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REVIEW

Fabricating the cartilage: recent achievements

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Abstract This review aims to describe the most recent achievements and provide an insight into cartilage engineering and strategies to restore the cartilage defects. Here, we discuss cell types, biomaterials, and biochemical factors applied to form cartilage tissue equivalents and update the status of fabrication techniques, which are used at all stages of engineering the cartilage. The actualized concept to improve the cartilage tissue restoration is based on applying personalized products fabricated using a full cycle platform: a bioprinter, a bioink consisted of ECM-embedded autologous cell aggregates, and a bioreactor. Moreover, in situ platforms can help to skip some steps and enable adjusting the newly formed tissue in the place during the operation. Only some achievements described have passed first stages of clinical translation; nevertheless, the number of their preclinical and clinical trials is expected to grow in the nearest future.

Keywords Cartilage regeneration · 3D bioprinting · Tissue engineering · Smart biomaterials · Hyaline cartilage

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Introduction

The cartilage tissue restoration is one of the most appealing goals due to the increased life expectancy worldwide, especially in the developed countries. Numerous strategies to treat articular cartilage lesions have been established to date and include both conservative and surgical approaches. The latter are mostly applied in case of intermediate and large defects and include both reparative and regenerative techniques (Gomoll et al. 2012).

Microfracturing is based on treating the chondral defects by inducing recruitment of multipotent stromal cells. It was reported that this technique can ensure efficient improvement and satisfactory results in long terms (Steadman et al. 2003); Mithoefer et al. 2009; Kowalczuk et al. 2018). Nevertheless, it is hard to be predicted; the newly generated tissue

may be fibrous and soft, so patients have to regulate their activities depending on the functionality of the restored tissues (Nehrer et al. 1999; Kraeutler et al. 2017). Therefore, this technique could be recommended only for acute and small cartilage defects. Another common reparative technique in clinics is mosaicplasty based on transplanting cylindrical cartilage fragments from a non-weight-bearing zone into the defect site. Despite promising results (Kowalczuk et al. 2018; Tetta et al. 2010; (Solheim et al. 2017), this technique is limited by defect size because of the material shortage.

Regenerative techniques are presented by cell-based approaches, e.g., autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), or tissue-engineered cartilage implantation, which remain to be attractive because of benefits such as the possibility to efficiently restore large defects and mimicking the native structure of the hyaline cartilage. However, the isolation and processing of autologous cell material require long time and cells may dedifferentiate. Moreover, there is a possibility of severe inflammation reaction after implantation.

Several recent papers have systematically reviewed ACI and MACI applications in clinics (Kraeutler et al. 2017; Mundi et al. 2015; Iordache et al. 2020; Migliorini et al. 2021). Spherox™ (Co.don AG) technique, three-dimensional spheroids from autologous chondrocytes and extracellular matrix, showed promising outcomes (Armoiry et al. 2019; Vonk et al. 2021; Eschen et al. 2020).

While the number of successful results in cartilage tissue engineering is constantly growing, it is essential to provide a framework of the novelties reached. This review aims to describe the most recent achievements and provide an insight into cartilage engineering development (Fig. 1).

A—Aspiration-assisted bioprinting of a 2-layer spheroid-based osteochondral construct: I—aspiration-assisted bioprinter; II—osteogenic ((BSP (red), RUNX2 (green), Hoechst (blue)) and chondrogenic (collagen II (red), aggrecan (green), Hoechst (blue)) spheroids; III—schematic diagram of the construct and histological sectioning. The images were adapted and changed from Ref. (Ayan et al. 2020) according to http://creativecommons.org/licenses/by/4.0/.

B—Fabrication of a 3-layer cell-laden osteochondral equivalent: I—scheme; II—Alcian Blue staining of the scaffold at 8 weeks post-implantation, scale bars = 200 μm (left) and 50 μm (right); III—Gross images and 3D μCT models of the scaffold after 0, 4, and 8 weeks after in vivo implantation, scale bars = 2 mm. The images were adapted and changed from Ref. (Kang et al. 2018) according to http://creativecommons.org/licenses/by/4.0/.

C—Cartilage repair using an acellular bone matrix (ABM) scaffold in a preclinical porcine model: I—Microscopic geomorphology and SEM image of the ABM scaffold; II—SEM and confocal microscopic images of the cell-laden ABM scaffold; III—Macroscopic appearance of the cartilage defect healing in a porcine model. The images were adapted and changed from Ref. (Dai et al. 2019) according to http://creativecommons.org/licenses/by/4.0/.

Anatomical and histological features

The cartilage is an avascular, alymphatic, and aneural connective tissue that is composed of chondrocytes embedded in a highly dense extracellular matrix (ECM). Chondrocytes, as the only cell type in cartilage, arise from mesenchymal stem cells and constitute up to 2% of the cartilage tissue. They maintain cartilage homeostasis by production and degradation of ECM components. Being avascular and having low cell density lead to the limited intrinsic regeneration capacity of the cartilage.

Owing to the lack of blood vessels in the cartilage, chondrocytes have mainly anaerobic metabolism and fluid flows are responsible for the nutrient diffusion across the tissue. Therefore, joint movements are more likely to help the nutrients distribution throughout the cartilage (Maroudas et al. 1968). It has been shown that the cartilage thickness decreases in immobilised joints (Vanwanseele et al. 2002), and this might be partially due to the influence of the nutrient diffusion and matrix decomposition.

The cartilage ECM is composed of 65–80% water and the rest is mainly presented by collagen (type II, IV, VI, IX, XI, and X), proteoglycans (aggrecan, biglycan, decorin, fibromodulin, etc.), and some non-collagenous protein (Sophia Fox et al. 2009). Aggrecan is a huge molecule composed of more than 100 glycosaminoglycans (GAGs) chains including chondroitin sulphate and keratin sulphate. It has a hyaluronan backbone that together with GAGs chains ensures

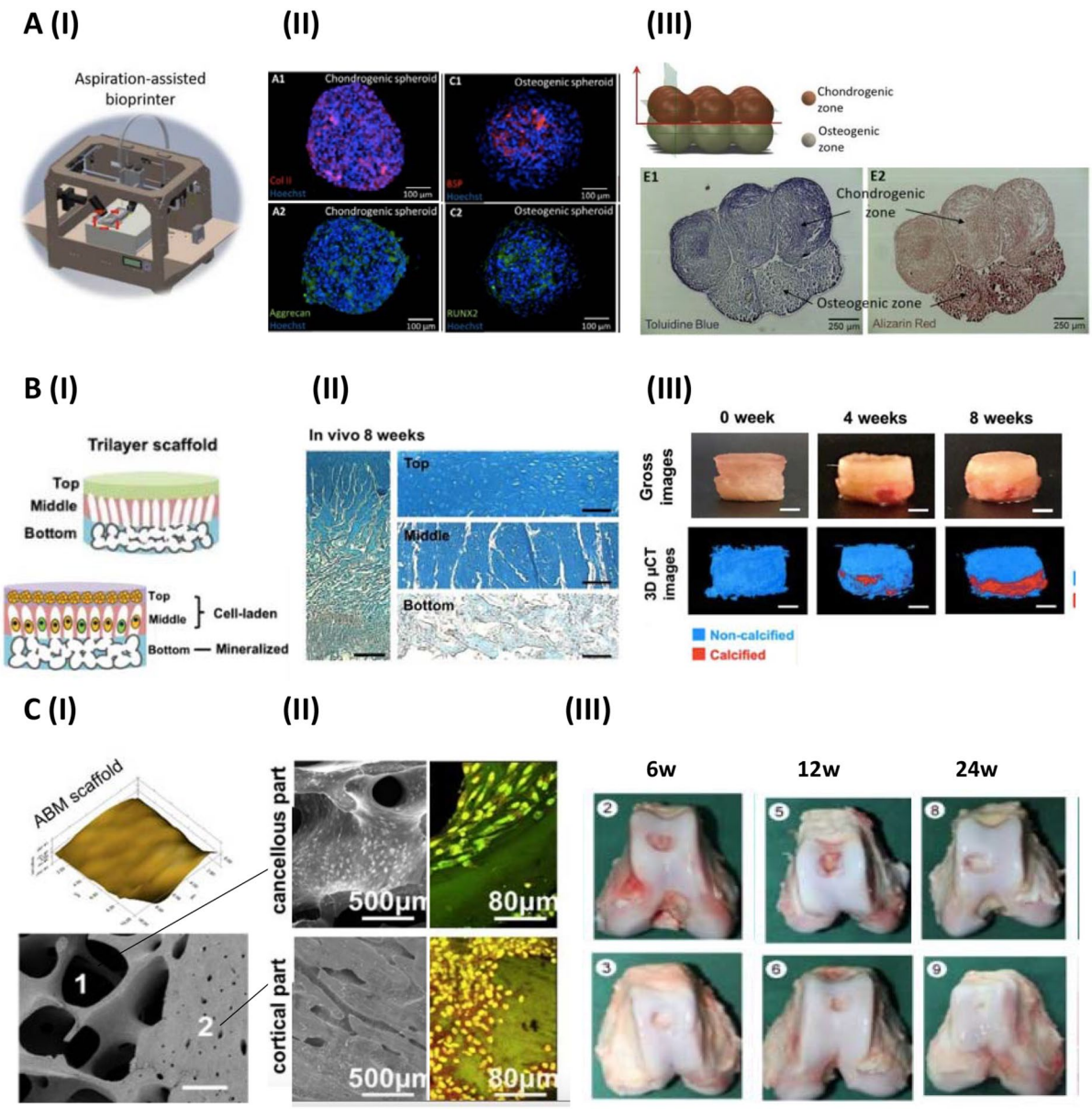

Fig. 1 Recent achievements in cartilage tissue engineering

a highly negative molecule charge. Due to the high affinity to water, aggrecan is responsible for cartilage viscoelastic properties and provides the tissue resistance to compressive loads (Kiani et al. 2002).

Depending on the composition and location of the cartilage tissue, it can be divided into three different types: hyaline, elastic, and fibrous ones. The articular and nose cartilage are examples of the hyaline cartilage that are enriched in type II collagen and GAGs. The elastic cartilage is located in the external ear and epiglottis and consists of elastic fibres. The fibrous cartilage contains high amount of type I collagen and is found in the intervertebral disc and menisci (An and Martin 2003). This review focuses on the hyaline cartilage which is the most common in the body.

The cartilage is a heterogeneous tissue and various mechanical properties and biochemical composition are detected within it, from the articular surface to

the underlying bone. This heterogenicity is emerged in four different zones: superficial, middle, deep and subchondral ones (Fig. 2). The zone sizes vary depending on age and location in the body; furthermore, their mechanical properties alter because of the differences in their composition and organization (Antons et al. 2018; Gannon et al. 2015). Ordinarily, 10–20% of the cartilage thickness in the articular surface is superficial zone, which is in contact with synovial fluid in the joints. During the daily activities, the cyclic hydrostatic pressure and contact pressure between superficial zones of the opposing cartilages are produced and the synovial fluid facilitates transmitting the forces to deeper zones. The superficial zone mainly controls the permeability of the fluid to the underlying zones and protects them from shear stresses. Presence of type IX collagen in this layer stabilizes the type II collagen fibril network and provides the resistance to shear stresses (Alford and Cole 2005). In this zone, collagen fibres are aligned parallelly to the joint surface and chondrocytes have a flattened morphology. Cells in this region express lubricin and superficial zone protein (SZP) to lubricate the articular cartilage and facilitate joint motions (Jay et al. 2001). The middle zone constitutes 40–60% of the cartilage and contains thicker collagen fibres which are randomly oriented. The chondrocytes are distributed in a less density than those of the superficial zone and have a spherical morphology. This zone ensures the resistance to the compressive loads in joints (An and Martin 2003). In the deep zone, which is 30% of the cartilage, collagen fibres are even thicker and oriented perpendicularly to the surface. The chondrocytes are also organized in the same direction as collagen fibres and make a columnar pattern. In this zone, there is the highest amount of proteoglycans responsible for the maximal resistance to compressive forces (Sophia Fox et al. 2009).

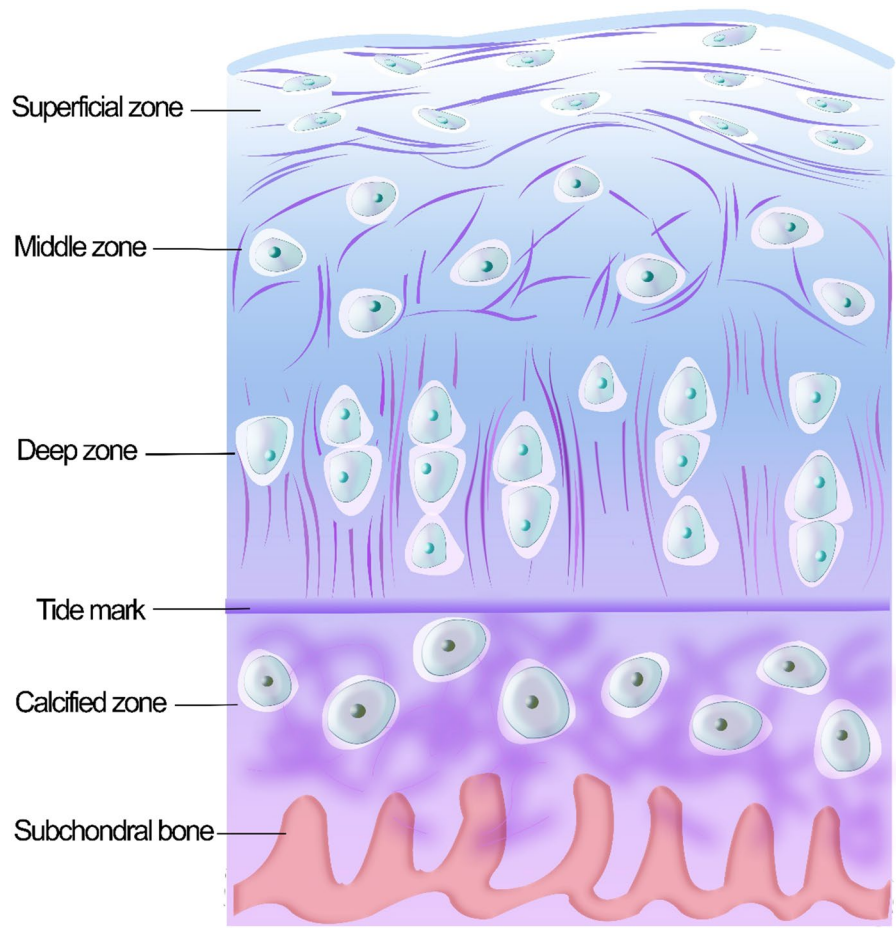

Fig. 2 Zonal structure of the articular cartilage

The deep zone is separated from the calcified zone by a tidemark that contains gaps providing the nutrient transport (Huber et al. 2000). The calcified zone consists of the rounded hypertrophic chondrocytes and collagen fibres that are organized perpendicularly to the cartilage surface. Type X collagen that is detected in this zone is associated with ossification and mineralisation (Nerlich et al. 1992). The values of compressive modulus increase from 0.079 ± 0.039 MPa in the superficial zone to 2.10 ± 2.69 MPa in the deep zone.

To fabricate functional tissue building blocks, it is important to consider the differences among the various zones while engineering the cartilage tissue.

Basic elements of cartilage tissue engineering

Cells

Although chondrocytes make up only 2% of the total volume of the articular cartilage, they play the most important role in maintaining the homeostasis of the tissue and ECM synthesis (Akkiraju and Nohe 2015). Therefore, selecting appropriate cell sources is of chief importance in cartilage tissue engineering. Various cell types with different differentiation potentials have been tested and include chondrocytes, stem cells, and genetically modified cells (Table 1).

Chondrocytes is the most common cell type used in cartilage tissue engineering. Several products based on autologous articular chondrocytes are marketed today for implantation, such as Cartigrow® (Regrow, India), Carticel® (Vericel Corp., USA), Cartogen® (Orthocell, Australia), Chondron ® (Sewon Cellontech corp., South Korea), Chondro-Celect® (Tigenix, Belgium), etc. It has been shown the source of chondrocytes (nasal, rib, external ear, costal, and articular cartilages) affects the quality of the cartilage repair. For example, in a subcutaneous implantation study, cells from the costal, nasal, and articular cartilages were used and the amount of the newly formed cartilage by costal and nasal chondrocytes was larger than that by articular chondrocytes (Isogai et al. 2006). The utilization of chondrocytes for cartilage tissue engineering is limited by two issues. One of them is an inadequate number of chondrocytes in the cartilage tissue and hence the need of their expansion before use (Poole et al. 2001; Chung and Burdick 2008).

Table 1 Cell types used in cartilage tissue engineering

Cell Type	Cell Source
Pluripotent Cells	
Embryonic Stem Cells	Embryo (Inner Cell Mass)
Induced Pluripotent Stem Cells	• Chondrocytes
	• Synovial cells
	• Fetal Neural Stem Cells
	• Dermal Fibroblasts
Multipotent Cells	
Mesenchymal Stem Cells	• Bone Marrow
	• Peripheral Blood
	• Muscle
	• Dental Pulp
	• Synovium
	• Adipose Tissue
	• Periosteum
	• Amniotic Fluid
	• Umbilical Cord Blood
	• Wharton Jelly
	• Placenta
Committed Cells	
Neonatal Cells	Chondrocytes
Foetal Cells	Chondrocytes
Juvenile Cells*	Articular Cartilage
Adult Cells	• Rib Cartilage
	• External Ear Cartilage
	• Articular Cartilage
	• Nasal Cartilage

* <13 yrs

Another issue is the rapid dedifferentiation of the chondrocytes' phenotype and decreased expression of specific chondrogenic markers such as aggrecan and type II collagen during the cell expansion in 2D in vitro systems (Coates and Fisher 2010). This phenomenon leads to the decrease in cartilage-specific properties by the expression of type I collagen and causes the dedifferentiation of chondrocytes (Albrecht et al. 2011). In spite of the reversibility of this phenomenon in 3D culture systems (Rederstorff et al. 2017), it is necessary to find alternative cell sources for clinical applications. Moreover, to avoid the chondrocytes' hypertrophy in culture, the special type of mesenchymal stromal cells (MSCs), multipotent articular cartilage-resident chondroprogenitor cells, can be added during the cartilage biofabrication (Jiang et al. 2020).

There is a significant research interest in application of stem cells (Negoro et al. 2018; Nam et al. 2018; Mastrolia et al. 2019; Lee and Wang 2017) due to their high proliferative and chondrogenic capabilities (McGonagle et al. 2017). Generally, stem cells are divided into three groups: embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells (ASCs) (Park and Im 2014). ESCs are found in the inner cell mass of the blastocyst of the mammalian embryo while ACSs exist in different tissues and iPSCs are reprogrammed and modified somatic cells. Tissue engineering may employ all three kinds of stem cells combined with various biomaterials and scaffolds.

ESCs are one of the most suitable alternative cell sources for cartilage tissue engineering (Qasim et al. 2020) due to their extensive proliferative capacities and differentiation capability into different somatic cell phenotypes (Ye et al. 2013). The study in a rat model demonstrated (Toh et al. 2010) that ESCs underwent effective chondrogenic differentiation and integrated into the surrounding cartilage tissue with no formation of tumours in 2/3rd of rats after 12 weeks. Moreover, Hwang et al. (Hwang et al. 2008) showed that ESCs-derived mesenchymal stem cells (MSCs) were capable to differentiate into the bone, cartilage, and fat tissue in vitro and ensured that they could form the normal cartilage tissue in a rat osteochondral defect. Nevertheless, the tumorigenicity and the risk of the teratoma formation limit the use of the undifferentiated ESCs in vivo. Obtaining ESCs-derived chondrocyte population which is purified under safety measurements has yet to be investigated.

Similar to ESCs, iPSCs provide a wide scope for cellular differentiation and expansion, but have no ethical issues (Koyama et al. 2013). The risk of tumour formation is always associated with the application of stem cells and especially ones transfected with viral vectors (Ye et al. 2013). The developed techniques to produce iPSCs without viral vectors have been established to decrease the risk of tumorigenesis (Poole et al. 2001; Chung and Burdick 2008; Lee et al. 2018; Goessler et al. 2006; Yu et al. 2009; Jia et al. 2010; Okita et al. 2011; Warren et al. 2012). Overall, the chondrogenic differentiation of iPSCs is still in its incipient developmental phases and future research is necessary to assess its potential in cartilage tissue engineering.

Adult MSCs are multipotent cells that can be derived from many tissues and are able to differentiate into various cell types, including chondrocytes, osteoblasts, adipocytes, and neuronal and myogenic cells (Suzdal'tseva et al. 2007). Another prominent feature of MSCs is their immunomodulatory properties due to the lack of molecules of the class II major histocompatibility complex (MHC-II) (Nasef et al. 2008) that ensures much attention to them in the clinical applications, especially as allogeneic therapeutics. Recently, several commercial products based on mesenchymal cells for the treatment of cartilage defects and joint pathologies have been introduced into the world market and include Cartistem® (Medipost, South Korea), allogeneic MSCs for knee osteoarthritis (Filardo et al. 2013), Cupistem® (Anterogen, South Korea), autologous MSCs for the inflammation reduction in the damaged joint tissues (Albrecht et al. 2013).

Thus, the analysis showed that both stem and committed cells are widely applied and ASCs can be successfully differentiated into chondrocyte-like cells. To better recapitulate the morphological structure of the hyaline cartilage and decrease time required for the maturation of cartilage equivalents, the self-organized cell aggregates (cell spheroids and sheets) may be of interest as they have the pre-established intercellular junctions and pre-synthetized ECM.

Biomaterials

Although chondrocytes dedifferentiate and lose their properties in 2D culture conditions, one of the proposed solutions is three-dimensional (3D) culture systems using materials similar to the native ECM. Recapitulating ECM properties can be provided by a variety of biomaterials that possesses the specific microenvironment essential for cell viability, proliferation, and function.

The cartilage-like ECM scaffolds can be formed from natural, synthetic, semi-synthetic and composite biomaterials consisting of polymers, polysaccharides, or proteins (Table 2) (Huang et al. 2018). They should have a proper biocompatibility to prevent immunological reactions in the host body, create a 3D structure suitable for cell adhesion, facilitate the exchange of nutrients, molecules, and growth factors, and have the mechanical properties similar to the native tissue. Despite all these features, the biomaterial injectability

Table 2 Biomaterial types used in cartilage tissue engineering

Biomaterial Type	Examples	Fabrication Methods	References
Natural			
Protein-based	Collagen	Extrusion bioprinting	Rhee et al. (2016)
		Inkjet bioprinting	Xu et al. (2013)
	Fibrin	Inkjet bioprinting	Xu et al. (2013)
		Encapsulation	Bahrami et al. (2018)
	Gelatin	Extrusion bioprinting	Singh et al. (2019)
		Electrospinning	Sharifi et al. (2020)
	Fibroin	Freeze drying	Zhou et al. (2017)
		Salt leaching	Zhou et al. (2017)
Polysaccharide-based	Hyaluronic Acid	Extrusion bioprinting	Antich et al. (2020)
		Encapsulation	Chen et al. (2017); Choi et al. (2020)
	Alginate	Extrusion bioprinting	Daly et al. (2016)
	Agarose	Encapsulation	Choi et al. (2020)
	Gellan gum	Encapsulation	Kim et al. (2019a)
	Chondroitin sulphate	Electrospinning	Sharifi et al. (2020)
		Freeze drying	Zhou et al. (2017)
		Salt leaching	Zhou et al. (2017)
	Pullulan	Encapsulation	Li et al. (2018)
ECM-based	Decellularized cartilage ECM	Stereolithography	Zhu et al. (2020)
		Extrusion bioprinting	Zhang et al. (2021)
		LDM	Chen et al. (2021)
	Predifferentiated MSC-derived ECM	Encapsulation	Antich et al. (2021)
Synthetic			
Cycle ester-based	Poly(trimethylene carbonate)	Stereolithography	Bochove et al. (2016)
Linear ester-based	Poly(ethylene glycol) diacrylate	Stereolithography	Zhu et al. (2020); Zhu et al. (2018)
	Polycaprolactone	Electrospinning	Girão et al. (2018)
		Melt electrowriting	Han et al. (2020); Diloksumpan et al. (2020)
	Poly(propylene fumarate)	Stereolithography	Ahn et al. (2018)
Urethane-based	Polyurethane	LDM	Chen et al. (2021)
Semi-synthetic			
Acrylate derivatives	Gelatin methacrylate	Extrusion bioprinting	Luo et al. (2020)
		Stereolithography	Lam et al. (2019)
		Freeze drying	Han et al. (2017)
	Methacrylate hyaluronic acid	Stereolithography	Lam et al. (2019)
		Freeze drying	Han et al. (2017)
Amino acids conjugates	Gelatin-tyrosine	Electrospinning	Agheb et al. (2017)
	RGD-functionalized pectin	Encapsulation	Chen et al. (2017)

ECM extracellular matrix; *LDM* low-temperature deposition manufacturing; *MSC* mesenchymal stem cells; *RGD* arginylglycylaspartic acid

can minimize the invasiveness of surgical processes and substances ensuring a proper biodegradation rate that leads to a better integration with host tissue (Grigore 2017). The most common ones used in cartilage tissue engineering are polyglycolic acid (PGA), polylactic acid (PLA), polyethylene glycol (PEG), polysaccharide (alginate and agarose-based (Almqvist et al. 2001; Mauck et al. 2000)) and protein (gelatin, collagen and fibrin)-based (Tzaveas and Villar 2010; Nixon et al. 2015; Horbert et al. 2019) gels.

Macroporous structures or hydrated polymeric networks, hydrogels, ensure the homogenous cell seeding within a construct. Hydrogel-based blends containing a suitable amount of water together with water insoluble factors are ideal biomaterials imitating the native articular cartilage structure. However, other parameters are needed to be considered to mimic the natural tissue, for example mechanical and chemical/biological ones.

The articular cartilage ECM components such as chondroitin sulphate (Wang et al. 2007; Sawatjui et al. 2018), hyaluronic acid (Bian et al. 2011a), and collagen can be added. One of the most widely used materials in this approach is chitosan, a polycationic polysaccharide, that can interact with collagen type II and aggrecan (Nettles et al. 2002).

Another approach is the use of decellularized cartilage slices. Indeed, the decellularized ECM provide a natural complex composition with chemical and biological factors to support differentiation of progenitor cells and reconstruction of the damaged tissues. During the decellularization process, all cells and cellular residues are removed and depending on the method, different ECM components can be maintained. To date, several methods have been reported to decellularize the cartilage tissue (Benders et al. 2013). Furthermore, the effects of different decellularized ECM on cartilage regeneration has been studied. They can be embedded in various hydrogels and different sizes of the ECM particles can be employed. Although there are many advantages of such materials, one of the most significant drawbacks is the loss of mechanical properties during decellularization. Various solutions have been proposed to solve this problem. For example, the natural matrix can be combined with natural (collagen (Rowland et al. 2018)) or synthetic (PLGA (Sutherland et al. 2015)) polymers. Since copolymer constructs and multilayered structures might improve mechanical properties, many studies developed different combinations, e.g. lactide-chain-extended poly (ethylene glycol) (PEG) gels functionalized with acrylate groups (Mellati et al. 2017).

Another limitation of the cartilage-derived ECM is the loss of tissue architecture that leads to the dedifferentiation of seeded chondrocytes. Among the structural features of the decellularized ECM, the fibrillar architectonics has an important role in controlling cellular behavior as chondrocyte phenotype can be affected by not only ECM composition, but also fiber diameter, distribution, pore sizes, etc. The quality of cell adhesion in 3D ECM grafts has been widely investigated in many studies. For example, chondrocyte-laden sponge scaffolds maintained the spherical shape of cells (Li et al. 2006), suggesting that the reduced surface area and the distance between fibers limited the formation of elongated cells (Kurashina et al. 2019). Material topography and microarchitecture are equally important in cartilage tissue engineering. For instance, MSCs seeded on a nanofibrous polycaprolactone (PCL) scaffold had a significant increase in the expression of transcript encoding collagen type II and GAG deposition compared to those seeded on microfibrous one (Yilmaz and Zeugolis 2020).

Despite many achievements, the mechanical properties of the engineered constructs require to be improved. Joints are subjected to tension, shear and compression loads in daily activities; thus, the fabricated cartilage equivalents should be resilient enough to ensure the joint reconstruction (Lai and Levenston 2010).

Biochemical factors

The influence of biochemical factors in cartilage tissue engineering could not be underestimated; the ratio of anabolic and catabolic compounds plays an important role by regulating the ECM synthesis and degradation. They are mainly presented by various growth factors such as transforming growth factor-beta (TGF-β), bone morphogenetic protein (BMP), insulin-like growth factor (IGF), etc.

TGF-β is one of the most essential factors used in cartilage tissue engineering, since it is involved in all stages of chondrogenesis, including growth, differentiation, and ECM deposition (Kwon et al. 2016). The TGF-β family can be divided into two subfamilies: TGF-β/Activin/Nodal and bone morphogenic proteins (BMPs). The TGF-β family consists of TGF-βs (TGF-β 1–3), activins (Act A–D), and Nodal/Nodal-related proteins. Nevertheless, using bone marrow-derived MSCs, adding activins and Nodal to the growth medium was shown to be less effective than adding TGF-β (Kroon et al. 2017). The normal TGF-β concentration in the synovial fluid of the joint is 1.8 ng/ml (Albro et al. 2012); its synthesis is increased in the hypertrophied chondrocytes and changes in its concentration correlate with the

osteoarthritis progression. Different strategies are used to deliver TGF-β into cells. For instance, TGF-β can be chemically (Sridhar et al. 2014; Cavalli et al. 2019) or physically (Zhou et al. 2017) incorporated directly into a bioink or loaded into microspheres (microparticles) made from alginate (Bian et al. 2011b) or gelatin (Guo et al. 2010). However, the efficient encapsulation of TGF-β into microspheres remains challenging (Sridhar et al. 2014). Therefore, many researchers still opt for direct load of TGF-β into scaffold (Zhang et al. 2021; Huang et al. 2019; Rathan et al. 2019). For instance, to induce the hyaline cartilage formation by MSCs with minimal hypertrophy, the two-stage procedure was offered: culturing two weeks within a TGF-β-loaded hydrogel and, then, 7 days using an inhibitor of Wnt/β-catenin signaling pathway (Deng et al. 2019). Moreover, the TGF-β synthesis can be modulated by using glucosamine (Sun et al. 2020) or hormones, e.g., leptin (Dumond et al. 2003), or injecting locally the transfected cells overexpressing TGF-β1 (Guo et al. 2006). To decrease the rise in TGF-β level caused by the chondrocytes' hypertrophy and downregulate TGF-β1/Smad signaling pathway, one can also apply monoclonal antibodies or inhibitors of TGF-β receptor (Wang et al. 2017; Chavez and Serra 2020).

Being the main subfamily of TGF-β superfamily, BMPs such as BMP2 and BMP7 modulate both chondrogenesis and osteogenesis. In cartilage tissue engineering, BMPs can be used together with TGF-β (Han et al. 2020; Lim et al. 2010; Gonzalez-Fernandez et al. 2016) to reduce the need for their high doses. Han et al. developed a complex multilayered PCL and PCL/hydroxyapatite (HA) scaffold incrustrated with TGF-β1, BMP-7, or IGF-containing microspheres (Han et al. 2020). Moreover, gene delivery systems to enhance BMP synthesis have been developed. It has been shown that fabricated constructs containing specific plasmid DNA-loaded alginate hydrogels provided the efficient cartilage tissue formation (Gonzalez-Fernandez et al. 2016). Interestingly, the combination of ligands activating simultaneously Activin A/BMP-2 was shown to induce more effectively chondrogenesis by MSCs than BMP-2 alone or the combination of Nodal/BMP-2 (López-Ruiz et al. 2018).

IGF contributes to the chondrogenic differentiation and ECM production (Kwon et al. 2016). This growth factor can be used either alone (Wei et al. 2020) or with TGF-β (Elisseeff et al. 2001). Non-viral IGF-1 gene delivery was successfully performed using collagen scaffolds seeded with adult articular chondrocyte that provided sustained IGF-1 production and enhanced chondrogenesis (Capito and Spector 2007).bFGF stimulates the chondrocytes' proliferation and regulates the ECM synthesis. It is usually used as a component of chondrogenic cocktails for the MSC differentiation (Mendes et al. 2018); however, bFGF was revealed to inhibit TGF-β and TGF-β-induced chondrogenesis (Chen et al. 2020a). It was shown that FGF-18 followed with the mechanical stimulation can efficiently induce the synthesis of cartilage ECM components by inhibiting key catabolic enzymes—matrix metalloproteinase-9 (MMP-9) and matrix metaloproteinase-13 (MMP-13) (Antunes et al. 2020).

Moreover, there is a particular interest in growth factors like noncanonical Wnt5a protein which suppresses Wnt signaling that allows chondrogenesis. Qi et al. showed that the in vivo use of Wnt5a could improve cell proliferation, spreading, and differentiation and collagenous fiber arrangement through the activated PI3K/AKT/JNK signaling pathway (Qi et al. 2020).

The inhibition of catabolic factors damaging and remodeling the cartilage can be achieved by chondroitin sulphate (Aisenbrey and Bryant 2019), hyaluronic acid (Lam et al. 2019; Erickson et al. 2012), vitamin D (Li et al. 2019), etc. The action of chondroprotectives is usually tested in an in vitro model formed using cartilage constructs or explants by adding IL-1 activating MMPs (Fu et al. 2020; Tan et al. 2015); moreover, to model inflammation in the cartilage tissue, TNFα can be also applied (Cho et al. 2015).

Moreover, various types of vesicles can be considered as another type of biochemical factors inducing the cartilage tissue formation and regeneration. Among them, matrix-bound vesicles (MBVs) that were recently discovered (Hussey et al. 2020) and can be derived from the native cartilage are of particular interest. Although the data on their role are limited (Merwe et al. 2017), MBVs are supposed to be one of the key players in the ECM-associated intercellular communication and tissue regeneration. It was revealed that MBVs can promote the macrophages' transition into anti-inflammatory phenotype (Huleihel et al. 2017) via the formation of pro-resolving lipid mediators from lysophospholipids and oxygenated

and non-oxygenated polyunsaturated fatty acids (Hussey et al. 2020).

Thus, biochemical factors are essential in cartilage tissue engineering. Tuning signaling pathways showed to significantly improve the chondrogenesis and can be performed using both blends of various cytokines and glycosaminoglycans and advanced delivery systems with sustained release.

Cartilage tissue engineering: tracing the future research route

Smart biomaterials

Smart, or stimuli-responsive, materials can be determined as hydrogels that response to various external stimuli by changing physicochemical properties such as volume phase or sol–gel transitions (Jagur-Grodzinski 2010). They can be classified by the required external stimuli as thermoresponsive, pH-sensitive, enzyme-responsive, redox-responsive, etc. Due to their adaptive properties, they have become highly attractive in cartilage tissue engineering that is proven by recently published papers.

Such materials can be injected into the defect site being "liquid" sol and transform into "solid" gel (Moreira et al. 2016; Yu et al. 2020). For temperature responsive systems, such transition occurs due to a temperature close to 37 °C and usually takes up to 5 min (Zhou et al. 2017; Moreira et al. 2016; Chen et al. 2020b); for metalloproteinase or aggrecanase-sensitive ones—due to the changes in enzymes expression and hence their concentration at the defect site (Chu et al. 2017; Skaalure et al. 2015; Schneider et al. 2019). They can be cell-laden or cell-free; the latter is especially attractive to treat extensive injuries. For instance, the cell-free smart system, PCL–PEG–PCL hydrogel loaded with TGF-β1, were shown to enable cell homing and full-thickness repair of the cartilage defect in vivo (Zhou et al. 2017). Smart materials, e.g. cholesterol-loaded PEG-polylactide-based hydrogels (Wang et al. 2019) or chondroitin sulphate-RGD-loaded PEG-based hydrogels (Aisenbrey and Bryant 2018) were shown to ensure the viability and proliferation of the encapsulated chondrocytes or MSCs and maintain their in vivo-like morphology and expression profile of the specific gene markers.

Smart biomaterials are of particular interest as drug delivery systems in treating cartilage defects. pH-responsive materials can release therapeutic agents (growth factors, monoclonal antibodies, etc.) under low pH because of the matrix-metalloproteinase (MMP) overexpression in the defect site caused by the osteoarthritis development (Lan et al. 2020); or thermoresponsive hydrogels—because of the temperature increase (Chen et al. 2020b); or MMP-sensitive systems—because of enzyme activity (63), etc. Particularly, Chen et al. (Chen et al. 2020b) developed a cell-free thermoresponsive hydrogel with the prolonged release of infliximab, TNF-α inhibitor, reducing inflammation. Deloney et al. (Deloney et al. 2020) showed that hollow thermoresponsive nanoparticles had more effective drug uptake and release than regular shaped solid particles. Moreover, Mohanraj et al. (Mohanraj et al. 2019) used mechanical strength to trigger on-demand drug release from microcapsules injected into the synovial joint.

Among smart biomaterials, there is a special group of so called "self-healing" hydrogel systems which can restore their properties after being exposed to changing external factors such as pH, temperature, shear stress, etc. (Yu et al. 2020; Hager et al. 2010; Taylor 2016). Their self-healing properties are based on reversible chemical bonds (imine, acylhydrazone, disulfide, etc.) or physical interactions (hydrophobic or electrostatic, hydrogen bonding, metal–ligand coordination, etc.) that can be disrupted under external stimuli, but form then again (Tu et al. 2019). The most common compounds to form such systems are polysaccharides, which are natural components of the cartilage ECM (Kim et al. 2019b; Mohamed et al. 2020). Self-healing hydrogels can be injected into the joint, and by restoring their structure within it, they reduce friction (Gao et al. 2020; Li et al. 2017). Moreover, they were shown the sustained drug release in treating osteoarthritis and rheumatoid arthritis (Mohamed et al. 2020; Zhao et al. 2020).

In recent studies, such materials, especially thermoresponsive ones, have become a basic element of multi-functional bio-responsive platforms used to restore the damaged cartilage tissue. For instance, Dehghan-Baniani et al. (Dehghan-Baniani et al. 2020) developed a kartogenin-loaded system consisting of thermosensitive chitosan-based hydrogel ensuring synovial fluid-like viscous properties and nano-patterned silk meshes ensuring mechanical

strength. The use of smart biomaterials in such systems can be followed with various therapeutic strategies, e.g., photodynamic therapy. Pan et al. (Pan et al. 2020) used phosphorus nano-sheets for local heating by near infrared irradiation to produce reactive oxygen species (ROS) against hyperplastic synoviocytes, and thermoresponsive chitosan-based hydrogel controlled the release of degradation products in addition to its protective and lubricating properties.

Bioprinters

Bioprinting is one of the most promising techniques for the chondroplasty of large defects and has been already used for cartilage tissue engineering. It rapidly develops that is followed with designing new solutions in its realization (Lee et al. 2018).

In general, bioprinting is a scaffold-free technology which uses cells or their aggregates suspended within a hydrogel system as a bioink. Nevertheless, most of recent papers describe the application of cell spheroids—microtissues—which enable to avoid cell redifferentiation. De Moor et al. generated fibrochondrocytes and articular chondrocytes spheroids which maintained their ability to synthetize a specific ECM protein profile (Moor et al. 2020).

New hydrogel-based systems have led to the rapid development of novel approaches such as 4D printing (Momeni et al. 2017). Compared to the trivial ones, 4D printed structures are dynamic systems which change in time due to external stimuli (magnetic field, irradiation, etc. (Zhang et al. 2021; Zhang et al. 2021); thus, they can self-assemble, self-heal or change their geometry as a response to various factors, in other words, they are "adaptable". 4D bioprinting has been shown to be applicable in fabricating cartilage constructs. For instance, Kim et al. developed constructs which self-assemble into a trachea-mimicking tubular structure and were successfully tested in vivo (Kim et al. 2020).

To date, the bioprinting technical realization is not only presented by inkjet-, extrusion- and laser-based systems, and various modifications are designed. Inkjet- and extrusion-based bioprinters were shown to be equipped with a bath filled with a solution of cross-linking reagents. So, during bioprinting, the bioink forms a structure by dropping into the bath and crosslinking there. Melo et al. (Melo et al. 2019) fabricated the cartilage-like tissue using the bioink containing MSC spheroids and fibrin by printing into the bath with PEG-alginate-thrombin hydrogel. Moreover, acoustophoretic force was recently offered as a new principle to eject droplets of various volumes (Foresti et al. 2018). Acoustophoretic printing enables printing single cells that is mostly required to study the role of the stem cell microenvironment (Leibacher et al. 2015).

Laser-based methods are becoming highly attractive in for cartilage tissue engineering due to the high processing speed and the possibility to fabricate complex structures (Regehly et al. 2020). While be printed, such structures are formed within the volume of viscous material (resins); so, this approach is also called volumetric printing. Using volumetric bioprinting, the meniscus-shaped construct has been fabricated whose cells could synthesize the neo-fibrocartilage matrix (Bernal et al. 2019).

To position cell aggregates (e.g., cell spheroids), new approaches such as aspiration-based ones are offered (Ayan et al. 2020). The applicability of aspiration-assisted bioprinting was tested in fabricating stratified cartilage constructs (Ayan et al. 2020; Wu et al. 2020). Ayan et al. (Ayan et al. 2020) formed the osteochondral interface by layer-by-layer printing of osteogenic and chondrogenic spheroids that fused while culturing.

Moreover, flow-based technologies are becoming more widely used and techniques such as co-axial bioprinting and continuous chaotic printing have been developed. Co-axial bioprinting is based on structuring only at the intersection point of two separate flows. Cells and scaffolding material containing photo initiator can be in two separate inks that maintain higher cell viability and enables forming a core–shell structure (Duchi et al. 2017). The most recent papers describe the continuous chaotic printing which is based on self-repeating patterns of chaotically dispensed bioink flows predicted by mathematical modelling (Trujillo-De Santiago et al. 2018; Chávez-Madero et al. 2020). This approach has enabled the fabrication of hierarchically structured cartilage constructs (Bolívar-Monsalve et al. 2021).

Nevertheless, in situ bioprinting is of the highest interest of clinicians. It enables fabrication of constructs on place during the operation. After removing the damaged tissue, a surgeon can "fill" the defect with an implant of the required shape and size at one time. In general, in situ bioprinters can be divided

into two categories: the robotic arm and hand-held devices. The former type requires less interventions than the latter one and is presented by a 3-axis moving bioprinter. Such set-up may contain one or more printing heads with different bioinks. The hand-held bioprinters are a portable device that can be easily transported and allows an easy access to the lesion. To the best of our knowledge, the first in situ hand-held bioprinter developed to treat cartilage tissue defects is "BioPen" by O`Connel et al. (O'Connell et al. 2016). This device is an extrusion-based bioprinter with a two-inlet mixing nozzle (Bella et al. 2018). In vivo testing showed that its use ensured the effective chondral regeneration with the early formation of hyaline cartilage (Duchi et al. 2017). In fact, new systems should appear in the nearest future because of the high promises for the rapid clinical translation.

Bioreactors

There is no doubt, intensive research in engineering human-scale 3D cartilage constructs requires the use of bioreactors for both cell biomass production and construct maturation (Mabvuure et al. 2012). Despite that main bioreactors' types were developed decades ago, they are being extensively upgraded and adapted for cartilage tissue engineering.

One of the most widely used bioreactor types is rotating wall vessel (RWV) bioreactor (Sikavitsas et al. 2002), which provides dynamic laminar flows and microgravity conditions. They are able to maintain the long-term cultivation of primary chondrocytes without losing morphology and specific gene expression profile (Mellor et al. 2014). Moreover, the cultivation in such bioreactors resulted in more successful chondrogenic MSCs differentiation than that under standard static conditions (Mellor et al. 2017). This can be caused by better mass transfer rate of glucose and TGF-β2 (Zhu et al. 2017) in RWV bioreactors. The microgravity conditions of such bioreactors were revealed to modulate LRP receptor expression in Wnt pathway, which is involved in response to mechanical signals in the cartilage tissue (Nordberg et al. 2019).

Another type of bioreactors is spinner flask ones where a culture medium is suspended by a stirring element at the bottom of a flask (Sucosky et al. 2004). In recent studies, they were successfully used to cultivate chondrocytes (Jin and Kim 2016; He et al. 2019). Culturing MSCs seeded on a porous scaffold in spinner flasks led to higher viability and proliferation rates and better chondrogenic differentiation than that under static conditions (Agrawal and Pramanik 2019; Agrawal et al. 2018). Embedded adipose derived stromal cells (ADSCs) differentiated in chondrogenic direction, produced GAG and other ECM components, and formed interconnections between top and bottom layers (Song et al. 2016). To recapitulate the synovial fluid-like environment for the large-scale studies, the upgrade of a spinner flask bioreactor was recently developed by Tekari et al. (Tekari et al. 2020). The designed robotic automated system could ensure the simultaneous standardized cultivation of 24 samples and was tested for both cartilage explants and tissue-engineered constructs.

The improvement of the nutrients delivery into the fabricated cartilage equivalents can be achieved using flow-perfusion bioreactors where a culture medium is pumped through the whole construct (Bancroft et al. 2003). Flow perfusion allows the homogenous cell distribution (Shakhawath Hossain et al. 2015) and stimulates cell proliferation and production of the cartilage-specific ECM (Dahlin et al. 2014; Theodoridis et al. 2019). Such bioreactors were successfully applied to mature different tissue-engineered structures, e.g. biphasic osteochondral constructs (Daley et al. 2019) and MSC seeded decellularized hypertrophic cartilage (Pigeot et al. 2020). Such bioreactors can facilitate the scalable in vitro antibacterial drug testing in cell-bacteria co-culture systems (Najmi et al. 2020). Compared to the previously described ones, one of the main advantages of perfusion bioreactors for cartilage tissue engineering is the possibility to recapitulate in vivo-like mechanical forces and standardize them. Gamez et al. (Gamez et al. 2020) upgraded a flow-perfusion bioreactor with a compression mechanism and force sensors that enabled to study the MSCs mobilization under mechanical loading.

As an alternative to the aforementioned bioreactor types, there is a growing interest in in vivo bioreactors that can be applied to mature the fabricated cartilage constructs. Their idea is quite simple: a construct is implanted into an animal where it is naturally supplemented with the required growth factors and morphogens. Recent papers have shown that this approach could ensure the successful cartilage tissue

formation and graft re-epithelization and re-vascularization (Park et al. 2018; Huang et al. 2013; Li et al. 2020). However, there is a limited number of studies on in vivo bioreactors because of the issues in maintaining the standard conditions and preventing host immune reactions (Fig. 3).

Preclinical and clinical trials

Nevertheless, the achievements described above are only started to be tested in preclinical trials. The most common species used as a model are mice, rabbits, sheep, goats, minipigs, etc. For instance, Kang et al. (Kang et al. 2018) subcutaneously implanted a cell-laden trilayer equivalent into immunodeficient mice and revealed that the implanted cells formed the neocartilage and the mineralized bottom of the scaffold recruited endogenous cells that resulted in the osteochondral tissue formation. Kuznetsov et al. (Kuznetsov et al. 2019) also used mice (immunocompromised ones) to show the formation of the hyaline-like cartilage due to the implantation of bone marrow-derived mesenchymal stromal cells covering hyaluronic acid-coated fibrin microbeads. However, mice and rats enable mainly heterotopic implantation and can be considered as a model to study general biocompatibility. Compared to them, rabbits allow the orthotopic implantation. Particularly, Wang et al. (Wang et al. 2018) injected into the rabbit synovial cavity the developed hyaluronic acid-modified poly(N-isopropylacrylamide) hydrogels loaded with adipose-derived stem cells.

However, only large animals such as sheep, goats, horses, can restore the cartilage tissue similar as humans do. Using a sheep model, Di Bella et al. (Bella et al. 2018) showed the applicability of "Biopen" to restore the chondral defects during a single session surgery. Dai et al. used minipigs to demonstrate that the implantation of acellular bone matrix combined with microfracturing ensured the formation of the neocartilage with mechanical properties similar to the native tissue (Dai et al. 2019).

There is a limited number of clinical trials which aims to assess cartilage tissue equivalents and are registered on Clinicaltrials.gov for the last five years (Table 3); most of cell-based products claimed to be

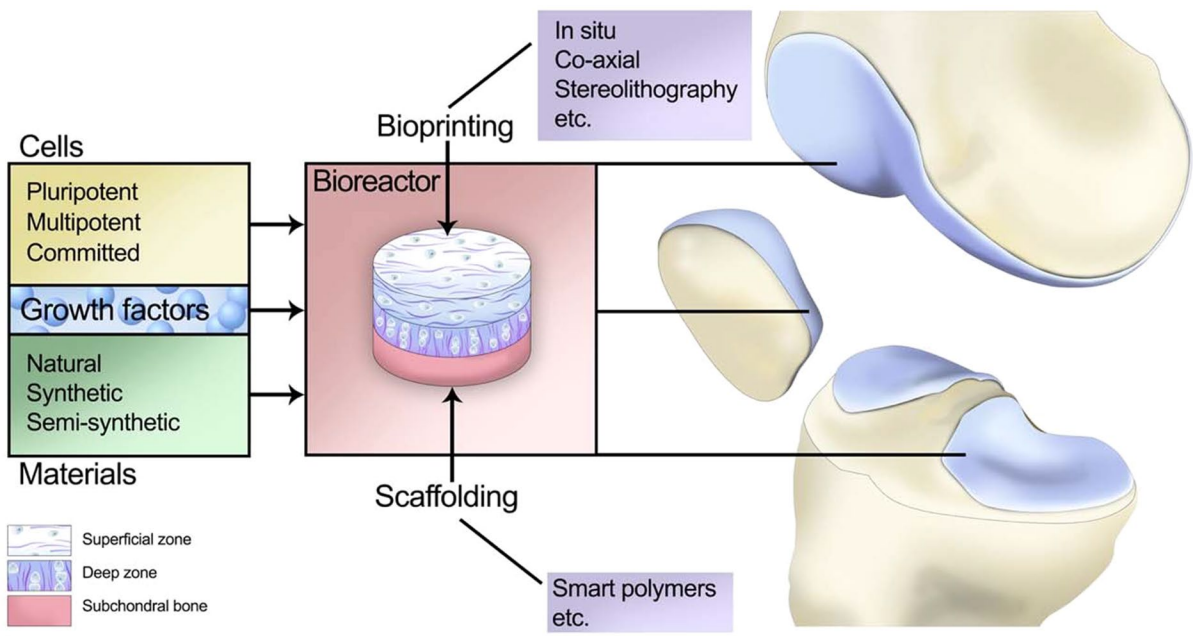

Fig. 3 Current achievements in cartilage tissue engineering. To restore large defects of cartilage tissue, only complex constructs can be efficiently used. Such constructs consist of at least two zones and can be fabricated using different autologous cell types and biomaterials mimicking native ECM properties. New platforms such as in situ bioprinting set-ups are developed as a personalized approach to each patient and can be more rapidly translated into clinics than trivial scaffold-based systems

Table 3 Clinical trials of cell-based products for the cartilage restoration registered on Clinicaltrials.gov for the last 5 years (2016–2021)

Product and Its Composition	NCT Number	Conditions	Phase	Status	Country	Starting year
CartiLife®: ECM-associated autologous chondrocytes	NCT05051332	Articular Cartilage Defect Articular Cartilage Degeneration	3	Recruiting	Republic of Korea	2021
	NCT04744402	Articular Cartilage Defect Articular Cartilage Degeneration	2	Recruiting	USA	2021
Allogeneic human chondrocytes expressing transforming growth factor-beta1	NCT03291470	Degenerative Osteoarthritis	3	Not yet recruiting	USA	2017
TissueGene-C: non-transduced human chondrocytes and irradiated transduced human GP2-293 cells expressing TGF-B1	NCT03203330	Degenerative Osteoarthritis	3	Active, not recruiting	USA	2017
NOVOCART®: Autologous chondrocytes	NCT03319797	Cartilage Defects of the Knee	3	Active, not recruiting	Czech Republic	2017
NOVOCART 3D: Matrix associated autologous chondrocytes	NCT03219307	Articular Cartilage Defect	3	Recruiting	USA	2017
ACI: Autologous chondrocytes	NCT04296487	Articular Cartilage Defect Chondral Defect Osteochondritis	NA	Recruiting	Switzerland	2020
MACI: autologous cultured chondrocytes on porcine collagen membrane	NCT03588975	Chondral Defect Osteochondritis Dissecans Articular Cartilage Defect Articular Cartilage Disorder of Knee	3	Recruiting	USA	2018
N-TEC: Autologous nasal chondrocytes cultured in a collagen type I//III scaffold	NCT04633928	Nasal Cartilage Septum Perforations	1	Recruiting	Switzerland	2020
	NCT02673905	Tear; Knee, Cartilage, Articular	NA	Active, not recruiting	Switzerland	2016
N-CAM: Autologous nasal chondrocytes cultured in a collagen type I//III scaffold	NCT02673905	Tear; Knee, Cartilage, Articular	NA	Active, not recruiting	Switzerland	2016
AuriNovo: 3D-bioprinted collagen hydrogel scaffold encapsulating the patient's auricular chondrocytes	NCT04399239	Microtia	1–2	Enrolling by invitation	USA	2020

Table 3 (continued)

Product and Its Composition	NCT Number	Conditions	Phase	Status	Country	Starting year
Chondrochymal®: Allogeneic bone marrow derived mesenchymal stem cells	NCT03589287	Knee Osteoarthritis	1–2	Completed	Taiwan	2018
Chondrogen: Mesenchymal stem cells derived from the umbilical cord in hyaluronic acid	NCT04520945	Knee Osteoarthritis	2	Not yet recruiting	Malaysia	2020
Mesenchymal stem cells derived from the umbilical cord	NCT05016011	Knee Osteoarthritis	2	Recruiting	Malaysia	2021

ECM extracellular matrix; *NA* not applicable

assessed are a cell suspension consisting of chondrocytes or mesenchymal stem cells. This situation is unsurprising as most of the tissue-engineered cartilage equivalents have been only recently developed and require to pass preclinical trials first.

The promotion of clinical trials of novel products to restore the cartilage tissue should be rational. The stimulation and growing concurrence in this field have led to the increase in data falsification or suppression. For instance, the most prominent incident happened in 2020 was related to the cell-based product Invossa-K, which consists of human normal chondrocytes and transduced cells and is produced by Kolon Pharma (South Korea). Despite controversial results of the performed clinical trials, the main issue was related to the mislabeling, i.e., while applying for the license, the company falsely reported or missed some data on its product. It was claimed that the transduced cells were cartilage-derived; nevertheless, later they were revealed to be kidney-derived—HEK 293 cell line. Thus, the Ministry of Food and Drug Safety of the South Korea revoked the license and all clinical trials on Invossa-K were stopped.

Conclusions

Tissue engineering is a rapidly developing field, and cartilage tissue engineering is not an exception. To date, the concept of the personalized cell product to treat vast and deep defects is based on newly developed platforms. These platforms are full cycle systems that are mainly presented by a bioprinter, which uses ECM-embedded autologous cell aggregates as a bioink, and a bioreactor to fabricate and mature the tissue. Nevertheless, in situ platforms are of particular interest as they can skip labor- and time-consuming steps such as tissue maturation and ensure the possibility to easily adjust a construct on place during the operation to restore large defects. Nevertheless, the cartilage equivalents fabricated using novel techniques have not yet been translated into clinical practice: only several preclinical trials have been initiated and only few clinical trials have been registered.

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Declarations

Conflict of interest The authors declare no competing financial interest.

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