54]. Hao et al. made a miniaturized bone chip based on simultaneous growth dialysis principles that spontaneously formed thick, mineralized osteoblast tissues, providing a powerful tool for *in vitro* studies of bone biology and metastasis modeling [84–86].

3.2 Integration and Control of Physical Stimuli

Mechanical stimulation is a key advantage of chip platforms. Cartilage-on-a-chip platforms have been engineered to apply defined mechanical loading regimes. Paggi et al. established a landmark model by making a cartilage-on-a-chip system that applies defined compressive and multidirectional mechanical stimuli to three-dimensional chondrocyte-laden agarose hydrogels. It is showed that this mechanical stimulation promoted chondrogenic gene expression—including upregulation of SOX9, COL2A1, and ACAN—and supported the deposition of a native-like extracellular matrix rich in type II collagen and sulfated proteoglycans [87].

Occhetta et al. advanced this concept toward disease modeling by making a cartilage-on-a-chip microphysiological model that applies strain-controlled compression to three-dimensional articular cartilage microtissues. Their platform employed a programmable actuator to deliver precisely quantified confined compression, enabling systematic investigation of the dose-response relationship between mechanical strain and cartilage degradation [52].

For bone, osteocytes regulate the process of bone remodeling by sensing the fluid shear forces around them [88]. Bone-on-a-chip platforms were designed to replicate this mechanosensory pathway by establishing perfusion channels with defined dimensions and flow rates that make relevant shear stresses at cell-laden surfaces. Mainardi et al. addressed the challenge of tissue-specific mechanical loading in multi-tissue systems by making an organ-on-chip platform capable of applying strain-controlled, tissue-specific compression to both cartilage and mineralized osteochondral interface makes within a single integrated device [89] (Fig. 5B). This platform showed that distinct compression levels could be kept across connected compartments for up to two months, sustaining tissue viability and compositional stability while replicating the mechanical strain gradients of the joint microenvironment. The ability to keep differential loading across cartilage and bone regions within one chip enabled the study of mechanical overload at the osteochondral interface—a key event in osteoarthritis initiation that is impossible to model in isolated cartilage or bone systems.

Beyond mechanical loading, cartilage/bone organ-on-a-chip platforms enable the precise establishment of spatial and temporal chemical gradients. Li et al. They built a chip-scale joint model from human MSCs that incorporated both an osteochondral complex and a reactive tissue chamber; exposure to IL-1 β within this device reproduced hallmarks of synovial inflammation and cartilage breakdown [53]. Lee et al. synchronized osteogenic differentiation periods and co-cultured osteoblasts, osteocytes, and osteoclasts to make bone chips showing normal, osteopenic, and osteoporotic bone states and simulated the bone metastasis process [90].

3.3 Real-Time Biosensing and Monitoring Technologies

Real-time biosensing enables non-destructive monitoring. Impedance-based readouts provide a non-invasive way to track cell growth, extracellular matrix accumulation, and tissue barrier function inside

microfluidic constructs. Electrochemical biosensors for metabolite monitoring provide essential information about tissue health, differentiation state, and response to pharmacological intervention. Dornhoff et al. introduced an organ-on-a-chip platform that integrates electrochemical biosensor arrays based on nanomaterials to detect essential energy metabolites, including oxygen, lactate, and glucose. The convergence of microfluidic chip technology with laboratory automation has enabled high-throughput experimental workflows [54]. Lipreri et al. developed a high-throughput microfluidic platform based on a 96-well microchip for large-scale preclinical evaluation to predict drug efficacy [91]. Conceição et al. made a sex-stratified osteochondral organ-on-chip model that showed sex-specific responses to inflammatory stimulation, showing that male and female bone cells exhibit differential cytokine profiles and matrix remodeling behaviors under inflammatory conditions [92] (Fig. 5C). As these technologies are refined to meet the particular needs of bone and cartilage research, their clinical relevance for modeling pathology, testing drugs, and developing cell therapies will continue to grow.

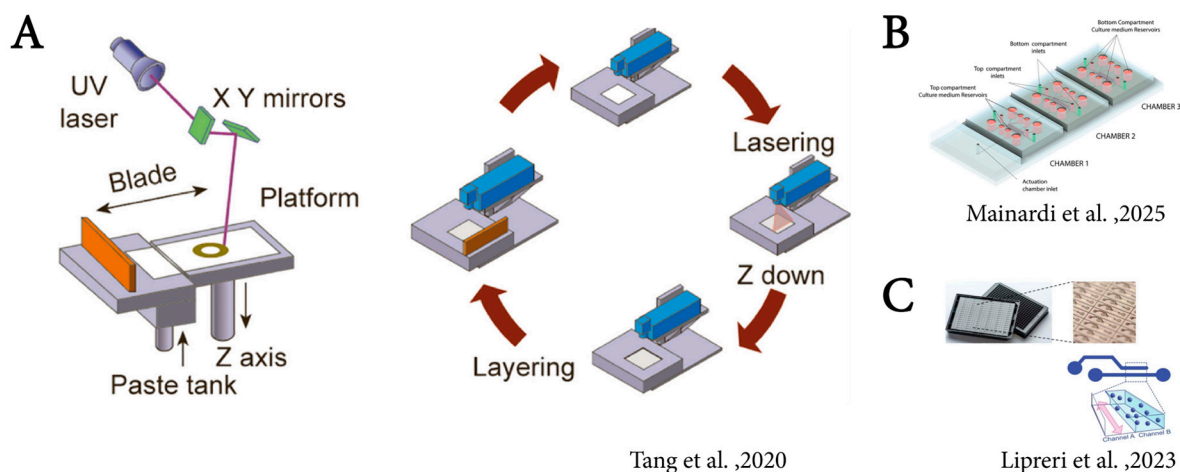


Figure 5: Method of Cartilage/Bone Organ-on-a-Chip. (A) Hybrid HA-PDMS microfluidic chips that supported osteoblast culture, matrix mineralization, and drug screening; (B) An organ-on-chip platform capable of applying strain-controlled, tissue-specific compression to both cartilage and mineralized osteochondral interface makes within a single integrated device; (C) A high-throughput microfluidic platform for large-scale preclinical evaluation. Panels (A–C) are reprinted with permission from Tang et al., 2020 [83] (Copyright 2020, KeAi), Mainardi et al., 2025 [89] (Copyright 2025, Wiley), and Lipreri et al., 2023 [91] (Copyright 2023, IOP science), respectively.

4 Single-Tissue Cartilage/Bone Organoid and Chip Models

4.1 Cartilage Organoid-on-a-Chip

Cartilage organoid-on-a-chip platforms have advanced toward integrated systems that combine the three-dimensional architecture of organoids with the microenvironmental control of microfluidic devices [36–39]. Miao et al. developed biomimetic gradient-structured cartilage organoids using decellularized cartilage extracellular matrix infused with SOX9-overexpressing bone marrow stem cell extracellular vesicles. These organoids were integrated into an osteoarthritis-on-a-chip model with cyclic mechanical stimulation, demonstrating sustained release of chondrocyte-protective factors and effective mechanical resistance through the Vimentin/14-3-3/FOXO3 pathway [49] (Fig. 6A). Upadhyay et al. developed an alginate-chitosan biopolymer composite with decellularized extracellular matrix bioink additive for organ-on-a-chip articular cartilage, showing improved cell adhesion and matrix deposition in microfluidic culture [93]. Xia et al. fabricated cartilage organoid precursors based on GelMA hydrogel microspheres, which promoted chondro-

cyte viability and maintained phenotypic stability under dynamic culture conditions [94]. These integrated platforms demonstrate that combining organoid self-assembly with chip-based perfusion and mechanical stimulation significantly improves cartilage tissue maturation and disease modeling capacity.

Cartilage organoid research still faces material hurdles. Human articular cartilage is simultaneously stiff, tough, and resilient, a combination that synthetic matrices struggle to emulate inside microfluidic devices. Current research struggles to leverage the synergistic potential of cartilage organoids combined with organ chip technologies. Most critically, current cartilage organoid-on-a-chip studies rarely explore underlying signaling pathways in depth, with most investigations limited to phenotypic observations. The distinction between structural biomimicry—recreating the physical appearance of cartilage—and functional biomimicry—recreating the load-bearing, lubrication, and biochemical properties of native tissue—remains a central unresolved issue. The generation of hyaline cartilage versus fibrocartilage continues to show a fundamental challenge, as the latter is biomechanically inferior and more prone to degeneration under physiological loading conditions.

4.2 Bone Organoid-on-a-Chip

Bone organoid-on-a-chip systems have emerged as powerful platforms for modeling bone formation, remodeling, and marrow physiology.

Stelzer et al. developed a human bone and bone marrow-on-a-chip model that integrates autologous primary bone and immune cells on decellularized human trabecular bone scaffolds within a xeno-free, perfused environment. Dynamic flow and sequential cell seeding enabled osteoclast-mediated resorption and osteoblast-driven matrix formation, recapitulating functional bone remodeling, while mature immune cells were maintained for up to forty-two days with preserved functional responsiveness. Single-nucleus RNA sequencing confirmed the presence of major donor-specific immune and bone cell populations, highlighting the potential of this platform for translational and personalized medicine research [43].

Glaser et al. presented an organ-on-a-chip model of vascularized human bone marrow niches containing both perivascular and endosteal compartments with dynamic, perfusable vascular networks. Their model replicated *in vivo* bone marrow function, including maintenance and differentiation of CD34-positive hematopoietic stem and progenitor cells and egress of neutrophils, while mimicking drug responses to doxorubicin and granulocyte-colony stimulating factors [57].

Bone organoid and chip development still confronts notable hurdles. From the inherent complexity and multifaceted functions of bone tissue, few studies have addressed the full spectrum of bone biology. Most, the coupled bone remodeling process mediated by osteoblast-osteoclast interactions remains inadequately modeled in most current systems. While individual studies have captured aspects of bone formation or resorption, the dynamic equilibrium between these processes under physiological and pathological conditions is replicated. Existing models often emphasize mineral content while overlooking bone's distinctive mechanical milieu—cyclic strain, interstitial fluid flow through lacunar-canalicular channels, and the piezoelectric behavior of the mineralized matrix. Similar to the situation in cartilage research, mechanistic pathway studies in bone organoids and chips remain scarce, with most investigations recreating simple phenotypes or biomineralization phenomena. The prevailing focus on structural biomimicry than functional biomimicry is insufficient to capture the adaptive, load-responsive nature of bone in the living organism.

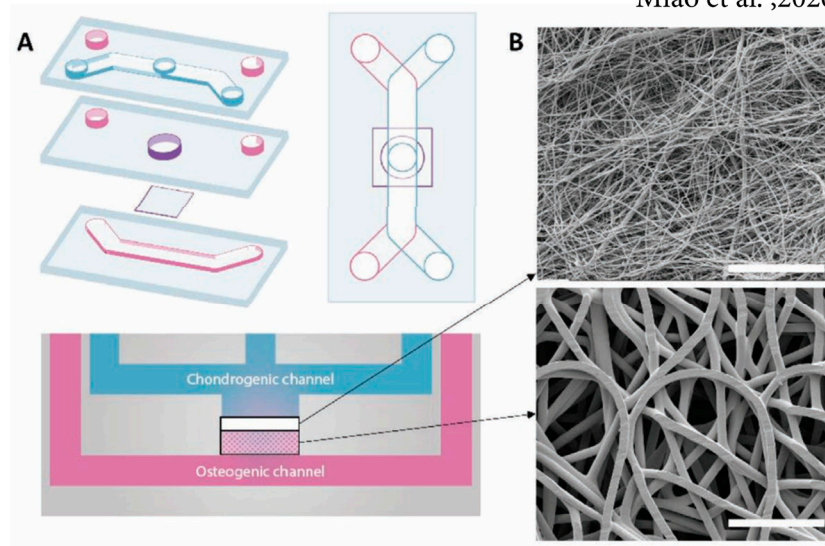
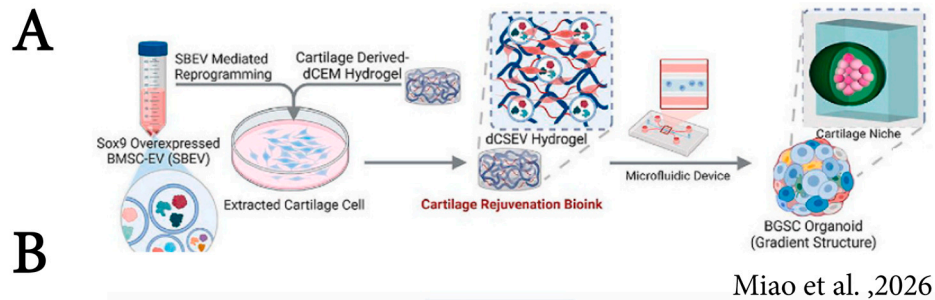


Figure 6: Single- and Multi-Tissue coupled Organoid-on-a-Chip systems. (A) A biomimetic gradient-structured cartilage organoids using decellularized cartilage extracellular matrix infused with SOX9-overexpressing bone marrow stem cell extracellular vesicles; (B) A fibrous polycaprolactone matrix into a chip design with microfiber and nanofiber layers to mimic bone matrix and separation interfaces, Scale bars: 100 μm . Panels (A,B) are reprinted with permission from Miao et al., 2026 [49] (Copyright 2026, KeAi) and Tuerlings et al., 2022 [55] (Copyright 2022, Wiley), respectively.

5 Multi-Tissue Coupled Organoid-on-a-Chip Systems

The transition from single-tissue to multi-tissue coupled systems shows the next frontier in cartilage/bone organoid-on-a-chip research, aiming to recreate the tissue interfaces, paracrine signaling networks, and mechanical couplings that define native joint physiology.

5.1 The Osteochondral Interface

The osteochondral interface involves a gradient from cartilage to bone. Its failure is a major cause of disability.

Tuerlings et al. introduced a fibrous polycaprolactone matrix into a chip design with microfiber and nanofiber layers to mimic bone matrix and separation interfaces, respectively. Upon exposure to active thyroid hormone, this system showed elevated hypertrophic markers, confirming its capacity to recapitulate osteoarthritis disease models [55] (Fig. 6B).

The integration of these signaling networks within osteochondral chip models remains in its infancy, with most current platforms focusing more on replicating structure rather than function.

5.2 Vascularization and Bone Marrow Niche Integration

Vascularization and bone marrow niche integration have advanced through organoid-on-a-chip systems that replicate the hematopoietic microenvironment. Georgescu et al. built a model that relied on the spontaneous self-organization of human blood-forming stem and progenitor cells alongside vascular endothelium within a 3D perfused environment. The resulting tissue replicated key features of the hematopoietic niche, sustaining multilineage blood cell production and enabling mature myeloid cells to enter the perfused vascular network [19].

Torisawa and colleagues created a bone marrow chip that mimics the hematopoietic niche by embedding engineered bone inside a perfused microfluidic device. Their system maintained normal hematopoietic stem cell proportions and supported multiple hematopoietic cell lineages, demonstrating functional reconstruction of the bone marrow microenvironment *in vitro* [56].

Aleman et al. constructed a deconstructed microfluidic bone marrow on-a-chip to study normal and malignant hematopoietic cell-niche interactions, providing a simplified yet physiologically relevant platform for investigating disease mechanisms [95].

The bone marrow niche presents additional layers of complexity that have only begun to be addressed in organoid-on-a-chip systems. Bone marrow serves as a protected niche where hematopoietic stem and progenitor cells are maintained and directed toward specific lineages through direct contact with osteoblasts, osteoclasts, endothelial and perivascular stromal populations, and the surrounding extracellular matrix. These systems have shown promise in supporting short-term hematopoietic progenitor maintenance and in modeling myeloma cell adhesion to bone surfaces. Vascularized bone chips would enable the study of drug delivery, distribution, and metabolism in a relevant context, improving the predictive accuracy of preclinical bone toxicity assessments [96].

Taken together, the two multi-tissue strategies summarized above are complementary rather than competing. Osteochondral interface chips prioritize structural continuity, aiming to reproduce the graded transition between cartilage and subchondral bone that defines joint physiology, whereas vascularized bone marrow platforms prioritize hematopoietic and vascular crosstalk within a mechanically protected niche. The former are maturing toward disease modeling of osteoarthritis and osteochondral defect repair, with readouts centered on matrix gradients and interface mineralization; the latter are advancing toward hematologic malignancy modeling and marrow-toxicity testing, with readouts centered on multilineage hematopoiesis and niche integrity. Both nevertheless face a shared bottleneck: robust, quantitative criteria for validating tissue-tissue crosstalk remain to be established before either platform can claim genuine functional biomimicry.

6 Conclusion

Cartilage/bone organoid-on-a-chip technology offers capabilities for microenvironmental control and high-throughput modeling. Monoculture platforms have matured enough to mimic disease phenotypes and support compound testing, and newer devices are beginning to link cartilage and bone compartments in a single microfluidic circuit [97].

Nevertheless, there remain numerous common challenges in current research within this field. First, biomimetic materials have unsatisfactory properties [98]. No single synthetic material yet recapitulates both the structural mechanics and biological responsiveness of native bone or cartilage matrix. Second, simulating multi-cellular systems and complex microenvironments poses great difficulties. The multicellular coupling effects and intricate microenvironments of bone tissues can hardly be precisely reproduced *in vitro*, and the physiological relevance of organoid and chip models needs to be further improved [36]. A

further limitation is the shallow coupling between organoid culture and microfluidic chip technologies: the spatial complexity of self-assembled tissues and the precise environmental control offered by perfusion devices remain largely separate capabilities. Fourth, prominent bottlenecks exist in clinical translation. Most existing studies are limited to small animal experiments, lacking data support from large animal trials and early clinical researches. Standardized build criteria and quality metrics are still lacking. Fifth, the scope of research is relatively narrow. While current models have expanded into muscle, synovium, and tendon, most applications still concentrate on degenerative diseases and injury repair, with limited use in areas such as bone tumors, rare bone metabolic disorders, and neuromuscular diseases.

Future work should target the following: (i) developing composite biomaterials that match the mechanical properties and biological activity of native bone and cartilage; (ii) establishing precise multi-cellular co-culture systems incorporating physiologically relevant mechanical loading, fluid flow, and chemical gradients; (iii) integrating organoid three-dimensional architecture with chip-based microenvironment control to improve model fidelity and enhance screening efficiency; (iv) standardizing construction protocols, quality assessment metrics, and validation frameworks to accelerate clinical translation; and (v) expanding disease models beyond osteoarthritis and osteoporosis to a broader spectrum of related conditions. Achieving these advances will require in-depth interdisciplinary collaboration to overcome existing technical bottlenecks and drive musculoskeletal organoid-on-a-chip technologies from the laboratory to clinical practice.

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Abbreviations

The following abbreviations are used in this manuscript:

BMSCs: bone marrow mesenchymal stem cells; dECM: decellularized extracellular matrix; GelMA: gelatin methacryloyl; HA: hydroxyapatite; hPSCs: human pluripotent stem cells; iPSCs: induced pluripotent stem cells; IL-1 β : interleukin-1 beta; OA: osteoarthritis; PDMS: polydimethylsiloxane; SMSCs: synovial membrane-derived mesenchymal stem cells; TGF- β : transforming growth factor beta; HSPCs: hematopoietic stem and progenitor cells.

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