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The osteochondral regeneration paradox: why biomimetic scaffolds are biologically superior but injectable systems dominate the clinic

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Musculoskeletal disorders (MSDs), particularly articular cartilage injuries and the progression of osteoarthritis (OA), represent a substantial global health burden. Conventional techniques fail to consistently achieve durable regeneration, yielding biomechanically inferior fibrocartilage due to the native tissue's avascularity and complex zonal architecture. This review translates the critical biological, mechanical, and architectural requirements of the osteochondral unit into quantitative design targets and critically evaluates two major regenerative strategies: structurally precise architected biomimetic scaffolds and minimally invasive injectable hydrogels. Our analysis reveals a fundamental trade-off between technical potential and translational feasibility. Architected scaffolds, fabricated using advanced methods like 3D printing and melt electrowriting, demonstrate superior capacity to meet structural demands. They achieve precise zonal stiffness gradients, secure bone anchorage, and immediate high-load-bearing capability necessary for long-term chondrocyte phenotype stabilization and faithful tissue reconstruction. In contrast, injectable hydrogels excel in defect conformability, logistical simplicity, and microenvironmental programming (*e.g.*, controlled growth factor release, viscoelastic tuning), offering a patient-friendly, single-stage delivery. However, clinical success is governed by a persistent paradox: the technical potential of a therapy is inversely related to its regulatory and commercial viability. Scaffold-based constructs, due to their complexity, surgical invasiveness, and customization needs, face severe regulatory hurdles (*e.g.*, ATMP/Class III classification) and high associated costs. Conversely, the batch manufacturability and minimal invasiveness of injectable systems grant them a smoother regulatory path and broader market adoption, despite often resulting in monophasic repair with limited long-term mechanical fidelity. We conclude that the field of osteochondral regeneration is shaped by this structural asymmetry. While scaffolds represent the platforms most capable of delivering faithful structural repair, injectable systems are the primary route by which innovation reaches the patient. Future success depends on either the development of hybrid strategies that reconcile architectural control with surgical simplicity, or the evolution of regulatory frameworks to accommodate the necessary complexity for true tissue regeneration.

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Introduction

Clinical context

Musculoskeletal disorders (MSDs) are a broad group of injuries and diseases that affect muscles, tendons, ligaments, bones and joints. They are among the most prevalent and disabling non-communicable diseases worldwide, and their burden is expected to rise, primarily due to extended life expectancy,[1] with it already reaching 1.71 billion people (about 22 in 100 persons)[2] globally. Among MSDs, conditions that involve the articular cartilage and the osteochondral junction are especially consequential. This is because cartilage has minimal intrinsic repair capacity, and defects destabilize joint mechanics, predisposing pain, recurrent symptoms, and structural deterioration, all of which diminish the quality of life of millions of individuals globally.

The prevalence of cartilage damage is significant. For example, people with painful knees where arthroscopy was used as a diagnostic tool (a minimally invasive procedure to look inside the joint) found that damage to the joint cartilage is seen in about 60–66% of cases.[3] Specifically, deep full-thickness defects make up roughly 4–6% overall and can reach ~36% of cases in athletes.[4] Beyond the knee, cartilage-involving conditions are common: osteochondritis dissecans of the knee (~6 per 100 000 people each year),[5] osteochondral lesions of the talus in the ankle (~27 per 100 000 per year),[6] and lateral

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patellar dislocation (~14 per 100 000 per year).[7] Across these presentations, about 43% show combined cartilage–bone injury, which underscores how frequently cartilage damage extends beyond the knee and how often bone is involved.

Beyond focal injuries is osteoarthritis (OA), the most common joint disease, which involves a whole-joint failure that begins with cartilage wear and progresses to changes in bone and the joint lining, causing pain and stiffness. Globally, about 528 million people live with OA (~7%), with the knee most often affected (≈365 million cases).[8] This means that over a lifetime, nearly 1 in 2 people may develop symptomatic knee OA, and injuries contribute meaningfully. Contextualizing these data, cartilage-related MSDs carry disproportionately poor functional outcomes compared with many other MSDs unless regeneration of the articular surface and osteochondral unit is achieved, a goal that remains unmet in routine care and is reflected in current clinical practice.

Biology and architecture of articular cartilage

Articular cartilage is a region only few millimetres in thickness located at the ends of long bones within synovial joints. It plays a critical role in joint function by distributing mechanical loads, minimizing friction and enabling smooth, pain-free movement.[9,10] The core challenge in its regeneration is its intrinsic biology: the tissue is avascular, aneural, hypocellular and architecturally graded.[11] Its mechanical resilience and load-bearing capacity derive from its highly organized extracellular matrix (ECM), which exhibits pronounced zonal anisotropy. The ECM is primarily composed of type II collagen, forming heterotypic fibrils with type XI and type IX collagens, and aggrecan, a large proteoglycan decorated with negatively charged glycosaminoglycans (GAGs), such as chondroitin sulphate and keratan sulphate.[12] These GAGs draw in water, creating an osmotic swelling pressure that is counterbalanced by the collagen network, resulting in a unique viscoelastic tissue capable of shock absorption and wear resistance.[13]

Of the tissue's architecture is organized into superficial, middle, deep, and calcified zones, where smooth, graded transitions in collagen orientation and proteoglycan content across these layers enable the tissue to accommodate shear, compression, and interfacial stresses (Fig. 1). The superficial zone has the highest water content (~80%), low proteoglycan concentration, and densely packed, flattened chondrocytes. It is rich in collagen type II, with minor amounts of type IX, and features collagen fibres aligned parallel to the surface, providing resistance to shear forces and contributing to lubrication. The middle (or transitional) zone contains rounded chondrocytes, randomly oriented collagen fibres, a high concentration of proteoglycans, and a moderate water content of approximately 70%. This composition enhances the zone's compressive properties, making it particularly well suited to absorb and distribute mechanical loads. Proteoglycans, particularly aggrecan, contribute to this function by attracting and retaining water through their glycosaminoglycan (GAG) side chains, thereby increasing the tissue's resistance to compressive forces. The deep zone is characterized by vertically aligned collagen fibres (mainly type II), the highest proteoglycan content, and a slightly lower water content (~65–70%), which together enable it to resist compressive forces. Chondrocytes in this zone are larger and arranged in columns perpendicular to the surface. Finally, the calcified zone has the lowest water content (~40–45%), contains type X collagen, and is mineralized, forming a mechanical and biochemical transition between cartilage and subchondral bone. Proteoglycan content in this zone is minimal, reflecting its low hydration and stiff,

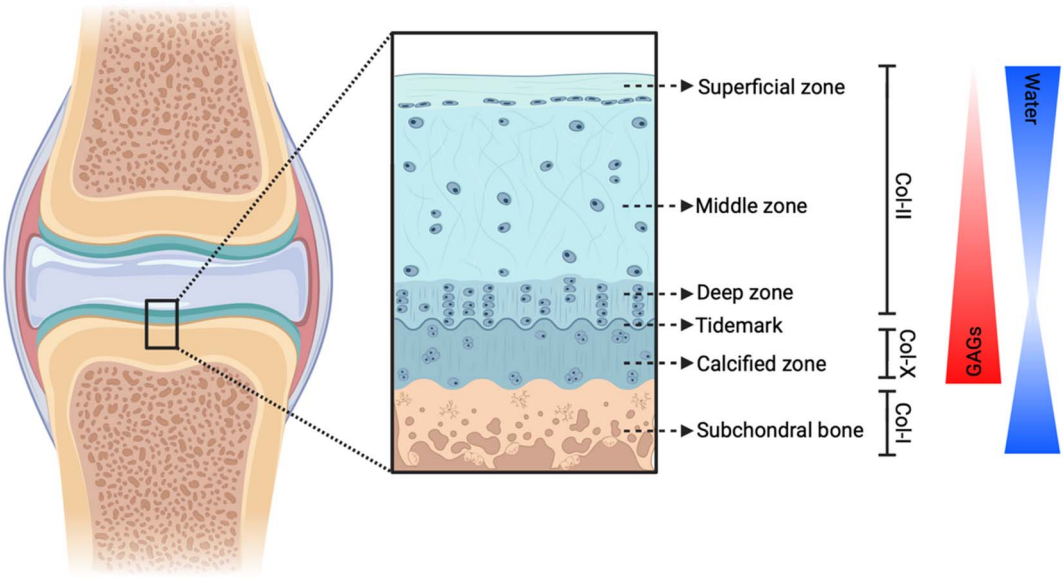

Fig. 1 Zonal Architecture of the Osteochondral Unit. Schematic of articular cartilage and subchondral bone showing zonal organization, collagen orientation, and gradients of water and glycosaminoglycans (GAGs). The tidemark marks the transition to the calcified zone anchoring the tissue to bone. Created with Biorender (R).

mineralized matrix. This reduction facilitates load transfer and contributes to anchoring the cartilage while maintaining osteochondral integration.[10,12,14]

Current clinical interventions

Consistent with these biological constrains, clinical interventions have been developed over recent decades to manage cartilage injuries and osteochondral defects, though with limited success. Main approaches (Fig. 2) can be characterized as palliative, reparative, or restorative. Palliative strategies, such as anti-inflammatory medications, are aimed at managing symptoms without targeting the underlying defect.[15,16] Reparative techniques, including microfracture or drilling, attempt to stimulate intrinsic healing by accessing bone marrow-derived cells, but typically result in the formation of fibrocartilage, which lacks the durability and biomechanical properties of native tissue.[17–19] Lastly, restorative procedures, such as autologous chondrocyte implantation or osteochondral grafting, seek to reconstruct the damaged area with more functional tissue. While often more effective in the short term, these approaches face challenges related to surgical complexity, integration, and long-term performance.[20–22] In this sense, while these clinical interventions have provided short-term improvements, they often fall short of achieving consistent, long-lasting outcomes, particularly in large or complex lesions.

Review scope and perspective

The limited and inconsistent outcomes of current interventions motivate the approach of the present review, which translates the underlying biological constraints into requirements for biomaterial scientists and biomedical engineers, and evaluates strategies across five domains: biological, mechanical, architectural, clinical, and regulatory. The article begins with the biological challenges, focusing on extracellular-matrix replication, cell sourcing, and the regulation of chondrogenesis. Then, the article assesses the mechanical requirements, including graded modulus, viscoelastic response, lubrication and wear, fatigue resistance, and degradation matched to tissue maturation. Next, we provide an examination of architectural strategies that recreate continuous gradients of composition, porosity, and stiffness with robust anchorage across the calcified layer and strong interlayer cohesion. The article follows with clinical

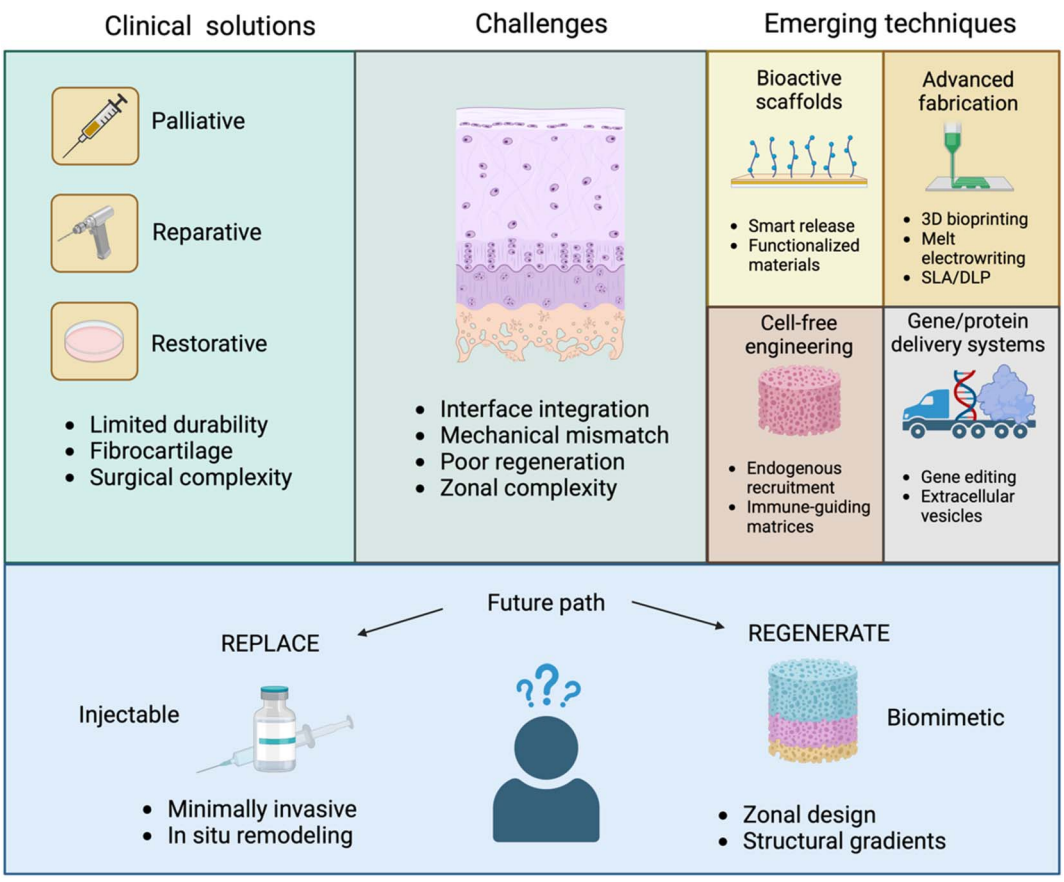

Fig. 2 Graphical abstract. This graphical abstract illustrates the progression from current clinical approaches to advanced regenerative strategies in osteochondral repair. While existing treatments—palliative, reparative, and restorative—are limited by fibrocartilage formation, poor integration, and surgical complexity, they highlight the biological and mechanical challenges of the osteochondral unit. Emerging techniques such as bioactive scaffolds, advanced fabrication methods, cell-free systems, and gene/protein delivery aim to overcome these limitations. Future approaches diverge between minimally invasive, injectable solutions and complex, biomimetic constructs that guide zonal regeneration. Created with Biorender (R).

and translational considerations that influence real-world performance, including model selection, advanced *in vitro* platforms, trial design, patient stratification, and surgical workflow. Finally, regulatory and commercial pathways are considered encompassing product classification, GMP manufacturing and quality, reimbursement, and adoption. Throughout, we emphasize quantitative design targets and decision points that distinguish regeneration from replacement, proposing criteria to judge readiness for clinical use. Where relevant, we position tissue-engineered products (cell-laden or pre-cultured constructs, including iPSC-/MSC-based grafts) within this landscape, while keeping the primary focus on biomaterial platform requirements rather than cell-manufacturing workflows.

Within this framework, two principal approaches shape how research groups seek to solve the core challenges of cartilage regeneration. The central question is: should damaged cartilage be replaced using injectable systems that promote *in situ* remodelling with minimal invasiveness, or regenerated using biomimetic scaffolds that encode zonal design and structural gradients? injectables promise single-stage delivery, defect conformability and shorter operative time, yet they must provide early mechanical stability, low friction and tightly controlled remodelling without hypertrophy. Biomimetic scaffolds can deliver immediate load bearing, graded stiffness and secure anchorage at the osteochondral junction, but they require precise fit, strong interfaces and more complex manufacturing and regulation. Comparing these strategies against a common performance target in the context of clinical translation can highlight what really matters for cartilage and osteochondral repair.

Barriers and directions in cartilage and osteochondral repair

Since Eric Lexer's first attempt at osteochondral repair in 1908,[21] restoring this complex tissue remains a major challenge in regenerative medicine. Given the burden and failure patterns outlined above, osteochondral repair is limited by interconnected challenges across biology, engineering and clinical translation (Fig. 3). Despite more than a century of attempts, these challenges present clinically as persistent failure to restore a low-friction surface, graded load transfer, and stable anchorage at the osteochondral junction across focal injuries and in early or post-traumatic osteoarthritis. The following sections reframe those deficits as design requirements and examines why solutions struggle to meet them, with subsections examining how the biological, mechanical, architectural, clinical and translational, and regulatory and commercial domains enable or block progress toward these targets.

Biological challenges

The most significant biological challenges in cartilage repair and regeneration are rebuilding a low-friction hyaline surface,

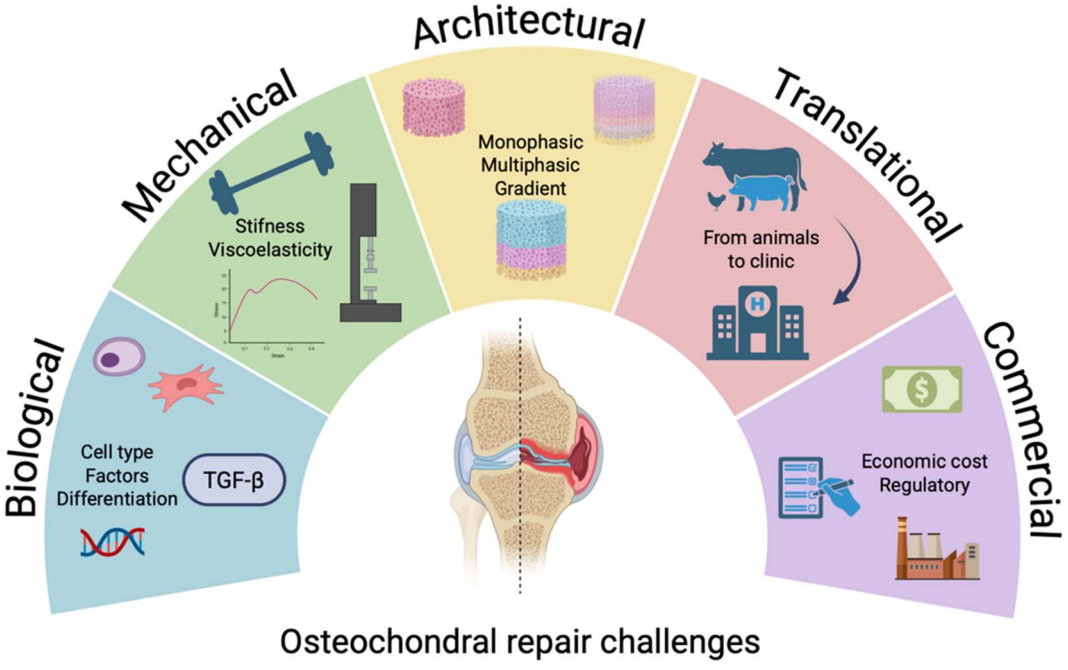

Fig. 3 Multifactorial challenges in osteochondral repair. Osteochondral repair requires addressing a complex set of challenges spanning biological, mechanical, architectural, translational, and commercial domains. Biologically, the choice of cell type, control of differentiation, and integration of signalling factors such as TGF-β are critical for directing tissue-specific regeneration. Mechanical challenges include replicating the native load-bearing properties and accommodating the stiffness gradient across cartilage and bone. Architecturally, the design of scaffolds—whether monophasic, multiphasic, or gradient—is essential to mimic the hierarchical structure of the native osteochondral unit. Translationally, differences between preclinical animal models and human anatomy present barriers to clinical application. Commercially, successful implementation depends on meeting regulatory requirements, achieving GMP compliance, and ensuring cost-effectiveness for large-scale production. Together, these interconnected factors define the current limitations and guide future directions in osteochondral tissue engineering. Created with Biorender (R).

restoring depth-wise load transfer with firm anchorage at the calcified layer, and maintaining a stable, non-hypertrophic matrix over time. These outcomes hinge on biological constraints that make this tissue unusual among musculoskeletal targets: a highly specialized extracellular matrix with pronounced zonal organization, a unique collagen–proteoglycan architecture, and a finely regulated, avascular microenvironment. These features are central to its mechanical resilience and biological function, but they also present major hurdles for regenerative strategies.

At the biological level, osteochondral repair is limited by five critical challenges: (1) replicating the complex extracellular matrix of native cartilage going a step further than "collagen plus proteoglycan"; (2) identifying stable and functional cell sources that do not lead to supply limitations and promotion of undesired cell behaviour such hypertrophy; and (3) fine-tuning the biochemical and mechanical cues that regulate chondrogenesis; (4) identifying stable, scalable and functional cell sources while preserving phenotype during expansion and after implantation; and (5) coordinating stage-specific biochemical and mechanical stimulation with spatial and temporal precision to yield durable, non-hypertrophic cartilage under physiological demand.

ECM replication. Replicating the extracellular matrix (ECM) of native hyaline cartilage remains a core biological challenge in osteochondral repair. Beyond molecular composition, success depends on reproducing the spatially organized and dynamic matrix that cells build and maintain. In native tissue, collagen II fibrils align parallel to the surface in the superficial zone to resist shear, rotate through the middle zone, and orient perpendicular in deeper zones to withstand compression. Minor collagens (IX, XI) stabilize the collagen II network, while collagen X localizes to the calcified cartilage, enabling mineral integration and secure anchorage to subchondral bone. Combined with depth-dependent proteoglycan content and matrix crosslinking, these gradients create the anisotropic, load-bearing architecture of cartilage.

From a biological standpoint, the recurring limitation in engineered constructs is not the initiation of matrix synthesis but the guidance and stabilization of these patterns under physiological demand. Constructs may deposit type II collagen and GAGs but still lack durable superficial fibrillar alignment, appropriate depth-wise increase in proteoglycans, or mature crosslinking. This results in lower tensile response at the surface, insufficient fluid pressurization in deeper regions, and heightened susceptibility to fatigue. Empirically, tensile behaviour in the superficial zone scales with collagen fibre alignment,[23] while depth-dependent increase in GAGs underlie compressive pressurization at depth,[24] and the maturation of enzymatic collagen crosslinks contributes to long-term strength and fatigue resistance.[25] Over time, a suboptimal organization can couple with joint loading to drive phenotypic drift (*e.g.*, hypertrophy) despite adequate early induction. Consistent with this, hMSC-based constructs exposed to non-optimal signalling/load frequently show hypertrophic drift and ectopic mineralization *in vivo*,[26] underscoring the need to couple architectural organization with stage-specific biochemical and mechanical cues.

Accordingly, ECM replication hinges on a small set of format-agnostic biological levers that act in concert across delivery formats. First, stage-specific morphogen exposure is essential: early TGF-β/BMP signalling initiates chondrogenesis, but anti-hypertrophic scheduling—tapering agonists or introducing counter-cues after lineage commitment—helps decouple induction from ossification. As an illustration of timed delivery, a bilayer microsphere hydrogel that released bevacizumab followed by IGF-1 improved regeneration *in vivo*.[27] Second, the microenvironment must be joint-like: hypoxia, physiological osmolarity/ion balance, and a tempered inflammatory tone promote aggrecan deposition and restrain catabolism. Hypoxia-mimicking scaffolds that elute DMOG/PTHrP exemplify this principle.[28] Third, mechanobiology consolidates the matrix when loading is staged to maturation: dynamic compression, hydrostatic pressure, and low-shear stimulation reinforce assembly and retention, whereas premature or excessive loading is counterproductive.[29,30] Fourth, pericellular matrix integrity and boundary lubrication sustain phenotype: a hyaluronan-rich PCM together with surface PRG4 maintains rounded morphology and low friction.[31,32] Finally, crosslink maturation under appropriate redox and nutrient conditions (*e.g.*, LOX-mediated) improves long-term mechanical fidelity.[25] These requirements apply to both biomimetic scaffolds and injectable hydrogels.

Chemical regulation of extracellular matrix and hypertrophy. The recurrence of phenotypic drift and ectopic mineralization in engineered constructs remains a central biological limitation, and material chemistry dictates these biological outcomes.[26,33] The stability of the engineered hyaline matrix under physiological demand hinges on chemical solutions. Preventing hypertrophy often relies on sophisticated anti-hypertrophic scheduling (tapering or removing pro-chondrogenic agonists like TGF) after lineage commitment.[34] This temporal control is achieved through specific material chemistry approaches, including controlled release kinetics and multiphase release systems. Controlled release relies on the tethering of bioactive molecules, like growth factors, using cell-sensitive bonds, such as MMP-cleavable linkers. As cells remodel the matrix, they enzymatically release the factor, enabling precise, cell-mediated sequential delivery schemes. The latter approach utilizes bilayer microsphere hydrogel systems that are programmed to release factors in sequence (*e.g.*, bevacizumab followed by IGF-1). These systems require finely tuned polymer degradation and encapsulation chemistry to improve regeneration outcomes.[27]

Chemomechanical tuning and viscoelasticity. Viscoelasticity is a property governed fundamentally by polymer network chemistry, specifically the nature and density of crosslinks and the relaxation time of the network. Polymer network chemistry also governs stiffness/modulus (largely set by polymer content and crosslink density), but viscoelasticity is emphasized because, across materials with comparable stiffness, stress-relaxation kinetics have emerged as a particularly tunable and cell-instructive lever. Stiffness/elasticity targets dictated by

joint-level load bearing are discussed in detail under "Mechanical Challenges". This material property acts as an instructive signal for cell fate, equivalent to morphogens. Articular cartilage exhibits complex viscoelastic behaviour essential for shock absorption. When designing materials to mimic this, the viscoelastic stress relaxation profile becomes a deterministic chemical control lever. Emerging evidence demonstrates that faster-relaxing collagen hydrogels promote long-term chondrogenesis and survival through ROCK-dependent pathways. This confirms that tuning the time-dependent mechanical signature of the scaffold (*e.g.*, through materials with dynamically reversible bonds) is a powerful method for stabilizing chondrocyte phenotype. While injectable hydrogels offer flexibility for microenvironmental programming, the chemical principles (ligand presentation, viscoelastic dissipation, controlled release) can be engineered into architected scaffolds (*e.g.*, by embedding viscoelastic interlayers).

The shared approach in both technologies consists in offering immediate load sharing and stable boundary conditions that help maintain phenotype. Hydrated networks can preserve a chondrogenic microenvironment, host precisely dosed morphogens, and provide viscoelastic dissipation that aids cell survival. For biomimetic scaffolds, concrete examples illustrate the biological levers implemented through architecture. For example, 3D-woven anisotropic scaffolds provided immediate load sharing and preserved a rounded chondrocyte phenotype while achieving native-scale tensile/compressive/shear properties.[35] If these lattices were formed by nanofibrous anisotropic composites, chondrogenic gene expression was promoted as well as functional maturation.[36] Another study showed that multilayer collagen-hydroxyapatite constructs, including clinically used tri-layers, sustain zonal microenvironments and have shown structural and clinical benefits in randomized trials.[37] Scaffolds can also biologically support superficial boundary conditions by presenting or recruiting PRG4 (lubricin) to reduce friction and wear.[31] Finally, scaffold-mediated spatiotemporal cueing enables staged or localized delivery of morphogens to enhance chondrogenesis while limiting hypertrophy. The main idea is engineering the scaffold so different zones deliver cues at specific times during the regeneration process. For example, a superficial layer releases PRG4 early on to stabilize boundary lubrication, a middle zone presents TGF-β3 for induction, and deeper regions release IGF-1 at later timepoints for matrix anabolism. Alternatively, growth factors can be tethered to the scaffold using MMP-cleavable linkers, so that cells release them as they remodel the matrix, enabling scaffold-based sequential or zonal delivery schemes. For instance, PLGA microsphere-based scaffolds programmed to release IGF-1 and TGF-β1 in sequence[38] or silk-fibroin/decellularized-cartilage composite scaffolds providing sustained TGF-β3 delivery.[39]

From a strictly biological perspective, injectable hydrogels do not confer an exclusive capability relative to biomimetic scaffolds. Rather, they offer a convenient way to program a highly hydrated, finely dosed niche. For example, fast-relaxing hydrogels that sustain long-term chondrogenesis[40] controlling the viscoelastic properties that can be reproduced in biomimetic scaffolds (*e.g.*, by embedding viscoelastic interlayers or MMP-responsive tethering), yielding very similar biological outcomes.

For injectable systems, complementary strengths arise from their microenvironmental programming flexibility (also achievable with scaffolds) and superior defect conformability. A few studies involving injectable systems demonstrated that cartilage-derived dECM hydrogels immunomodulate and sustain chondrogenesis,[41,42] self-assembling peptides support hyaline-like repair in primate defects,[43] photocurable HA networks improve retention and early repair in large animals,[44] and fast-relaxing viscoelastic hydrogels promote long-term chondrogenesis *via* ROCK-dependent pathways.[40] Even when chondrogenic differentiation is robust, the absence of zonal fibrillar alignment and depth-dependent proteoglycan gradients limits long-term biomechanics. The features that implement these patterns are therefore not merely structural choices but biological enablers of a stable hyaline matrix; their practical realization is addressed next in the architectural domain.

Cell sourcing. Beyond matrix production, a second major biological hurdle lies in cell sourcing. Autologous chondrocytes remain the clinical gold standard in techniques like autologous chondrocyte implantation (ACI),[22] but they have limited proliferative capacity, require harvesting through invasive procedures, and tend to dedifferentiate during expansion, leading to fibrocartilage formation rather than hyaline matrix.[45] Although protocols to preserve chondrocyte phenotype during culture have been proposed, they often come at the expense of cell yield or viability. Mesenchymal stem cells (MSCs), commonly derived from bone marrow or adipose tissue, have gained popularity due to their accessibility and multipotency.[46,47] However, MSCs are a heterogeneous population, and their chondrogenic potential is highly sensitive to subtle variations in culture conditions and local environments.[47] These factors contribute not only to inconsistent cartilage formation but also to a frequent tendency toward hypertrophic differentiation and subsequent ossification *in vivo*, outcomes that compromise the long-term stability and function of the regenerated tissue.[33] Despite ongoing efforts to refine sorting techniques or apply preconditioning protocols, reliably generating MSC-derived cartilage that is both phenotypically stable and hyaline in character remains a major challenge.

Alternative sources such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) offer virtually unlimited proliferation and the ability to generate chondrocyte-like cells.[48–50] However, these sources come with unique biological and safety challenges. Achieving full and stable chondrogenic differentiation is nontrivial, and the risk of incomplete reprogramming or residual pluripotency raises concerns about tumorigenicity.[51,52] In addition, pluripotent-derived chondrocytes often lack the zonal identity of native cartilage. Although promising protocols have been developed to guide differentiation through developmental pathways, they often require complex, multi-step processes that are difficult to scale or standardize. As a result, ESCs and iPSCs remain largely confined to preclinical research.

For cell sourcing decisions, delivery platform selection (architected biomimetic scaffolds *versus* injectable hydrogels) directly conditions post-implantation performance of autologous chondrocytes and MSCs. Emerging evidence indicates that the spatially ordered architecture of biomimetic scaffolds (fibre diameter and alignment, pore interconnectivity, and multiphasic zonal layering) acts as a primary stabilizer of chondrogenic behaviour in a cell-source-dependent manner. For autologous chondrocytes, electrospun nanofibre composites preserve a rounded morphology and upregulate COL2A1/ACAN while keeping COL1A1 low compared with flat or microfibrous controls, isolating topography as the driver of phenotype maintenance.[53] Likewise, 3D-woven anisotropic scaffolds seeded with chondrocytes generate constructs whose compressive, tensile and shear properties approach native cartilage, indicating that an architected load-bearing lattice can promote functional maturation without exogenous biochemical conditioning.[35]

For bone-marrow-derived MSCs, ordered architecture alone rarely abolishes hypertrophy, yet it is a necessary determinant of fate under physiologic loading and interface context: in osteochondral implants, chondrogenesis under kinematic load depends on the presence of an underlying osteo component. This shows that coupling between zones lets the structure mediate mechanotransduction.[54] When architectural cues are combined with a defined ECM signal, hypertrophy markers (COL10A1, RUNX2) are suppressed while chondrogenesis is maintained, underscoring architecture as an enabling scaffold for cue delivery rather than a dispensable add-on[55] (Liu *et al.*, 2018). In pluripotent-derived chondrocytes, 3D nanofibrous scaffolds alone increase chondrogenic markers and support defect repair *in vivo versus* non-architected controls, pointing to architecture as the principal instructive signal in this cell type.[56] Lastly, from a mechanistic perspective, recreating the calcified-cartilage-to-bone transition introduces a diffusion- and vascular-ingress barrier and a stiffness gradient that together favour hyaline cartilage stabilization at the interface.[57] Taken together, ordered biomimetic architectures are key to stabilizing specific cell sources (especially autologous chondrocytes and pluripotent-derived cells) and, while foundational for MSCs, it will likely be coupled with biochemical and mechanical conditioning in next-generation designs.

In parallel to architected solids, injectable hydrogels provide a material-intrinsic microenvironment (hydration, HA–receptor interactions, viscoelastic stress relaxation, and *in situ* anchoring) that stabilizes chondrogenic behaviour, while also serving as carriers for precisely dosed morphogens. For autologous chondrocytes, hyaluronic-acid (HA) networks with tuneable crosslinking and macromer content preserve a rounded phenotype and support neocartilage deposition *in vitro* and after implantation, indicating that the gel's chemistry and network structure by themselves sustain chondrocyte identity.[58] For MSCs, time-dependent mechanics are determinative: faster-relaxing collagen hydrogels promote long-term chondrogenesis and survival *via* ROCK-dependent pathways, identifying matrix viscoelasticity as an instructive, hydrogel-intrinsic variable.[40] Conversely, when the clinical goal is suppressing hypertrophy, controlled local delivery of TGF-β3 from within the gel is typically required, underscoring that the hydrogel provides the niche and kinetics rather than the sole stabilizing signal.[59] For iPSC-derived chondrocytes, GelMA encapsulation alone preserves phenotype and matrix-forming capacity *in vitro* and supports hyaline-like repair potential *in vivo*, pointing again to the microenvironmental contribution of a hydrated, cell-adhesive network.[60] Additional hydrogel-intrinsic traits not directly related with cell-sourcing but important include immunomodulatory cues for signalling in injectable cartilage dECM that sustains chondrogenesis,[41] photopolymerizable HA that improves retention and early repair in large animals,[44] or piezoelectric composites that transduce ultrasound or joint loading into local bioelectric cues.[61] It is important to highlight that, despite injectable hydrogels can present a more convenient scenario in terms of viscoelasticity, none of these advantages is exclusive to injectables. Ligand presentation, viscoelastic dissipation, adhesive fixation, controlled release, and even piezoelectricity can be engineered into architected biomimetic scaffolds, arguing that injectable hydrogels do not confer an inherent edge over scaffolds for overcoming the biological challenges of phenotype stabilization, but rather offer a complementary route that can be leveraged synergistically in hybrid designs.

Chondrogenesis regulation. Beyond selecting the right cell source, a major biological challenge lies in the precise regulation of chondrogenesis itself. While issues like hypertrophic differentiation and ossification often arise from poorly controlled signalling environments, they ultimately reflect a deeper problem: the difficulty of delivering biochemical and mechanical cues with the spatial and temporal precision needed to guide stable cartilage formation. In native cartilage, these signals are tightly coordinated within a load-bearing, avascular matrix, a level of complexity that remains difficult to replicate *in vitro*.

Growth factors such as transforming growth factor-beta (specifically TGF-β3) and bone morphogenetic proteins (BMPs) are essential for promoting chondrogenic differentiation and stimulating ECM synthesis.[62,63] However, their effects are dose- and context-dependent: while they drive early chondrogenesis,[64] excessive or prolonged stimulation often results in hypertrophic differentiation and eventual ossification. To address this, anti-hypertrophic scheduling (*i.e.*, tapering or removing chondrogenic agonists after commitment, or counter-balancing them with hypertrophy-suppressive cues) can decouple early induction from late hypertrophic drift.[34] Beyond growth factors, the tissue context (low oxygen tension, avascularity, and physiological osmolarity) acts as a co-determinant of fate stability. Hypoxia, in particular, enhances chondrogenic gene programs and can mitigate hypertrophy when applied at the appropriate stage. Practically, achieving the necessary precision hinges on delivery platforms able to stage factor exposure and shape gradients, as discussed in the section on biochemical augmentation.

Mechanical stimuli are equally critical to stabilize chondrogenesis. Most mechano-stimulation studies aiming at hyaline-like chondrogenesis therefore prioritize dynamic

compression and/or cyclic hydrostatic pressure, which are generally associated with increased cartilage-like matrix synthesis when applied at physiological amplitudes and appropriate maturation stages. Shear loading (or fluid-flow shear) can modulate superficial-zone programs and boundary lubrication, but in isolation it is often less chondrogenic than compressive regimes and is highly dependent on magnitude and context. Tensile strain, while present *in vivo*, tends to bias cells toward more fibrous or mixed phenotypes and is therefore typically controlled or used deliberately in fibrocartilaginous contexts; comprehensive discussions are available elsewhere.[65,66] Taken together, these biological challenges reveal a central question: how to coordinate stage-specific biochemical induction with appropriately sequenced loading to yield stable, non-hypertrophic cartilage under physiological demand? overcoming this will require integrative strategies that not only support cell viability and differentiation but also provide spatial and temporal control over the signals that drive stable cartilage formation.

In the context of our comparison between architected scaffolds and injectable hydrogels, the delivery format may play a role in this coordination. The chondrogenic cues themselves are not unique to any single format, as is also the case for cell sourcing; both architected scaffolds and injectable hydrogels can, in principle, present the requisite biochemical signals and mechanical context when properly engineered. Injectable hydrogels promote chondrogenesis primarily through implementation of biological cues in the elements of the hydrogel. An injectable GelMA hydrogel delivering TGF-β1 to BMSCs used this growth factor as the principal inductive signal and repaired rabbit nasal septum cartilage, with higher histological scores and ECM deposition.[67] A RADA-16 self-assembling peptide hydrogel provided sustained TGF-β1 release to maintain the chondrogenic program over time and yielded superior tissue morphology *versus* controls.[68] Moving beyond single cues, a bilayer-microsphere composite applied a sequential schedule in which bevacizumab first preserved the avascular niche and IGF-1 subsequently drove matrix anabolism, improving cartilage regeneration in a growth-plate injury model.[27] Besides providing immediate load-bearing and anisotropy, architected scaffolds can localize biological cues in space. 3D-printed scaffolds with a kartogenin (KGN) biochemical stimulus gradient enhanced osteochondral regeneration *in vivo*, showing that architectural zoning can spatially localize inductive cues to direct chondrogenesis.[69] In a different study, gradient, dual-factor-releasing 3D-bioprinted constructs delivered pro-chondrogenic morphogens in zonal patterns, restoring anisotropic properties and improving integration in preclinical models.[70]

From a biological challenge perspective, injectable hydrogels are often the better choice to initiate and stabilize chondrogenesis because they allow precise programming of dose, timing, and gradients of inductive cues while conforming to complex defects and preserving an avascular milieu. Architected biomimetic scaffolds are preferable when spatial localization of signals, cell alignment, and immediate load-bearing under early load are needed to maintain phenotype.

Mechanical challenges

The osteochondral unit must withstand complex, dynamic loads while preserving the structural and functional integrity of both cartilage and bone. This mechanical performance arises from its hierarchical, anisotropic architecture, in which depth-dependent stiffness, viscoelasticity, and zonal organization enable seamless load distribution. Replicating these biomechanical features in engineered constructs remains one of the most formidable challenges in osteochondral repair.

Recreation of stiffness gradient. The first mechanical challenge is to reproduce graded load transfer and robust interfacial cohesion. Any therapy designed to heal cartilage must present the same mechanical behaviour of the bio-environment, otherwise mechanical mismatch will drive stress concentrations, interfacial failure, and early loss of function under physiological loading. Native articular cartilage exhibits distinct zonal properties: the superficial zone resists shear with aligned type-II collagen and boundary lubrication, the middle and deep zones absorb compressive forces through a hydrated proteoglycan-rich matrix, and a calcified layer anchors the construct to subchondral bone, enabling depth-dependent mechanics across only a few millimetres. The large shift in stiffness from sub-MPa cartilage to much higher values in bone is difficult to recapitulate in engineered materials[37,71] and, if mismatched, disrupts physiological load transfer and accelerates failure.[38,72] If too stiff, they concentrate stress on adjacent cartilage or loosen over time; if too soft, they may bottom out and overload the bone. Beyond matching bulk stiffness, constructs should emulate a continuous rise in stiffness and mineral content into a collagen X-rich calcified interphase that can sustain approximately 0.5–1.0 MPa of interfacial shear in wet conditions. Concurrently, the superficial zone should reach a tensile response in the 3–10 MPa range supported by collagen II fibril alignment. It is worth to mention that porosity and percolation have an impact in mechanical behaviour and therefore, in the parameters to reproduce the stiffness gradient. However, because these are primarily architectural variables, they will be treated in the next section.

Recent studies on biomimetic scaffolds provide specific implementations of stiffness gradients. Wu *et al.*[73] incorporated a biomimetic calcified interlayer bridging a cartilage-like GelMA compartment and a PCL-hydroxyapatite bone-like base, increasing wet interfacial shear and maintaining cyclic load transfer across the soft–hard junction. Parisi *et al.*[74] produced a continuous collagen-hydroxyapatite gradient that yielded a monotonic increase in modulus across the thickness and zone-appropriate cell behaviour. Wang *et al.*[75] engineered a triphasic construct with a dedicated calcified-cartilage membrane that enforced mechanical transition and protected the cartilage layer from bony overgrowth under load. Golebiowska *et al.*[76] combined a 3D-printed porosity gradient with a decellularised cartilage superficial zone, capturing tensile and shear performance at the surface while raising compressive stiffness toward the base. Conoscenti *et al.*[77] implemented a continuous pore-size gradient in PLLA, translating architectural variation into a coupled gradient of permeability and stiffness suitable for

osteochondral repair. Taken together, these exemplars show that architected biomimetic scaffolds can predefine both compositional and structural cues to realise a depth-dependent stiffness profile that is continuous rather than layered, elevates wet interfacial shear, and reduces delamination. In practice, the addition of a biomimetic calcified interlayer and the use of continuous (not stepwise) gradients are the two design decisions most consistently associated with successful gradient replication under physiologically relevant loading, as supported by scaffold studies demonstrating improved interfacial shear and depth-dependent mechanics with calcified interlayers and continuous compositional/architectural gradients.[73–77]

Injectable hydrogels can recreate stiffness gradients when the gradient is actively imposed during or immediately after injection. *In situ* strategies that stratify crosslink density or filler content have achieved spatially varying modulus profiles, including diffusion-limited dual-network gelation and co-injection devices that generate graded mixing[78,79] and composite formulations that couple chondral nanoparticles with mineral-loaded phases to create continuous composition-mechanics gradients and higher interfacial push-out forces *in vivo*.[80] More pragmatic bilayer injectables establish a stepwise stiffness transition and improve integration but still approximate rather than reproduce a continuous depth-dependent profile.[81] Considering these reports, maintaining a stiffness gradient in an injectable hydrogel complicates what is intended to be a straightforward local therapy, and consequently, this approach is less frequently explored in the literature.

Time-dependent mechanical fidelity under physiological conditions. Another major challenge in terms of mechanical properties is to maintain time-dependent mechanical fidelity under physiological cyclic loading and low-friction conditions, and to schedule loading according to the stage of construct maturation. Beyond stiffness, articular cartilage displays complex viscoelastic behaviour, including stress relaxation, creep, and time-dependent recovery under load. These properties are essential for shock absorption and protecting the underlying bone.[39,82] Viscoelasticity also varies with depth: the superficial zone responds quickly to shear forces, while deeper regions exhibit slower, more elastic behaviour under compression.[40,83] Materials that are purely linear-elastic, or that lose viscoelasticity near 37 °C, struggle to preserve congruence under sustained loading, which elevates interfacial shear, accelerating the stress in the interface as well as the damage on the tissue.

Frictional behaviour is equally critical: in boundary or mixed lubrication (when the contacting surfaces or only a thin molecular film carry most of the load) the effective coefficient of friction and the wear rate control the shear transmitted to the calcified interface and thus the risk of interfacial damage. Synthetic materials must provide ultralow friction, ideally achieving a coefficient of friction (μ) of 10–2 or below under physiologic pressures in the boundary or mixed lubrication regimes.[84] This is achieved through surface chemistry modifications, such as grafting zwitterionic polymer brushes[85] or incorporating injectable hydrogel microspheres with embedded lipid reservoirs for self-renewable hydration lubrication.[86–88]

In this context, mechanical stimulation is not only a load-bearing requirement but also a biological cue for phenotype and matrix deposition. Dynamic compression, hydrostatic pressure, and controlled shear promote a chondrocyte-like phenotype when waveform, magnitude, and timing are matched to the maturation stage of the construct.[89,90] Premature loading can blunt induction, whereas staged application after biochemical commitment tends to stabilize the phenotype.[91] The existence of load-sensitive pathways, such as TRPV4- and

Table 1 Design targets and required material properties for hydrogel-based scaffolds intended for osteochondral or cartilage repair. Target performance ranges are based on representative values from healthy articular cartilage. Each mechanical metric is linked to its relevant biological function and the material properties required to replicate that function in engineered scaffolds. References indicate key literature sources for each property and benchmark

Design target	Performance metric (target range)	Biological function	Required material property	Ref.
Superficial tensile strength	3–10 MPa (wet)	Resist surface shear and tensile stress	Anisotropic architecture, collagen II fibril alignment, mature crosslinking	96 and 97
Interfacial shear strength	0.5–1.0 MPa (wet)	Ensure secure mechanical anchorage and prevent delamination	Continuous composition/ stiffness gradient, biomimetic calcified interphase	98
Bulk compressive modulus	0.5–1.5 MPa (equilibrium)	Load bearing, fluid pressurization, shock adsorption	High GAG content, highly hydrated networks	24 and 99
Friction coefficient	≤0.02 (boundary/Mixed regime)	Minimize wear and mechanical damage	Lubricin (PRG4) recruitment/grafting, zwitterionic polymer brushes, self-renewable hydrogel boundary layers	100
Porosity interconnec-tivity	≥90% (volume)	Ensure adequate solute diffusion and convective flow	Open, percolating pore network (*e.g.*, TPMS lattices, MEW)	101 and 102

Piezo-mediated mechanotransduction, underscores why the spatiotemporal profile of loading, not only its magnitude, matters.[92,93]

Both biomimetic scaffolds and injectable hydrogels explicitly target time-dependent mechanical fidelity under physiological cyclic loading and lubrication. Architected, zonal scaffolds report frequency-dependent complex modulus and sustained performance during prolonged cyclic compression, especially when a compliant, lubricious superficial layer is combined with a stiffer subchondral support.[93,94] Complementarily, injectable systems achieve congruent behaviour *via* dissipative or reversible networks and boundary lubrication that renews under shear. For example, shear-responsive HA-based hydrogels and injectable microspheres form *in situ* hydration layers to reduce friction and stabilise modulus across repeated sliding cycles.[86,95]

The following Table 1 summarizes the quantitative design criteria necessary for next-generation osteochondral biomaterials:

Architectural challenges

Architectural design is the main factor responsible of how cells, nutrients, cytokines, and loads are spatially distributed across the construct. While mechanical targets define the mechanical performance under static or cyclic loads, architecture provides the levers: pore-size distribution and interconnectivity, graded geometry and interphase continuity, and surface micro-topography. This makes it possible to ensure mechanical performance without sacrificing transport or integration.

Porosity, interconnectivity, and permeability for mass transport. Cartilage is avascular; solute transport relies on diffusion and pressure-driven flow through a hydrated porous network. To facilitate transport, scaffolds should provide a predominantly open, percolating pore network with very high interconnection (≈≥90% of pore volume interconnected and communicating with the exterior[103,104]) so that protein-scale solutes traverse 1–2 mm within minutes to hours. However, raising porosity and interconnectivity can undermine stiffness and interfacial cohesion if not carefully architected. In osteochondral constructs, transport targets are zonal: deeper regions adjacent to bone can tolerate larger pores to favour vascular ingrowth and osseointegration, whereas cartilage-side layers require smaller pores and more tortuous pathways to preserve low friction and proteoglycan retention; additionally, tortuosity should moderate convective shear while preventing stagnation.

In architected scaffolds, we can find open-cell lattices (TPMS-inspired) and melt electrowriting (MEW) fibre grids that can decouple stiffness from flow by channelling fluid along preferred paths while preserving load support.[105] Architected designs using tightly controlled fibre deposition create an aligned superficial layer and perpendicular deep layers that orient chondrocytes while maintaining transport. Additionally, gradient porosity and multi-material layouts further help decouple stiffness from flow, channelling fluid along preferred routes without sacrificing load-bearing capacity. In a representative study of this, Parisi *et al.* introduced a one-step freeze-drying strategy that builds a truly continuous collagen-low-crystalline hydroxyapatite gradient, moving beyond discrete layers to couple composition and stiffness transitions that program region-specific hBMSC responses *in vitro* and remain biocompatible *in vivo*.[74] Another study by Wu *et al.* described a printed osteochondral construct with a biomimetic calcified interfacial layer to improve fixation.[73] Lastly, Han *et al.* build high-precision multilayer scaffolds by melt electrowriting for zonal cartilage repair.[106]

Injectable approaches address the same mass-transport constraints without relying on a pre-defined, architected pore network. In this context, "porosity" and "permeability" map to effective network mesh size and hydraulic/poroelastic permeability, while "interconnectivity" for cell ingress can emerge over time through remodeling/degradation or be engineered *via* secondary microporosity when required. Decellularized cartilage hydrogels, self-assembling peptide networks and granular/microgel systems create fibrillar or fibril-like environments that conform to irregular defects and can be delivered arthroscopically with minimal disruption. For example, Zeng *et al.* develop an injectable pig cartilage-derived decellularised ECM hydrogel encapsulating human urine-derived stem cells that skews macrophages toward a pro-regenerative phenotype and accelerates repair in a rat cartilage defect model.[41] Further, Dufour *et al.* show that an IEIK13 self-assembling peptide hydrogel, used with or without chondrocytes, supports hyaline-like repair in cynomolgus monkey full-thickness defects.[43] Gong *et al.* formulate a porcine ear cartilage dECM hydrogel with concentration-tuneable gelation that supports chondrocytes and forms cartilage-like tissue subcutaneously in mice.[42] Overall, both delivery formats must satisfy the same transport envelope for an avascular tissue, even if it is implemented through an architected pore network in scaffolds or through network-scale mesh size and permeability in injectables.

Zonal gradients and cartilage–bone interface continuity. The native osteochondral unit features a seamless cartilage-to-bone transition with continuous changes in composition, mineral

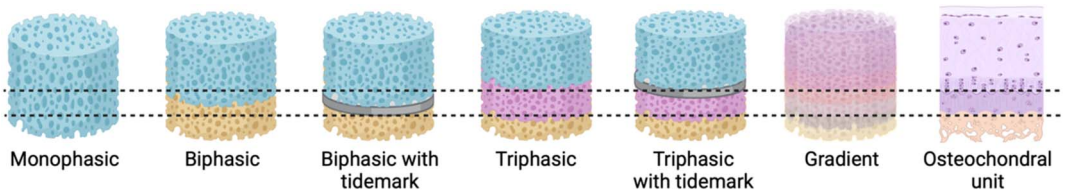

Fig. 4 Scaffold architectures for osteochondral repair. Overview of scaffold designs ranging from simple monophasic to complex gradient and triphasic structures, aiming to replicate the native osteochondral unit's zonal organization and improve regenerative outcomes. Created with Biorender (R).

content, porosity and stiffness (Fig. 4). Engineered constructs must avoid sharp step-changes that concentrate stress, promote delamination, and disrupt osseointegration. For optimal results, a thin, stiffer calcified-cartilage mimic is often needed to anchor the cartilage cap while transmitting forces to subchondral bone.

Several scaffold platforms predefine anisotropy, graded porosity, and zonal transitions. Representative structure-biomimetic scaffolds show how graded architecture and a calcified interphase distribute interfacial stresses and promote integration without compromising surface function. Dufour *et al.*[107] combined melt electrowriting with inkjet deposition to fabricate a zonal osteochondral graft incorporating a biomimetic calcified interface that improved anchorage. Steele *et al.*[93] reported a microstructured, zonal design in which aligned superficial fibres overlay graded mechanics validated *in vitro* and *in vivo*, aligning surface lubrication requirements with subsurface support. Using thermally induced phase separation, Camarero-Espinosa *et al.*[108] produced a three-layer PLA/CNC scaffold with a mineral-rich basal region that favours subchondral integration, while Levingstone *et al.*[109] developed multilayer collagen-hydroxyapatite constructs that recreate a calcified gradient and achieve tidemark-like integration *in vivo*. Most recently, Wu *et al.*[73] printed an osteochondral construct with a biomimetic calcified interfacial layer to enhance fixation. Taken together, these studies converge on the same architectural principle: continuous gradients in composition and porosity anchored by a calcified interphase, while also reminding that lateral cohesion under wet conditions must be secured during handling and implantation.

Injectable systems can conform to irregular interfaces, and some incorporate adhesive/photocurable chemistry or *in situ* mineralization to improve bonding and anchorage under wet conditions. For instance, a photocurable adhesive hydrogel is developed to enhance tissue-implant integration and lateral bonding under wet conditions.[110] Self-assembling peptides and dECM gels can also be formulated to mineralize gradually at the bone site. However, when gradients require precise spatial control of stiffness and mineral content at sub-millimetre scales, pre-fabricated scaffolds currently offer more deterministic control than fully *in situ*-forming gels.

Surface microtopography and boundary lubrication. The superficial cartilage zone must provide a smooth, lubricated surface with a low frictional coefficient while transmitting loads. A simple, practical design window can be anchored to three representative scales: the ≈14–15 μm long axis of superficial-zone chondrocytes[111,112] (the 5–40 μm fibre diameter range that MEW/extrusion can reproducibly print,[113] and ∼1 μm-deep microtextures that have been reported to guide chondrocyte behaviour.[114] These scales justify using microtopographies in the 1–50 μm band to organize the superficial layer while retaining low friction under synovial media.

Architected scaffolds present a set of technologies aligned in this sense. First, they enable the aligning of print paths with principal sliding directions and imposing shallow, periodic textures create an aligned superficial layer over perpendicular support; beyond topography, these constructs now build boundary-lubricated skins by grafting zwitterionic polymer brushes or phosphorylcholine-rich layers at the surface. For instance, PMPC-based top coats and bilayer/tough-network hydrogels consistently lower the coefficient of friction (to $\sim10^{-2}$ or below under physiologic pressures) and reduce surface damage, providing a tractable way to pair microtopographic alignment with a brush-like boundary layer.[88,115,116] Moreover, friction can be further reduced on porous lattices (*e.g.*, MEW PCL) by lubricin-capturing nanocoatings that enrich PRG4 at the surface while preserving subsurface support.[117]

Injectable systems address boundary lubrication *via* dispersed, *in situ*-active reservoirs that are distinctive to hydrogels. For instance, embedded phosphatidylcholine liposome microreservoirs migrate or expose at the sliding interface under shear to create hydration-lubricated layers, achieving ultralow friction.[118] Building on this, shear-responsive HA-liposome hydrogels present liposomes on demand and simultaneously deliver drug, maintaining boundary lubrication *in vitro* and *in vivo*.[95] Moreover, injectable hydrogel microspheres with liposome-coated surfaces exhibit self-renewable hydration lubrication after wear (replenishing boundary layers from mobile reservoirs), which is an inherently injectable mechanism.[86] Unlike pre-fabricated scaffolds, these hydrogels do not rely on fixed surface brushes; they recreate and replenish boundary layers *in situ* during motion *via* embedded lipid reservoirs.

Clinical and translational challenges

Translating osteochondral therapies from preclinical studies to clinical application remains a major challenge. Ultimately, the choice between architected scaffolds and injectable hydrogels is fundamentally a clinical decision that balances the degree of biological reconstruction against surgical and logistical complexity. Outcome measures across osteochondral repair studies are inherently heterogeneous, reflecting differences in defect models (size, location, acute *vs.* chronic), comparator treatments, follow-up duration, and the specific therapeutic goals of each approach. As a result, direct cross-study comparisons (and especially platform-level claims between architected scaffolds and injectable hydrogels) should be interpreted cautiously. Nevertheless, most animal studies converge on a common set of endpoints (macroscopic and histological scoring, interface integration, subchondral bone remodelling often assessed by microCT, and functional mechanical readouts such as indentation or compression testing), whereas clinical evaluation typically relies on patient-reported outcomes (*e.g.*, KOOS/IKDC/WOMAC) complemented by MRI-based structural and compositional assessments (*e.g.*, MOCART and T2 mapping when available[119–121]).

As already discussed above, architected scaffolds present key advantages that drive successful clinical translation. First, they have superior architectural and mechanical fidelity, especially those fabricated using 3D printing and MEW, which can precisely replicate the native zonal gradients of the osteochondral unit (stiffness, porosity and composition).[122,123] As a result,

these scaffolds provide immediate, high-load-bearing capacity upon implantation.[124,125] They also promote chondrogenic phenotype stabilisation and mitigate hypertrophic drift, as well as targeted integration at the bone interface.[126,127] However, architected scaffolds also present a number of disadvantages that hamper their clinical translation. First, they require open-joint surgery for implantation, increasing patient morbidity, recovery time, and infection risk compared to minimally invasive procedures.[128] Second, their success depends on precise matching of the implant shape to the patient's defect size and geometry, often requiring customisation (*e.g.*, CAD/CAM).[129] Finally, preclinical validation in large animals remains challenging because no model fully replicates human bipedal gait and complex joint kinematics, therefore limiting the confidence in long-term biomechanical performance translation.[129]

Injectable hydrogels also have many advantages that facilitate translation, like minimally invasive delivery, defect conformability and logistical simplicity.[130,131] These hydrogels can be delivered arthroscopically or *via* simple injection, eliminating the need for open surgery and the associated complications described in the previous paragraph. The *in situ* formation of these materials ensures perfect filling of irregularly shaped defects and interfaces, maximising tissue contact.[132,133] Finally, it can be marketed as an off-the-shelf product (especially if a cell-free variant), simplifying the surgical workflow and reducing handling complexity compared to multi-stage ACI or custom scaffold procedures.[133] On the other hand, injectable hydrogels suffer from limited mechanical integrity, providing limited initial support and making them unsuitable for large or high-load-bearing defects.[134] Moreover, achieving a continuous, depth-dependent stiffness or compositional gradient *in situ* is extremely difficult, resulting in monophasic repair that lacks the structural anisotropy required for long-term function.[135] This, in turn, also increases the risk of cells migrating away from the defect.

Regulatory and commercial challenges

The biological and mechanical requirements of the osteochondral unit define a level of complexity that few therapeutic platforms can fully reproduce. However, translational success depends less on how faithfully a construct mimics native cartilage and more on how smoothly it can navigate regulatory pathways, manufacturing constraints and healthcare logistics.[136] This discrepancy, anticipated in the introduction of this review, helps explain why the most architecturally sophisticated technologies seldom reach routine clinical practice, whereas simpler injectable systems dominate the regulatory and commercial landscape despite their intrinsic biomechanical limitations.

Across major jurisdictions, regulatory classification systematically penalizes product complexity. Architected biomimetic scaffolds that incorporate cells, growth factors, multiphasic architectures or patient specific geometries are frequently categorized as advanced therapy medicinal products by the European Medicines Agency or as Class III combination products by the United States Food and Drug Administration.[137–139] These designations impose the heaviest evidentiary burden, with requirements for large and expensive clinical trials, fully validated GMP facilities, stringent process control and extensive post market surveillance. When scaffolds require anatomical customization through CAD or CAM workflows or individualized three-dimensional printing, standardisation becomes even more difficult. In such cases, the line between product and surgical procedure becomes blurred and the regulatory framework is forced to accommodate something that behaves less like a conventional batch made device and more like a bespoke intervention.[140,141] Predictably, timelines and development costs increase, and commercial interest becomes highly selective.

A major determinant of translational viability is the simplicity of the product itself. Therapies that require little or no preparation are more easily absorbed into standard surgical workflows, particularly in busy orthopaedic settings. Cell free scaffolds and injectable systems exemplify this advantage because they can be delivered in a single operative session without specialised infrastructure. The *Agili-C*[142] implant and the *Hyalofast*[143]scaffold are illustrative examples, since both are designed for straightforward, single step implantation and do not require cell expansion or multistage surgical protocols, which has supported their adoption across a wider range of clinical environments. In contrast, autologous cell therapies such as MACI[144] or *Spherox*,[145] although capable of delivering strong clinical outcomes, face limited uptake because they rely on two stage procedures, carry the cost of GMP grade cell expansion and are constrained by regulatory requirements inherent to patient specific biological products.

Injectable hydrogels follow a regulatory trajectory that capitalises on these advantages. Their relative simplicity, reproducible batch manufacturing and minimally invasive delivery allow many of them to be regulated as Class II or lower risk Class III devices, or in some cases as biologics that avoid the most stringent advanced therapy routes.[119] Regulatory strategies such as CE marking under the Medical Device Regulation or 510(k) and *De Novo* pathways in the United States can be based on equivalence to existing products and on moderate sized pivotal studies, rather than on the extensive programmes expected for complex cell-based constructs.[146,147] Because injectables conform to the defect *in situ* and rarely require patient specific design, they align naturally with existing regulatory categories and can be integrated into healthcare systems without substantial reorganisation of infrastructure.

Commercial considerations amplify this divergence. Scaffold based therapies usually require open joint procedures, longer operative times, specialised instrumentation and highly trained teams. Their manufacturing processes involve multistep fabrication, quality control across several materials and sometimes cell processing, all of which translate into high per patient cost. Without unequivocal long-term evidence of superiority over comparatively simple procedures such as microfracture or bone marrow stimulation, payers are reluctant to reimburse these therapies at scale.[148,149] In contrast, injectable products integrate smoothly into established arthroscopic workflows, can often be administered as day case procedures and target large patient populations, for example individuals with early

Table 2 Clinical-stage and approved cartilage repair technologies: regulatory classification, composition and trial status

Product	Classifications	Year	Approval?	Composition	Company	Trial id.	Ref.
Hy2Care®	**Reparative**. Injectable. Cell-free	2014	IDE approval (FDA)	Dextran and hyaluronic acid conjugate	Tech med (University of Twente)	NCT05186935	150
JointRep®	**Reparative**. Injectable. Augmentation for microfracture	2021	CE mark (Europe)	Deacylated chitosan	Oligo Medic Inc.	NCT04840147	151
CaRes®	**Restorative**. Injectable. Augmentation for ACI (MACI)	2003	CE mark (Europe)	Collagen I with/ without autologous chondrocytes	care.com (IAC)	N/A	152 and 153
Arthrosamid®	**Palliative**. Injectable	2021	CE mark (Europe)	2.5% cross-linked polyacrylamide and 97.5% non-pyrogenic water	Contura	NCT05086068; NCT05057559	154
CARTISTEM ®	**Restorative**. Injectable. Augmentation for microfracture	2009	CE mark (Europe)	Hyaluronic acid with allogenic human umbilical derived MSCs	Medipost Co Ltd	NCT01733186; NCT01041001	155
ChondDux	**Reparative**. Injectable. Augmentation for microfracture	2010	—	PEG/HA functionalised by CS	Zimmer Biomet Holdings, Inc. (USA)	NCT01110070	156 and 157
NOVOCART® inject plus	**Restorative**. Injectable. Hydrogel-based ACI	2015	CE mark (Europe)	Autologous chondrocytes, modified human albumin, isotonic sodium hyaluronate, PEG crosslinker	Tissue engineering technologies AG	NCT02941120; NCT03319797	158 and 159
Gelrin C™	**Reparative**. Injectable. Augmentation for microfracture	2009	CE mark (Europe)	PEG diacrylate and denatured fibrinogen	Regentis biomaterials Ltd	NCT03262909; NCT00989794	160 and 161
CARGEL bioscaffold (Previously BST-CarGel)	**Reparative**. Injectable. Augmentation for microfracture	2006	CE mark (Europe)	Chitosan solution mixed with autologous whole blood before application after bone marrow stimulation technique	Smith & Nephew	NCT00314236; NCT01246895	120, 121 and 162
NOLTREX™	**Palliative**. Injectable	2020	FDA and CE mark	Polyacrylamide with silver ions	Noltrex	NCT06429319	163
HYMOVIS®	**Reparative**. Injectable	2011	FDA and CE mark	Hyaluronic acid derivative	Fidia Farmaceutici S.p.A	NCT04293861; NCT01372475	164
HYMOVIS ONE ®	**Reparative**. Injectable	2016	FDA and CE mark	Hyaluronic acid derivative	Fidia Farmaceutici S.p.A	NCT04661111	165
Synvisc-One®	**Reparative**. Injectable	2005 -	FDA and CE mark	Hyaluronic acid derivative (hylan G-F 20)	Sanofi SA	NCT01618708; NCT02389452; NCT01771952; NCT03190369	166
Ostenil plus	**Reparative**. Injectable	2011	FDA and CE mark	2% Hylauronic acid + 0.5% mannitol	TRB Chemedica (UK) Ltd	NCT03203408; NCT03809962; NCT03734315; NCT01288001	167
Cellular Matrix™	**Reparative**. Injectable	2020	CE mark	Autologous platelet-rich plasma (PRP) and hyaluronic acid	RegenLab SA (Switzerland)	NCT02964143	168
Hyalofast	**Restorative**. Surgical	2009	CE mark	Hyaluronic acid–based, biodegradable, cell-free scaffold that can be used alone or combined with bone marrow aspirate concentrate (BMAC) for cartilage defect repair. Acts as a 3D matrix supporting endogenous cell	Fidia Farmaceutici S.p.A. (Italy)	NCT02673905	143

Table 2 (*Contd.*)

Product	Classifications	Year	Approval?	Composition	Company	Trial id.	Ref.
				migration and tissue regeneration			
Agili-C™	**Reparative (and regeneration)**. Surgical	2011	FDA and CE mark	Bi-phasic calcium carbonate derived from coral exoskeletons	CartiHeal Ltd (isreal)		142 and 169
BioCart™ II	**Restorative**. Surgical. Augmentation for ACI	2012	—	Fibrinogen, thrombin matrix & FGF2v1 cells	ProChon biotech Ltd	NCT00729716	170
MaioRegen®	**Reparative**. Surgical	2007	CE mark	Trilayer of collagen & hydroxyapatite	Medina discovery (Spain)	2013-000493-30 (ES); 2020-003949-11 (ES); 2022-002679-12 (ES)	171 and 172

osteoarthritis or small cartilage defects. Their commercial success depends on safety, ease of use and clinically meaningful but not necessarily curative effects, rather than on fully restoring the mechanical and architectural integrity of the osteochondral unit.[133,135] In practice, this reflects a cost-benefit threshold in which "good enough" symptom relief and function preservation may be preferable to more complex restorative strategies unless durable superiority is clearly demonstrated and reimbursable.

This combination of regulatory and commercial forces becomes particularly evident when examining the current landscape of clinically tested and approved products. The therapies that have successfully progressed to clinical trials and market authorisation are overwhelmingly injectable systems, whereas architected scaffolds remain confined to niche indications, academic trials or preclinical development. The table summarising products in clinical evaluation and their approval status Table 2 illustrates this imbalance and highlights how regulatory and commercial pressures shape innovation in cartilage repair.

Taken together, these observations expose a structural paradox. The more faithfully a therapy reproduces the architecture and mechanics of native cartilage, the more likely it is to encounter regulatory classifications that are costly, slow and difficult to satisfy. Conversely, technologies that accept a degree of compromise in biomimicry but excel in simplicity, manufacturability and surgical practicality are those that progress through regulatory review and into clinical use. Until regulatory frameworks explicitly recognise and accommodate zonal, gradient based and patient specific constructs, the translational landscape will remain skewed toward injectable systems that are convenient for health systems but incomplete from the perspective of tissue level regeneration.

Conclusion & future directions

The analysis across biological, mechanical, architectural, clinical and regulatory domains converges toward a clear and somewhat uncomfortable conclusion. Biomimetic scaffolds are the platforms that most closely address the true demands of osteochondral regeneration, yet injectable systems are the therapies that actually reach patients. This divergence is not accidental. It reflects the tension between what cartilage biology requires and what current regulatory and commercial ecosystems can realistically support.

At the level of biological and mechanical performance, architected scaffolds consistently emerge as the superior option. Their graded stiffness, anisotropic fibre alignment, controlled porosity and engineered calcified interfaces allow them to recreate depth dependent mechanics, secure anchorage and zonal organisation in a way that injectable systems cannot match. By constraining cell morphology, guiding matrix deposition and protecting the cartilage bone interface from abnormal stress, scaffolds offer an environment that favours stable hyaline like cartilage rather than fibrocartilage or hypertrophic tissue. They are therefore better positioned to overcome key challenges such as long term phenotype stabilisation, prevention of ectopic mineralisation, preservation of a low friction surface and restoration of graded load transfer across the osteochondral junction.

Injectable hydrogels, in contrast, excel when the critical barrier is not biological fidelity but translational viability. Their minimally invasive delivery, defect conformability, modular chemistry and batch manufacturing make them highly attractive in clinical practice. They can be integrated as augmentations to existing procedures, particularly microfracture and other bone marrow stimulation techniques, and they are especially suitable for patients in whom the therapeutic objective is to alleviate symptoms and delay joint replacement rather than to reconstruct a fully biomimetic osteochondral unit. Through viscoelastic tuning, controlled release and immunomodulatory design, injectables can create supportive microenvironments that improve short and medium term outcomes, even if they do not fundamentally resolve the mechanical and architectural deficits of the joint.

When the main challenges are considered together, a nuanced picture emerges in which the superiority of scaffolds in terms of regenerative potential coexists with their inferiority in terms of regulatory and commercial feasibility. For problems that are dominated by structural and mechanical requirements, such as recreating stiffness gradients, achieving strong interfacial shear strength or maintaining low friction under repeated loading, scaffolds clearly provide the more complete solution. For challenges centred on microenvironmental control, such as

staging biochemical cues, modulating inflammation or conforming to irregular defects in a single operative step, injectable systems offer practical and often sufficient answers. However, the decisive factor in determining which technologies enter clinical trials and receive approval is neither biology nor mechanics, but the ability to satisfy regulatory criteria and to fit into healthcare delivery models. Direct head-to-head comparisons between architected scaffolds and injectable systems remain scarce, largely due to differences in indications, workflows, comparators, and outcome measures, highlighting the need for harmonized comparative studies.

Current frameworks strongly favour therapies that are standardised, minimally invasive and compatible with existing surgical workflows. As a result, injectable platforms advance through clinical pipelines, accumulate post market data and become part of routine care, while scaffold based constructs struggle to justify the cost and complexity of the evidence required for authorisation and reimbursement. The field of osteochondral repair therefore evolves under a persistent asymmetry in which the technologies that are most capable of delivering long term, structurally faithful regeneration are those that face the greatest regulatory resistance, and the technologies that fit most comfortably within regulatory and market constraints are those that offer only partial solutions to the underlying biomechanical problem.

From a clinical perspective, these findings invite a reconsideration of how osteochondral therapies are deployed across the lifespan of the joint rather than in isolated episodes of care. In current practice, younger and biologically younger patients with focal defects are often treated with marrow stimulation procedures, sometimes augmented with injectable formulations, while older patients with more diffuse degeneration are channelled towards symptom-modifying injectables and, ultimately, prosthetic replacement when disability becomes unacceptable. If biomimetic scaffolds and advanced injectable systems were both available with robust evidence, a more rational strategy might be to prioritise smaller, highly targeted scaffold interventions in younger patients, who are better able to tolerate rehabilitation and benefit from durable structural repair, and to position injectable therapies as minimally invasive tools for older or higher-risk patients in whom the primary objective is to maintain function and delay or avoid prosthesis. In this scenario, the clinical paradigm would shift from using injectables early and prostheses late to a more nuanced sequencing in which scaffold-based regeneration is offered at the most favourable biological window, while injectables are reserved as flexible, repeatable options for managing progression in more fragile joints.

The central message of this review is that this asymmetry has become one of the dominant challenges in cartilage regeneration. From a scientific standpoint, biomimetic scaffolds represent the best available response to the multifactorial biological and mechanical demands of the osteochondral unit. From a translational standpoint, injectable systems are the primary route by which new therapies are delivered to patients. Unless regulatory and reimbursement models evolve to accommodate the complexity inherent to scaffold based products, or unless new hybrid strategies succeed in combining scaffold like architectural control with injectable like simplicity, as several studies already point in this direction through *in situ* reinforcement or maturation of injectable phases (*e.g.*, ref. 78–81), the clinical landscape will continue to be shaped more by what can be approved and deployed than by what is most capable of restoring joint function. In this context, it is accurate to state that scaffolds are superior for regeneration, but injectable systems are superior for approval, and this disparity ultimately determines which innovations reach the clinic.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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