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Review

Bioprinting and its applications in tissue engineering and regenerative medicine

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ABSTRACT

Bioprinting of three-dimensional constructs mimicking natural-like extracellular matrix has revolutionized biomedical technology. Bioprinting technology circumvents various discrepancies associated with current tissue engineering strategies by providing an automated and advanced platform to fabricate various biomaterials through precise deposition of cells and polymers in a premeditated fashion. However, few obstacles associated with development of 3D scaffolds including varied properties of polymers used and viability, controlled distribution, and vascularization, etc. of cells hinder bioprinting of complex structures. Therefore, extensive efforts have been made to explore the potential of various natural polymers (e.g. cellulose, gelatin, alginate, and chitosan, etc.) and synthetic polymers in bioprinting by tuning their printability and cross-linking features, mechanical and thermal properties, biocompatibility, and biodegradability, etc. This review describes the potential of these polymers to support adhesion and proliferation of viable cells to bioprint cell laden constructs, bone, cartilage, skin, and neural tissues, and blood vessels, etc. for various applications in tissue engineering and regenerative medicines. Further, it describes various challenges associated with current bioprinting technology and suggests possible solutions. Although at early stage of development, the potential benefits of bioprinting technology are quite clear and expected to open new gateways in biomedical, pharmaceutics and several other fields in near future.

Contents

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1. Introduction

Bioprinting is one of the advanced and innovative technology of this century that has received growing interest worldwide and revolutionized pharmaceutical industry, tissue engineering, and regenerative medicines fields, etc. [1]. It refers to utilization of three-dimensional (3D) printing technology to print various biomaterials with incorporated viable cells. For bioprinting of cells, tissues, and organs, and biomaterials, polymers and viable cells are concurrently deposited in a premeditated layer-by-layer stacking pattern [1]. Currently, this technology has received immense consideration and is widely used for broad-spectrum applications such as regenerative medicines, tissue engineering and transplantation, screening of drugs, and cancer research, etc. It offers several advantages such as precise and controlled deposition of cells, hormones, drugs, and growth factors, etc. thus directing improved tissue regeneration. Further, it provides a base for development of tissues constructs, organs and organoids, and organ-on-a-chip, mimicking natural ones [2,3]. To date, several biomaterials including bone and cartilage tissues, cardiac tissues and heart valve, neural, lung, liver, pancreatic, skin, retinal, vascular, and composites tissues have been fabricated through this technology [4]. It offers several merits, importantly reduces treatment time, for example during transplantation of tissues and organs [5].

Conventionally, biomaterials are synthesized by various fabrication strategies including molding, blending, microfluidic techniques, and magnetic assembly, etc. In contrast, bioprinting technology manufactures more accurate tissue constructs and tissue-models in a high-throughput fashion and develops porous structures with controlled architecture. Besides, it allows local co-culturing of multiple cell-types and defined patterning of live cells and biologics. Furthermore, it facilitate controlled delivery of drugs, genes, and growth factors, and integration of vascularization within the engineered tissues, etc. [4]. The success of bioprinting technology relies on efficiency of 3D bioprinters and availability of bioink (comprised of polymer solution and viable cells) and its structural, physico-chemical, mechanical, thermal, and biological features. Currently, various companies are making and marketing new bioprinters with advanced features, design, and efficiency. Similarly, different types of bioinks such as polymer-based hydrogels, polymer-based micro-carriers preloaded with cells, cell-aggregates and pellets, tissue spheroids and strands, and decellularized matrix (dECM), etc. are used for bioprinting of various materials [4,6–8]. Despite extensive advantages offered by modern bioprinting technology, currently it is facing several challenges mainly associated with tuned properties of polymers used for preparation of bioink. For example, printed hydrogels are fragile enough to support the growth of hard tissues such as bone and cartilage. Besides, limited availability, viability, adhesion, and proliferation of cells on selected polymer-based scaffolds hinder bioprinting of different tissues. Mostly, the cells have limited ability to maintain their physiological state and develop specialized function in *in vivo* environment [9]. Further, cells selected from different donor risk the provoking of immunogenic response [10]. Stem cells, if used as source cells, have limited ability to differentiate into all types of cells [11]. Similarly, simultaneous bioprinting of various cell types requires the preparation of different bioinks which further complexes the printing process. Besides, these bioinks have limited shelf-life and face storage difficulties [12]. Further, optimization of printing conditions lowers the efficacy of 3D printers [8]. Together, all these factors limit the bioprinting of natural-like full-scale organs.

The current review describes the potential of various polymers for their applications in 3D bioprinting of different biomaterials by describing their various tunable properties. It also overviews the selection of various cells to form bioink with various polymers and their adherence, proliferation, and migration on printed scaffolds to form various tissues and organs like cell-lade constructs, bone and cartilage cells and tissues constructs, skin cells and tissues, blood vessels, and neuronal tissues, etc. for their applications in tissue engineering and regenerative medicines. It also describes various challenges currently associated with bioprinting technology and details their possible solutions for broad-spectrum practical applications of this technology in different fields. This review can potentially attract wide readership in materials and polymer sciences to find novel applications of bioprinting technology.

2. Choice of materials for bioprinting

The choice of materials used in bioprinting is a hard job as the materials are often complex and antagonistic in nature. Bioprinting technology requires three main components: polymer solution, viable cells, and 3D printers. The polymer solution and viable cells constitute bioink. Several factors are considered during selection of these components, for example, the selected polymer solution should demonstrate low viscosity, low stiffness, and low cross-linking as these features enable cell migration, nutrients and oxygen diffusion, and new tissue formation. On the other hand, the selected polymers should demonstrate high mechanical properties, dimensional accuracy, and better structural properties which require more viscous, stiff, and rapidly gelating materials. These features are contradictory to each other, thus a balance must be maintained between structural, physico-mechanical, and biological properties of the selected polymeric materials to ensure bioprinting of constructs with high cell viability. Various natural and synthetic polymers are used for bioprinting applications (Fig. 1). The following section overviews various polymers-based hydrogels used for bioprinting of biomaterials, characteristic features of these

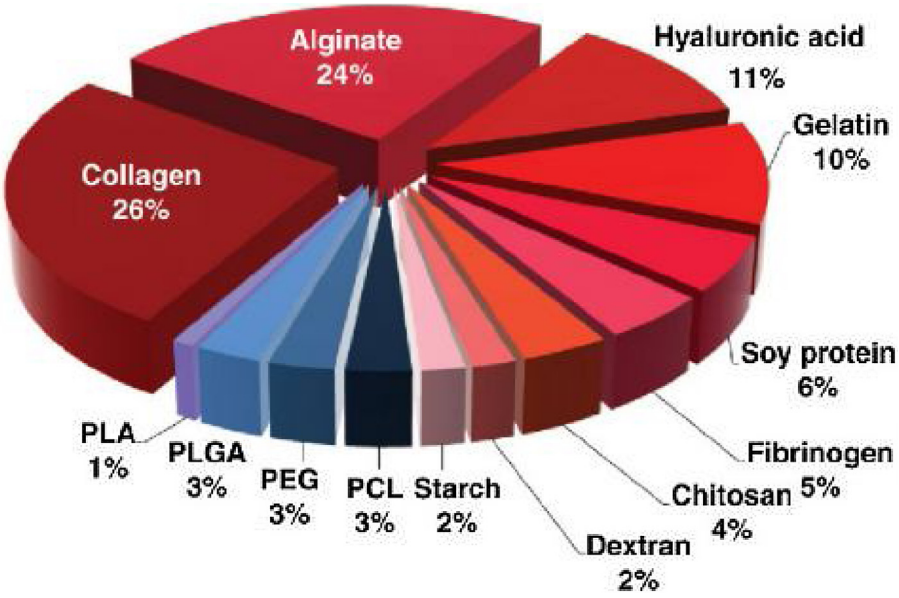

Fig. 1. Chart diagramming natural (red) and synthetic (blue) polymer distributions for use as bioinks. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
The figure has been reproduced from [20] with permission from Academic Press.

hydrogels, and selection of viable cells: choice, selection, and characteristic features etc. of all these components:

2.1. Polymers-based hydrogels for bioprinting

Hydrogels are high molecular-weight cross-linked structures and are essential components of bioink. These remain in direct contact with cells, maintain their viability, and support their growth and proliferation. Further, these can also serve as substrate and scaffolds for cell adhesion and proliferation. The hydrogels determine the physico-mechanical properties of the bioink and are considered as ideal materials for cell bioprinting owing to their unique chemical and physical properties, high water content, and *in vivo* biodegradability, etc. However, in general, hydrogels are weak in nature and do not meet the requirements to support 3D structures such as bone, cartilage, and other organs which require a mechanically strong ECM. Earlier, electrospun fibers were used for scaffoldings to substitute blood vessels, however, currently these have been largely replaced by various polymers such as collagen, ployanhydride, fibronectin, alginate, chitosan, agarose, and matrigel, etc. [9,13]. The mechanical properties such as elasticity and stiffness of hydrogels have been improved by various strategies such as blending and cross-linking with other materials, impregnation with different nanoparticles (organic and inorganic), or through reinforcement of various agents [14–16]. However, conventional hydrogels face several challenges such as inability to provide appropriate protection to viable cells and maintain low resolution during their stabilization. Therefore, mechanical and biological properties of hydrogels should be improved for high resolution bioprinting and cell viability. An ideal hydrogel should demonstrate several characteristic features including highly porous structure that allow exchange and filtration of nutrients and oxygen, high mechanical stability, improved biocompatibility and biodegradability, excellent printable and cross-linking features with adequate viscosity and thinning properties, and controlled byproducts formation, etc.

Two types of hydrogels, natural and synthetic polymers-based or combination of both, are used based for preparation of bioinks and their selection is carried out based on hydrogel design for a specific application [17–19].

2.1.1. Natural polymers-based bioprinting of biomaterials

Natural polymers are those present in ECM components of cells including gelatin, hyaluronic acid (HA), fibrin, collagen, laminin, and fibronectin, etc. Besides, several other biopolymers such as alginate, chitosan, cellulose, starch, and silk fibroin, etc. have also been used as hydrogels for bioink preparation. Interaction of natural hydrogels with live cells has been well-studied both *in vitro* and *in vivo* [18]. dECMs have been effectively used for bioprinting of various tissues and have shown promising results. Although, dECMs do not possess desired mechanical properties, these contain various components possessing characteristic features of different tissues and can function as a natural tissue. In a study, dECMs of three different tissues were successfully solubilized into bioink and bioprinted [6]. The following sections overview the applications of various natural polymers in bioprinting:

2.1.1.1. Cellulose. Cellulose is most abundant natural polymer available on earth. It is unbranched, comprised of nanofibrils, and is composed of glucose units linked together through β-(1–4)-glycosidic linkages. The linear glucan chains in cellulose form regular intra- and inter-molecular hydrogen bonds that stabilize its reticulate structure on one hand, but causes its limited solubility in common solvents [21–23]. Based on its source and processing conditions, there are three types of cellulose: micro-fibrillated, nano-crystalline cellulose, and bacterial nanocellulose (BNC) [24]. Recently, cellulose has received immense consideration for broad spectrum biomedical applications owing to its unique features such as hydrophilicity and high water holding capacity, chemical modification capacity, better mechanical properties, high crystallinity, and biocompatibility, etc. [23,25]. Most of biomedical applications of cellulose are based on BNC. Bacterial nanocellulose produced by microbial cells and cell-free system [26–29], due to its similarity with collagen fibrils in term of size (100 nm), has received immense consideration for applications in scaffold development for soft tissues, for example cartilage [30]. Besides, ultrapure nanocellulose is obtained from wood source in large quantities and demonstrates

biocompatibility with human tissues which make it a promising material in scaffold development [31]. These nanocellulose based scaffolds find various potential applications such as in development of artificial ligament [32], as a component of bioink for 3D printing [33,34], and wound dressing [24,35], etc. Bioprinting applications of cellulose usually require ductile films, however, cellulose nanofibrils obtained from wood source are commonly brittle, thus limiting its potential applications. Therefore, various additives such as cationic hydroxyethylcellulose (CHEC) and glycerol [36] and quaternary alkylammoniums (QAs) by casting on 2,2,6,6-tetramethylpiperidine-1-oxyl-oxidized cellulose nanofibrils (TOCNs) [37] are usually used to increase the ductility of nanocellulose films.

Nanocellulose based bioinks have been reported to serve as hydrogel for 3D bioprinting with live cells. For example, a nanocellulose-alginate bioink containing human nasoseptal chondrocytes (hNSCs) was developed for bioprinting of cartilage tissue constructs with desired properties, such as human ear and sheep meniscus using MRI and CT images as blueprints [33]. In another study, Ávila et al. developed a bioink composed of nano-fibrillated cellulose and alginate (NFC-A) for bioprinting of auricular cartilage tissue constructs with human nasal chondrocytes (Ávila et al., 2016). The NFC-A bioink facilitated the biofabrication of cell-laden patient-specific auricular constructs, high cell density, and uniform cell distribution within the tissue construct which demonstrated excellent shape and size stability; and cell viability, proliferation, and differentiation. Nanocellulose based nanocomposites with various nanoparticles have been developed where nanoparticles are absorbed by the abundant −OH groups in cellulose. Tang et al. developed photoelectric bioink based on nanocellulose/CdS quantum dots for application in screen-printing. In this bioink, CdS quantum dots served as pigment while nanocellulose as binder. The developed bioink demonstrated high stability with excellent fluidity and rheology [39].

2.1.1.2. Gelatin. Gelatin, a natural water-soluble protein, is derived from collagen through hydrolytic degradation. This process involves the breakage of triple helix of collagen to obtain single stranded gelatin molecule. It shows amphoteric behavior due to the presence of alkaline and acidic amino acid functional groups in its chemical structure. It finds several applications in food, pharmaceuticals, photographic, and biomedical fields, etc. [40]. In nature, it is obtained from different sources such as mammalian, warm and cold water fish skins, bones, and fins, etc. However, gelatin obtained from mammalians such as bovine and porcine skins and bones do not meet the desired properties for applications in tissue engineering. Further, there is a risk of transmission of pathogenic vectors associated with these mammalian origin gelatin [41]. In contrast, fish-derived gelatin offers high viscosity and lower melting temperature and thermal stability owing to differences in amino acid composition and sequence [42].

Gelatin has been effectively used in development of bioink for bioprinting of materials owing to its unique properties including high biocompatibility and biodegradability, considerable cross-linking potential, and better thermal stability in physiological environment [42]. It accounts for 10% of total polymer distribution used for bioink preparation in bioprinting applications [20] (Fig. 1). Das et al. developed directly printable bioink comprised of silk fibroin and gelatin (SF-G) through *in situ* cross-linking which supported multi-lineage differentiation of stem cells for fabrication of 3D tissue constructs [43]. Gelatin is made photopolymerizable by adding methacrylate groups to the amine-containing side groups which results in formation of gelatin methacrylate (GelMA). GelMA is a versatile matrix, closely resembling the properties of natural ECM and provides characteristics features such as cell attachment sites, proteolytic degradability, contains matrix metalloproteinase responsive peptide motif, and can be used to engineer tissue analogs [44,45]. These hydrogels have received immense consideration due to the inherent bioactivity of gelatin and physicochemical tailorability of photo-crosslinkable hydrogels [44]. These GelMA hydrogels when combined with other materials have been extensively used for various biological applications such as directed 3D alignment of cells, tissue engineering, gene and drug delivery, cell signaling, directional control of endothelial cells morphogenesis, development of functional capillary network, and patterning of cells, etc. [45–47], etc. It has been shown that GelMA-based constructs with varying architectures can be designed through bioprinting [48]. For example, for bone engineering, MSCs were seeded on polylactide microspheres for extensive cell expansion and resulted multicellular aggregates were printed within a GelMA-gellan gum ink [7]. For enhanced tissue-specific functionality, composites of GelMa have been developed with various materials such as hyaluron [49,50], ECM particles [14], PEG [51,52], and polysaccharides [53], etc.

2.1.1.3. Alginate. Alginate or sodium alginate (raw form) is an anionic polysaccharide obtained from seaweed. Chemically, it is comprised of mannuronic acid and guluronic acid units. The mannuronic acid forms β-(1 → 4) linkages and thus exhibits linear and flexible conformation. Due to its structural similarities with natural ECM and possession of excellent biocompatibility, high viscosity, and ease of gelation at room temperature, it is an attractive candidate for applications in bioprinting where it accounts for 24% of total polymer distribution used for bioink preparation [13,20,54] (Fig. 1). However, it does not possess cell-adhesion moieties such as RGD, thus it does not support cell adhesion and proliferation. Such limitations are overcome by the addition of cell adhesive molecules and blending with compatible polymers. Besides, Blaeser et al. developed a novel laser ablation technique for *in situ* embedding of Au and Fe nanoparticles into alginate hydrogel which served as alternative material owing to their biofunctionalization ability (coupling of RGD ligands) and favored endothelial cell adhesion [55].

Several bioprinting strategies have been developed to produce cell-laden alginate hydrogel structures; however, these strategies are limited to fabrication of 2D or simple 3D structures. For example, Tabriz et al. developed a new extrusion-based bioprinting technique to produce more complex alginate hydrogel structures by simply dividing alginate hydrogel cross-linking process into three steps: primary calcium ion cross-linking for printing of hydrogel, secondary calcium cross-linking immediately after printing for rigidity of hydrogel, and tertiary barium ion cross-linking for long-term stability of hydrogel [56]. At first, simple 3D structures (i.e. tubes) were printed followed by printing of complex structures (i.e. branched vascular grafts). Yan et al. successfully carried out laser-assisted printing of alginate long tubes and annular constructs with a nominal diameter of 3 mm [57]. Kundu et al. fabricated 3D cell-printed scaffolds of alginate and PCL through layer-by-layer (LbL) method using chondrocytes for cartilage tissue engineering [58]. In a similar study, Kim et al. developed mechanically reinforced multi-layered cell-laden scaffolds by using alginate-based bioink printed on the surface of an alginate-PCL mesh structure for regeneration of hard tissues [59]. Yu et al. developed a scaffold-free fabrication strategy by using engineered scaffold-free scalable tissue strands of alginate as bioink for robotic assisted bioprinting and printed 8 cm long tissue strands with rapid fusion and self-assemble potentials, thus avoiding the need of solid support or mold [60]. Another study reported the development of a mitogenic hydrogel system based on alginate sulfate to support the growth of chondrocytes. To impart printing properties, nanocellulose was added to alginate sulfate

bioink which thereafter supported cell adhesion, proliferation, and collagen II synthesis by the encapsulated cells [61].

2.1.1.4. Chitosan. Chitosan is a linear amino-polysaccharide comprised of β-(1–4)-linked D-glucosamine residues and randomly distributed N-acetyl-D-glucosamine units. It is the second most abundant polymer on earth after cellulose, produced through exhaustive deacetylation of chitin. It is semi-crystalline in nature and serves as a structural component in the exoskeleton of crustaceans and insects. It is insoluble in aqueous environments above neutral pH; however in acidic environment (<5) it is completely soluble due to protonation of free amino acids. Owing to its aqueous solubility in acidic environment, it is largely utilized for bioprinting applications where it accounts for 4% of total polymer distribution used for bioink preparation [20] (Fig. 1). For this purpose, chitosan solution is extruded and gelled through neutralization of acetic acid by basic solution (NaOH). The residual NaOH and excess water are removed through soaking of scaffold in ethanol and heating at high temperature followed by freeze-drying, respectively. Animal cells effectively adhere on these scaffolds and show viability and proliferation. However, cells cannot be printed directly with the gel due to harsh processing conditions. Besides, limited solubility of native chitosan at neutral pH further limits its bioprinting application. This issue has been addressed by developing various alternative strategies. For example, Li et al. introduced UV cross-linking ability in chitosan to allow it to support the fabrication of patterned cell-laden and rapid transdermal curing hydrogel *in vivo* through photolithography [62]. In another study, Araujo et al. fabricated 3D porous scaffolds using chitosan and carrageenan for application in tissue engineering [63]. In another study, Costantini et al. developed a new strategy for fabrication of artificial skeletal muscle tissue using a novel microfluidics based 3D bioprinting approach [64]. For bioprinting and myogenic differentiation, they formulated a tailored bioink with a photocurable semi-synthetic biopolymer comprised of poly(ethylene glycol) (PEG) and fibrinogen and encapsulated muscle precursor cells (C2C12) into 3D constructs composed of aligned hydrogel fibers.

2.1.1.5. Silk. Silk is naturally occurring protein polymer produced in the glands of arthropods such as silkworm cocoons (*Bombyx mori*) and spider. The silk fibers obtained from *Bombyx mori* consists of fibroin and sericin. The primary structure of fibroin is rich in glycine amino acid and contain repetitive sequence GAGAGS. The fibroin fibers contain two chains, heavy (350 KDa) and light (25 KDa), which are connected by disulfide bonds. Structurally, two fibroin fibers are covered by sericin and form silk-fibers [65]. Earlier, it was believed that only silk fibroin is used for biomedical applications, however, several researchers have utilized silk sericin for tissue engineering and drug delivery applications [66]. However, for application where only silk fibroin is used, sericin part is removed in the degumming process which usually involve boiling in $NaHCO_3$ solution to cleave the peptide bonds of sericin followed by washing to remove sericin and subsequent drying [67]. However, large scale harvesting of silk from spiders is not possible due to their cannibalistic nature, hence recombinant silk is produced in microbial hosts such as bacteria and yeast; and insects, plants, and mammalian cells, etc. through genetic engineering strategies. Such recombinant silk can be easily modified and its structural features can be easily tuned and precisely controlled.

The 3D structures of silk-fibroin usually exist as hydrogel and sponge materials and is commonly used as printing material where printing is achieved in range of $20 - 600\ \mu m$ using silk solution with different concentrations (0.5–300 mg/mL) [67–69]. The gelation of fibroin is achieved through sonication, vortex mixing, heating, solvent treatment, photo cross-linking, and electro-gelation, etc. [70]. However, gelation is a slow process and in most cases gelation conditions are not cell-friendly which limits broad-spectrum bioprinting applications of silk. To over the issue, Compaan et al. developed a two-step gelation process by using alginate as a sacrificial hydrogel during an inkjet-based bioprinting process [71]. This process involved the blending of alginate with silk fibroin to achieve rapid gelation by calcium alginate formation during printing followed by horseradish peroxidase (HRP) catalyzed covalent cross-linking of fibroin protein at tyrosine residues after printing. The printed constructs supported the adhesion and proliferation of NIH 3T3 fibroblasts. The silk-based bioink can be easily formulated to serve different functions through addition of various additives such as enzymes, antibiotics, nanoparticles, and growth factors, etc. Tao et al. developed a silk-based bioink as water solution at mild temperature and pressure and the properties of ink were tuned by changing the silk concentration, polymorphism, and molecular weight [69]. Schacht et al. developed a recombinant silk-based bioink by mixing human fibriblasts with recombinant eADF4(C16) silk and its RGD modified variants for microvalve droplet ejection [72]. The printed scaffold allowed unlimited diffusion of particles in hydrogel.

2.1.1.6. Hyaluronic acid. Hyaluronic acid (HA) is a non-sulfated linear polysaccharide composed of β−1,4–linked glucuronic acid and N–acety–Dkglucosamine disaccharide units. It is naturally present in ECM and possesses high visco-elasticity, biocompatibility, and degradability which make it a promising material for bioprinting applications. It accounts for 11% of total polymer distribution used for bioink preparation [20] (Fig. 1); however, high hydrophilicity of HA makes its bioprinted constructs less stable which limits its applications [73]. This dilemma has been resolved through several strategies such as incorporation of hydrophobic moieties and cross-linking various chemical functional groups such as blending with photo cross-linkable dextran derivative, hydroxyethyl methacrylate derivatized dextran (dex-HEMA) [73]. Skardal et al. printed thiolated HA and gelatin derivatives based cellularized tubular vessel-like constructs using a rapid prototyping device [74]. These well-maintained shaped micro-capillaries supported the adhesion and proliferation of NIH 3T3 cells. In another study, Skardal et al. employed gold nanoparticles (AuNP) as multi-functional cross-linkers for thiolated HA and gelatin bioink [75]. After formation of intra-gel cross-links, robust hydrogel tubes were extruded and layered in a computer based printer. The printed dynamic cross-linking synthetic ECM supported the adhesion and growth of NIH 3T3, HepG2 C3A, and Int-407 cells. Park et al. printed HA grafted poly(lactic-co-glycolic acid) (PLGA) scaffolds with incorporated hone morphogenesis protein-2 (BMP-2) using solid free-form fabrication (SFF) printer [76]. Another study reported the fabrication of self-crosslinkable smart HA hydrogels [77]. This novel small hydrogel was applied as 3D scaffold to mimic native ECM that supported adhesion and proliferation of fibroblasts and chondrocytes.

2.1.1.7. Fibrin. Fibrin is a fibrous protein and component of native ECM formed by interaction between protease thrombin and fibrinogen which cause its polymerization. The polymerized fibrin when combines with platelets form a hemostatic clot at a wound site, a mechanism known for blood coagulation. The thrombin is a glycoprotein comprised of multiple pairs of polypeptide chain including Aα, Bβ, and γ. Importantly, it possess a cell-signaling domain that contains protease degradation and cell-adhesion motifs. During formation of fibrin gel, thrombin protease cleaves the Aα and Bβ chains to fibrino-peptide A and B which subsequently polymerize to form protofibrils which later form fibrin fibers and ge, respectively [78].

The presence of cell adhesion motifs and cytocompatibility bless fibrin with bioprinting applications. However, soft and fragile nature of fibrin makes it difficult to maintain 3D the structure of

printed scaffolds. Therefore, extensive efforts have been devoted to overcome this issue by combining fibrin with various polymers. For example, England et al. developed a technique for bioprinting of fibrin scaffolds. Briefly, they extruded fibrinogen solution into thrombin and increased their viscosities by adding HA and PVA, respectively. Further, the blood-clotting factor XIII was also added to the bioink to enhance the fibrin cross-linking. Fibrinogen, accounting for 5% of total polymer distribution used for bioink preparation (Fig. 1), is extensively used as a stromal substitute to fabricate human skin tissues owing to several advantages it offers such as low price, compatibility with cells, and easy availability [20,79]. Hakam et al. synthesized a biopaper made of fibrin-gelatin hybrid hydrogel for application in skin bioprinting [80]. In another study, Cubo et al. developed a two-layer skin model based on human plasma to treat burns and traumatic and surgical wounds [81]. In this two layer model, the lower layer (dermis) was comprised of plasma-derived fibrin matrix seeded with hFB while the upper layer (epidermis) contained hKC which were seeded on top of fibrin scaffold. Histological and immunohistochemical analyses of printed skin in 3D *in vitro* cultures and after long-term transplantation in mice revealed its similarity to human skin.

2.1.1.8. Starch. Starch, also known as amylum, is a polymeric carbohydrate produced by green plants and serves as energy storage material. It is composed of large number of D-glucose units joined together by glycosidic bonds. Two types of glucoses are present in starch, amylose and amylopectin, whose ratio varies according to its origin. Starch is yet to be fully evaluated for applications in 3D bioprinting and accounts for only 2% of total polymer distribution used for bioink preparation [20] (Fig. 1), hence limited literature is available to this end. However, it has the potential to be used for bioprinting when combined with other polymers. Lam et al. reported the 3D printing of cylindrical scaffolds of different designs using a blend of corn starch, dextran, and gelatin in water using rapid protyping technique [82]. Starch is insoluble in water at room temperature and forms a suspension. However, these granules swell and gelatinize and form a paste upon heating. It enables the separation of amylose from amylopectin and forms a continuous phase around the swollen granules. By decreasing the temperature of suspension, amylose phase separates and results in gel formation and retrogradation. The resulted structure is highly stable and resists hydrolysis even at elevated temperature. The printed starch-based scaffold requires heat treatment for drying and maintaining structural integrity which prevents the use of starch blend for bioprinting [82].

2.1.1.9. Soy protein. Soy protein, obtained from dehulled and defatted soybean, is an important natural polymer that accounts for 6% of total polymer distribution used for bioink preparation in bioprinting applications. Off the three classes of high protein commercial products; soy flour, concentrates, and isolates, soy proteins are concentrated in protein bodies and accounts for 60–70% of total soybean proteins. This protein has role in plant germination where its digestion into amino acids provides energy to the growing seedlings [83]. The structural and physiological properties of soy protein can be tuned through various processing treatments. The improved thermoplastic nature and high biocompatibility allows its use in bioprinting such as the development of porous scaffolds for tissue engineering applications. For example, Chien et al. developed soy protein scaffolds using 3D Bioplotter. The printed scaffold were treated with 95% ethanol and lyophilized to remove water from protein to impart structural stability to scaffold. The dehydrated scaffolds supported the growth of human mesenchymal stem cells (hMSCs) [84]. The *in vivo* biocompatibility of soy protein scaffolds has been assessed in model mice which were completely degraded after 14 days [85]. Bioprinting of soy protein can be carried out at room temperature and allow adhesion and growth of cells and introduction of growth factors; however, treatment of scaffolds after printing usually affects cell viability and limits thus its application in bioprinting.

2.1.2. Synthetic polymers-based bioprinting of biomaterials

Unlike natural polymers, providing a positive environment by mimicking native components of ECM, synthetic polymers prepared by various chemical synthesis methods usually improve the biocompatibility, biodegradability, physico-mechanical, chemical, thermal, biological, and conductive properties of natural polymers through synthesis of composites. Such modifications usually results in formation of cross-linkable structures for applications in tissue engineering and regenerative medicines. However, interaction of synthetic polymers with cells is not well-studied [18]. Efforts have been made to develop conductive biomaterials for applications in bioprinting using various synthetic polymers [86]. For example, Jakus et al. formulated a printable bioink containing high content of graphene:polyactide-coglycolide which demonstrated improved electrical conductivity (800 S/m) and supported the growth of hMSC [87]. Thus, this highly conductive material can find potential applications where high biocompatibility and electrical conductivity is required such as biomedical devices and scaffolds, etc. Similarly, desired pre-patterned tracks can be introduced into printed scaffolds by simply changing the bioink which can complement previously developed method of Villar et al. who used α-hemolysin containing droplets for introduction of such tracks [88]. Despite the possibility of releasing some toxic products after degradation of various synthetic polymers and possessing low biocompatibility, synthetic hydrogels are considered preferable for bioprinting as they allow for fine tuning of both chemical and physical properties and demonstrate a controlled degradation rate [17].

Poly(ethylene glycol) (PEG), an attractive material for cell encapsulation due to its solubility in water, is extensively used in bioprinting applications where it accounts for 3% of total polymer distribution used for bioink preparation [20] (Fig. 1). However, it cannot form physical or chemical networks required for hydrogel formation, and thus requires further chemical modification. Acrylation of PEG, involving its cross-linking *via* photo-initiato induced polymerization under UV exposure to form PEG- dimethacrylate (PEG-DMA) has resulted in cell-laden bioink containing articular chondrocytes [89]. Daniele et al. developed bio/synthetic interpenetrating network (BioSINx), containing GelMA polymerized with PEG which supported both internal cell encapsulation and surface cell adherence. The BioSINx network displayed superior physical properties and lower gelatin dissolution [52]. In another study, Cha et al. developed a strategy to enhance structural integrity and fracture toughness of cell-laden hydrogels by printing 3D scaffolds of photo-crosslinkable poly(ethylene glycol) diacrylate (PEGDA) with photo-crosslinkable gelatin hydrogel which showed improved stress and provided structural support for weak hydrogels. The 3D scaffolds showed highly biocompatibility for encapsulated fibroblasts [51]. Similarly PLGA, a copolymer of lactide and glycolide obtained *via* ring polymerization, has received immense consideration for bioprinting applications where it accounts for 3% of total polymer distribution used for bioink preparation (Fig. 1) [20]. For example, Barron et al. utilized PLGA as stackable biopaper substrate and stacked vascular cells to create high resolution 3D constructs using 2D biological laser printing technique [90]. Similarly, poly(ε-caprolactone) (PCL), a biodegradable synthetic polyester, accounting for 3% of total polymer distribution used in bioink preparation [20] (Fig. 1), imparts elongation properties to material. It has been utilized in tissue engineering applications due to its remarkable thermoplastic behavior, high mechanical strength, biodegradability, and low melting point, etc. Wei and

Dong bioprinted mechanically stable 3D scaffolds at 10 μm resolution using PCL plates under electrostatic filed [91]. In another study, Visser et al. printed PCL-based soft hydrogels with highly organized and porous microfiber networks through eletrcospinning-writing method which showed improved stiffness and elasticity and supported the growth of human chondrocytes which retained their cell morphology, viability, gene expression, and matrix production potency after printing [92]. Visser et al. also presented several models of complex anatomically shaped porous thermoplastic polymer scaffold constructs through co-deposition of poly(vinyl alcohol) (PVA), PCL, GelMA/gellan gum, and alginate hydrogel as a temporary support to achieve overhang geometries. The constructs supported adhesion, growth, and proliferation of chondrocytes within the GelMa/gellan component and remained viable [93]. In another study, Shim et al. developed PCL and PLGA biomaterials to print desired organ using the scaffold-free cell printing technology [94]. PLA, an aliphatic polymer known for its process-related viscosity and high mechanical properties, offers desired viscosity during extrusion and high rigidity and stiffness after printing to impart structure stability to the printed scaffold [95] (Fig. 1). Kesti et al. developed a versatile bioink comprised of thermoresponsive polymer poly(N-isopropylacrylamide) grafted hyaluronan (HA-pNIPAAM) with methacrylated hyaluronan (HAMA) for 3D printing of high resolution scaffolds with improved mechanical stability, rheological properties, swelling, printability, viability, and biocompatibility of encapsulated bovine chondrocytes [96]. Polyurethane (PU), a synthetic thermoresponsive synthetic polymer possessing good physical properties and biocompatibility, has received immense consideration for biomedical applications such as printing of muscle, nerve, and bone tissues. Hsieh et al. developed thermoresponsive biodegradable PU hydrogel without the addition of any cross-linker which showed improved stiffness. Neural stems cells (NSCs) were integrated into the PU dispersion before gelation, printed, and maintained at 37 °C which showed improved proliferation and differentiation. *In vivo* analysis of printed hydrogel in zebrafish embryo showed successful rescue of neural injury. Further, implanted 3D printed scaffolds successfully rescued the function of adult zebrafish with traumatic injury [97]. Hsu et al. developed a process for the synthesis of biodegradable PU nanoparticles and developed a waterborne PU-based PCL soft segment with improved biocompatibility [98]. In another study, a bioink containing synthetic PU elastic nanoparticles, hyaluronan, and bioactive ingredient TGFβ3 was developed for bioprinting of scaffolds. The printed scaffolds supported the growth of MSCs which differentiated into chondrocytes due to release of TGFβ3 and produced a matrix for cartilage, thus can be used for customized cartilage tissue engineering [99]. Such versatile thermoresponsive biodegradable PU bioink can be used for future 3D printing of neural tissues.

2.2. Properties of polymers for bioprinting

The following sections overview various properties of polymers used for bioprinting and are summarized in Fig. 2.

2.2.1. Printability and cross-linking

Excellent printability of polymers, designated by the relationship between bioinks and substrate, ensures accurate and high-quality patterned bioprinted materials [12]. The printability of polymers is largely dependent on hydrophilic/hydrophobic properties of polymer solution based on specific applications (Fig. 2a). Besides, it is largely dependent on surface tension, a measurement of contact angels between two surfaces or media components. This indicates that cell adhesion, proliferation, and establishment of tissues or scaffolds is greatly influenced by the surface tension of supporting material [11]. During fabrication of 3D scaffolds, the surface tension of hydrogel pre-polymer solution should be maintained in vertical direction and maintaining a large contact angles with the substrate, however, should not be present completely flat on to the substrate. This can be achieved by using Petri dishes or glass slides where hydrogel pre-polymer solutions build highly vertical structures upon bioprinting. However, applications of most glass slides as substrate are limited by their poor contact angles. Besides, bioprinting is also greatly prejudiced by the cross-linking ability of polymeric materials (Fig. 2b). The current limitation of bioprinters to dispense only liquid materials requires that all hydrogels should be made available in liquid or semi-liquid state for bioprinting applications. Further, viscosity of such liquid or semi-liquid polymers should be controlled according to the requirements of a particular bioprinter and structural features of scaffold (Fig. 2c). In general, all bioinks should form quasi-scaffold structures that should support adhesion and proliferation of cells after bioprinting. These conditions can be fulfilled by using hydrogel pre-polymer solutions which are photo-, chemical-, or cross-linking polymers [63,100].

2.2.2. Mechanical properties

Polymers used in bioprinting should demonstrate excellent mechanical features including shear stress, elongation strain, mass swelling, and compressive modulus after polymerization and provide appropriate environment for adhesion, proliferation, and differentiation of cells [101]. It is noteworthy that mechanical features of polymers are tunable and are greatly dependent on the method of synthesis (physical, chemical, or biological), mechanism, types of materials (natural or synthesized) and their concentrations, and exposure time, etc. Further, adhesion of living cells on scaffold is greatly influenced by the dynamic cell-hydrogel interaction [102]. However, same scaffolds cannot support the growth of all cell-types and specific mechanical properties are required for bioprinting of soft (e.g. cartilage) and hard (e.g. bone) tissues, etc. [103] (Fig. 2d). For example, collagen is chemically cross-linked *via* covalent bonding agents which bind either free amine or carboxyl group of collagen or bound by dehydrothermal treatment (DHT) or UV irradiation, or biologically by transglutaminase [104]. These methods bless polymers with diverse mechanical properties.

2.2.3. Thermal properties

Ideal polymeric materials for bioprinting should remain intact at relatively higher temperature. Ideally, thermally stable polymers possess low viscosity and are solidified at 37 °C [104]. For example, Tsai et al. developed a PCL based hydrogel with waterborne PU nanoparticles (PU-NPs) through a two-step chemical reaction process for application in bioprinting. The PU-NPs, due to relatively low viscosity, can reduce cell damage. Further, PU-NPs possessed high Young's module and swelling ratio. The hydrogel demonstrated up to 40% viability of MSCs after one day of bioprinting. The difference in cell survival and cell growth rate was attributed to the stiffness of hydrogel [15]. The swelling of PUs was further enhanced by adding poly(ε-caprolactone)-diol (PCLd), poly(L-lactide)-diol (PLLAd), and poly(D, Llactide)-diol (PDLLAd). The swelling ratios of these gels were less than 10%. Culturing of neural stem cells on these gels showed that PUs based on PDLLAd supported cell growth and proliferation and demonstrated up to 70% cell survival and growth rate after one day of bioprinting [97].

2.2.4. Biocompatibility and biodegradability

Biocompatibility of polymers refers to their potential to remain in direct contact with living tissues without causing toxic effect or provoking allergic or immunogenic response [105] (Fig. 2e). It is one of the salient features and should be administered by any biomaterial for *in vitro* applications. Similarly for *in vivo* applications, biocompatibility refers to additional degradation and integration potential of ECM of cells without producing harmful byproducts

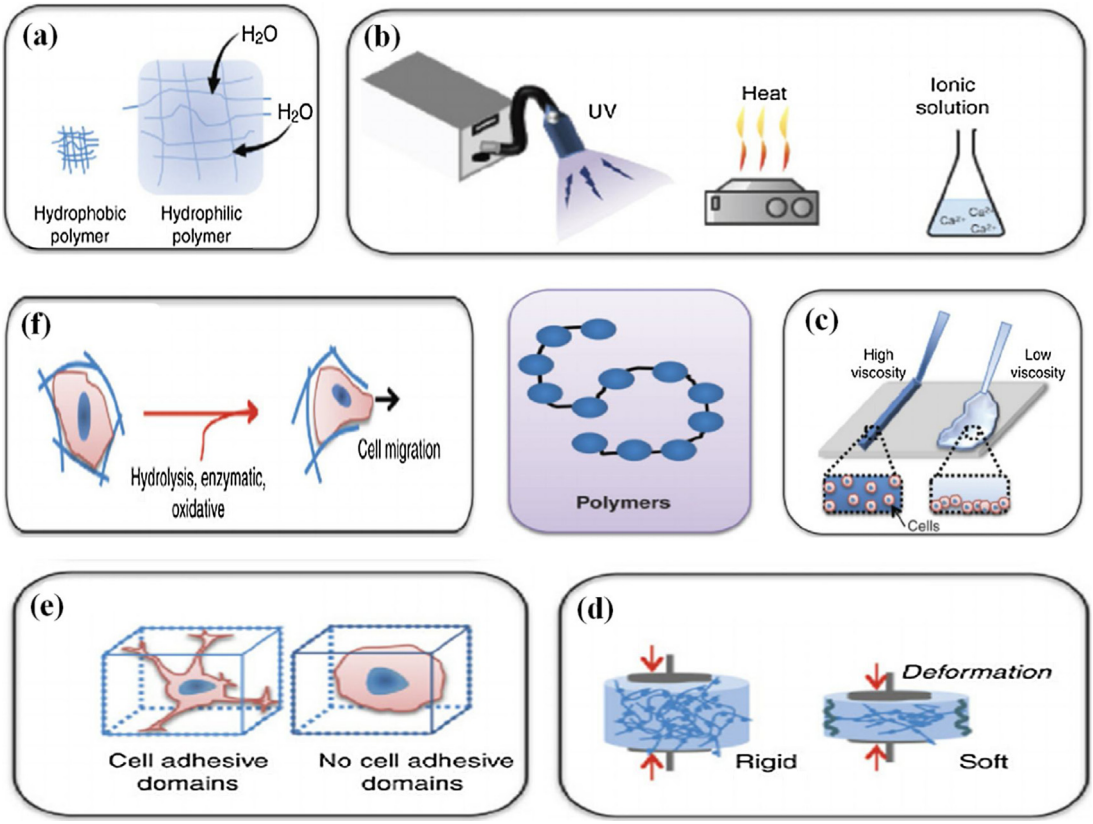

Fig. 2. Illustration of various features of polymer important from bioprinting perspective: (a) hydrophilic and hydrophobic properties, (b) cross-linking potential, (c) viscosity, (d) mechanical features, (e) cell adhesion and biocompatibility, and (f) biodegradation ability.
The figure has been reproduced from [20] with permission from Academic Press.

or generating negative interaction with the cells (Fig. 2f). The polymer-based scaffolds should eventually fuse with the *in vivo* tissues and be degraded or integrated with the *in vivo* ECM environment. The polymers used in bioprinting should be gelled at a relatively faster speed in order to achieve high printing resolution. To this end, alginate hydrogels are formed in no time *via* ionic cross-linking [106,107], however, these are not considered ideal due to inadequate biodegradability. The implanted scaffold should be degradable at a rate nearly identical to the growth rate of native ECM [12].

2.3. Viable cells

Bioink formation requires the availability of active viable cells. Further, these cells must be able to adhere to a scaffold, and divide and differentiate under appropriate growth conditions and form micro– or macro–scale tissues and organs. The selection of cells is carried out under certain criteria: (1) cells should closely mimic the physiological state of the cells in *in vivo* environment and (2) the bioprinted cells should maintain or develop their *in vivo* functions in appropriate microenvironment [12].

There is always a risk of provoking immunogenic response if source cells are obtained from a different donor. Therefore, in order to avoid such risks, live and active cells should be ideally obtained from the patient themselves [10]. Several strategies are used for seeding of artificial tissues such as printing of functional primary cells with supporting cells [108,109] or progenitors or stem cells followed by their subsequent differentiation into specific cell types [14,110]. In contrast, direct printing of primary cells usually makes bioprinting process very complex due to parallel bioprinting of various types of cells which are embedded either within the same or different hydrogels and require the preparation of several bioinks. Further, parallel use of several bioinks make real-time alignment of multiple cells a difficult process as switching from one type of bioink to another raise the risk of errors during the bioprinting process. Further, several cell types such as neurons and cardiac muscles cells have limited regenerative capacity, therefore, stem cells are usually preferred and serve as promising alternative due to their greater potential to differentiate into different cells types. The complexity of using multiple cell types together has been resolved to some extent by using stem cells which lowers the number of required bioinks to be prepared at a give point. However, use of stem cells cause some of its own complexities, for example, the formulation of bioink using stem cells require addition of specific growth factors and small molecule signals to induce specific-cell differentiation. Further, to guarantee controlled differentiation, these specific growth factors and other cell differentiating factors must be deposited accurately in post-printing cultures which further complex the process [11].

2.4. Bioprinters

A bioprinter is a device used for printing of 3D structures such as tissues and organs, etc. using various bioink solutions for different biological applications. A typical bioprinter has the ability to simultaneously dispense various biomaterials to fabricate structures with high resolution and accuracy and maintain high degree of freedom motion and ensure sufficient motion speed. Further, these bioprinters are user-friendly, fully automatic, easily sterilized, affordable, durable, versatile, and compact instruments [111]. Bioprinting technology is advancing rapidly, however, technological modalities are based on four fundamental strategies including

Table 1
Comparison of four types of bioprinting techniques. The table has been reproduced from [11] with permission from Elsevier.

Parameters	Inkjet	Laser-assisted	Extrusion	Stereolithography	Ref.
Cost	Low	High	Moderate	Low	[10,115–117]
Cell viability	>85%	>95%	40%–80%	>85%	[118]
Print speed	Fast	Medium	Slow	Fast	[12]
Supported viscosities	3.5 to 12 mPa/s	1 to 300 mPa/s	30 mPa/s to above 6×10^7 mPa/s	No limitation	[12,48]
Resolution	High	High	Moderate	High	[10,119]
Quality of vertical structure	Poor	Fair	Good	Good	[119]
Cell density	Low $<10^6$ cells/mL	Medium $<10^8$ cells/mL	High (cell spheroids)	Medium $<10^8$ cells/mL	[12]
Representative materials for bioinks	Alginate, PEGDMA, Collagen	Collagen, Matrigel	Alginate, GelMA, Collagen	GelMA, GelMA-PEGDA hybrid hydrogel	[89,117,119–121]
Reported applications	Tissue engineering (blood vessel, bone, cartilage, and neuron)	Tissue engineering (blood vessel, bone, skin, and adipose)	Tissue engineering (blood vessel, bone, cartilage, neuron, muscle, tumor) Controlled release of biomacromolecules Organ-on-a-chip	Tissue engineering (blood vessel and cartilage) Organ-on-a-chip	[114,122]

the inkjet or droplet, extrusion, laser-based, and stereolithographic bioprinters [111,112]. The droplet-based bioprinting strategy is based on thermal, piezo, or acoustic-driven mechanisms; and utilizes heat energy, electrical energy, and sound energy, respectively for generation of droplets of cell suspension in a high-throughput fashion. These droplet-based bioprinters have received immense consideration owing to their simplicity, versatility, agility, and high-throughput potential to dispense a variety of biologics such as viable cells, growth factors, genes, and pharmaceutics, etc. [113]. Similarly, extrusion-based bioprinting system is a hybrid of a fluid dispensing system and an automated robotic system for extrusion and bioprinting, respectively. These bioprinting systems utilize mechanical or pneumatic-driven systems and deposit viable cells in the form of a filament [112]. In such systems, bioink is dispensed using a deposition in a computer-controlled manner which ensures a precise dispensing of viable cells encapsulated in a cylindrical filament. In contrast, viable cells from a donor-slide to a receiver-slide are dispensed without the assistance of a nozzle using laser energy in a laser-based bioprinting system. This modality offers several advantages in dispending a variety of biologics such as live cells, biomaterials, growth factors, genes and vectors, and drugs, etc. The stereolithography bioprinters have been modified from laser-assisted printers. Likewise laser-assisted bioprinter, stereolithography modality utilizes light for selective solidification of bioink in a layer-by-layer pattern during fabrication of scaffold. Usually, these bioprinters use a digital projector that ensures same printing time even for complex planes in a structure and thus are more advantageous over conventional bioprinters. Further, such printers are simpler in operation, offer high resolution (100 μm) printing in short time, and maintain high cell viability [114]. A comparative analysis of various bioprinters in term of their costs, cell viability, printing speed, supported viscosities, resolution, quality of vertical structure, cell density, representative materials for bioinks, and their various reported applications, are shown in Table 1.

3. Bioprinting applications: tissue engineering and regenerative medicine

Bioprinting is a fascinating and emerging technology of this century, which is expected to revolutionize the fields of tissue engineering and regenerative medicine. Bioprinting of living mammalian cells, tissues, and organs is an exciting development of the current era of medical and engineering technologies (Table 2). Compared to conventional metallically ordered 3D printed devices, current 3D bioprinting models and tools provide a base for further development of various biomedical applications including scaffolds, tissues constructs, synthetic organs, drug development and screening systems, and medical devices, etc. The following sections highlight various potential applications of bioprinting in tissue engineering and regenerative medicine:

3.1. Bioprinting of cell-laden constructs

Live cells serve as structural and functional unit of life; therefore, their bioprinting has received immense consideration. Currently, bioprinting of cell-laden assemblies with organized architecture and defined conformational distribution of cells is basic requirement for advanced tissue engineering strategies. Embryonic stem cells (ESCs) are printed with hydrogel into 3D macroporous structure where more than 90% cells remained viable after bioprinting and formation of cell-laden construct [123]. To date, several 3D tissue models have been developed to study the complex cellular interactions required not only for tissue development but also for regeneration of damaged tissues [17]. Kolesky et al. developed a method for printing of 3D cell-laden, vascularized tissues by integrating parenchymal cells, stromal cells, and endothelial cells into a thick tissue through simultaneous bioprinting of different inks composed of hMSCs and human neonatal dermal fibroblasts (hNDFs) within a customized ECM alongside an embedded vasculature lined with human umbilical vein endothelial cells (HUVECs). The thickness of tissue was 1 cm which was perfused on chip for more than 6 weeks [124]. In another study, Kang et al. developed an advanced integrated tissue-organ printer (ITOP) to fabricate human-scale tissue constructs. Mechanical stability, specific shape, and diffusion of nutrients in tissue constructs were achieved by using biodegradable polymers, clinical imaging data as a computer model to control motion of printer nozzle, and introduction of micro-channels, respectively [125].

3.2. Bone and cartilage cells and tissues constructs

Bioprinting technology has shown promising results in bone tissue engineering. Several studies have shown the use of bioprinted scaffolds for development of bone tissues. For example, polycaprolactone-hydroxyapatite scaffolds were successfully printed using the information from rabbit computed tomography (CT) scans which were in closed matching with physiologically relevant loads [126]. In another study, poly(propylene fumarate) (PPF) based porous scaffolds were printed which showed degradation process for over 224 days, thus showed their suitability for applications in bone tissue engineering [127]. In a more advanced study, PCL/PLGA/ß-TCP based printed scaffolds showed improved *in vitro* and *in vivo* osteogenic properties (osteoinductive and osteo-

Table 2
Illustration of bioprinting of various types of organs, tissues, and scaffold by using different materials and cells through various bioprinting techniques.

Organ/tissues/ scaffolds	Polymeric materials	Cell type/source	Bioprinting method	Ref.
Blood vessels	Alginate and carbon nanotubes (CNTs)	Smooth muscle cells	Extrusion	[108]
	GelMA, fibrin gel, alginate, matrigel, and agarose	HUVECs	Extrusion	[120]
	Matrigel and acrylated HA-PEG	Fibroblasts, mouse endothelial cells, hMSCs	Inkjet	[110]
Bone tissues	n- hydroxyapatite	Mouse osteoblastic cells	Inkjet	[137]
	Alginate	MG-63 cells	Extrusion	[138]
	Collagen I, Chitosan, Agarose	MSCs	Microextrusion	[139]
	PLGA, PEG	MSCs	Microextrusion	[129]
	hydroxyapatite	MSCs	Inkjet	[128]
Cartilage	GelMA, PCL, and GelMA-gellan hydrogels	Equine chondrocytes, MSCs	Extrusion	[14]
	GelMA	Human meniscus cells	Stereolithography	[140]
	Nanocellulose, Alginate, PCL	Nasal chondrocytes	Microextrusion	[33,58]
	GelaMA/Melt spinning PCL	Chondrocytes	Extrusion	[14]
	PEGDA	Articular chondrocytes	Inkjet	[141]
	Glycosaminoglycans (GAGs)	Articular cartilage	–	[142]
	Alginate, PCL, PEG	MSCs	Microextrusion	[135]
	Silk fibroin-gelatin	Stem cells chodrocytes and osteocytes	–	[43]
	Nanocellulose-alginate	hNSCs	Microvalve dispenser	[33]
Skin	Collagen	NIH3T3 fibroblast, HaCaT keratinocytes	Laser-assisted	[109]
	Collagen	Keratinocytes and fibroblasts	Droplet dispersion	[143]
	Bioink (RegenHU), MatriDerm®	Fibroblasts keratinocyte	Microextrusion	[109,144]
Liver	Thiol-HA and Gelatin	Tissue-derived dECM	Extrusion	[145]
	Gelatin methacrylamide	Hepatocarcinoma cell line	–	[115]
Scaffolds	Single cell protein	Breast cancer cell lines	Direct printing	[146]
	Soy protein and glycerol	MSCs	Indirect printing	[84]
	GelMA	Live cancer cell line, HepG2	Direct printing	[147]
	HA and GelMA	Chondrocytes	Direct printing	[49]
Skeletal muscle	Alginate, gelatin, PU, and PCL	C2C12 mouse myoblasts,	Extrusion	[148,149]

conductive) and supported the growth of human mesenchymal stromal cells (Htd-MStCs) derived from nasal inferior turbinate like a bone ECM [6]. Besides, different stem cells possessing varying potential to differentiate into different cell types and tissues under appropriate growth conditions have been evaluated for their ability to print bone forming cells and subsequent tissue formation and have shown promising results due to improved stability of constructs and greater cell viability. Usually soon after their isolation, stem cells are immediately cultured without differentiating to increase their number and obtain enough number of potential bone forming cells. These cells are then cultured on natural-based scaffolds and allowed to grow and differentiate and printed as bioink. However, due to limited stability and low mechanical strength of natural-based scaffolds, these are often mixed with several other materials such as bioglass [128], PEG [129,130], and PLA [7] to impart additional mechanical stability to these composite scaffolds. Such composite scaffolds of hydroxyapatite and gelatine/alginate hydrogels have also been prepared to enhance the stiffness and improve bioprinting potential of the gel which favored unaltered cells growth and maintained cell viability [131]. For example, potential of MSCs derived from bone marrow and adipose tissues for bioprinting of various bone tissue constructs has been evaluated and shown promising results [132]. To assist bioprinting of bone tissue constructs, currently several growth factors such as FDA approved morphogenic protein-2 (BMP-2) and several others are added during bioink formulation [133]. These growth factors have been used effectively in several clinical trials, for example during reconstruction of craniofacial hard tissue defects (e.g. frontal sinus, cranium, mandible, and nasal septum) [134].

Development of cartilaginous tissues has received immense consideration in field of tissue engineering. In an earlier study, an alginate based encapsulated chondrocytes with supportive PCL structure were developed and evaluated [58]. Later, a more effective PEG and PCL based construct seeded with chondrocytes was developed which demonstrated the potential to print an ear-shaped structure [135]. A nanocellulose-alginate bioink containing hNSCs was also bioprinted with desired properties of cartilage tissue constructs [33]. Currently, efforts have been made to bioprint human craniofacial cartilage by depositing different cell types such as human nasal chondrocytes (hNCc) and adipose-derived stromal cells (ADSCs) which differentiate into chondrocytes, thus can form cartilage tissue constructs [33,135]. For growth and differentiation, chondrocytes are grown on mechanically stable scaffolds to provide stability to cartilage tissues. For example for ear and nasal construction, the mechanical properties of bioprinted cartilage structure have been improved by using different pre-polymer solutions such as nanocellulose [33], Pluronic F-127 [136], and glycosaminoglycan-based hydrogels [96], etc.

3.3. Bioprinting of skin cells and tissues

The conventional approaches of engineering skin constructs are often overshadowed by limited donor skin. Besides, such tissue constructs induce a paradigm shift in wound management from employing a passive wound dressing to utilizing bioactive cell-impregnated skin tissue constructs. The conventional ways of skin cells and tissue constructs rely on using scaffold which support adhesion and proliferation of cells which thereafter secrete ECM and remodel the microenvironment in vicinity [105,150]. However, such tissue constructs are merely masses of cells which are synthesized with defined conformational structures and provide off-the-shelf availability. Such constructs have shown promising results with patients suffering from burns and chronic wounds, however, these fabricated tissue constructs do not fulfill all requirements of an ideal tissue such as vascularization, pigmentation, and missing hair follicles, etc. in *in vivo* microenvironment [151]. These limitations demonstrate that current scaffolding-based strategies are deficient in fabricating ideal skin tissue constructs.

The major discrepancies associated with conventional scaffolding based strategies have been overcome by current bioprinting technology. This technology provides an advanced manufacturing platform for depositing viable cells, pre-polymer hydrogels (biomaterials), and growth factors, etc. through a computer-aided-design (CAD). CAD ensures controlled fabrication in a layer-by-layer (LbL) fashion, shows high degree of flexibility, and assists fabrication of more complex constructs with better homology and functionality [12,151]. This technology has shown to be promising and give reproducible results in bioprinting of skin cells and tissues. It

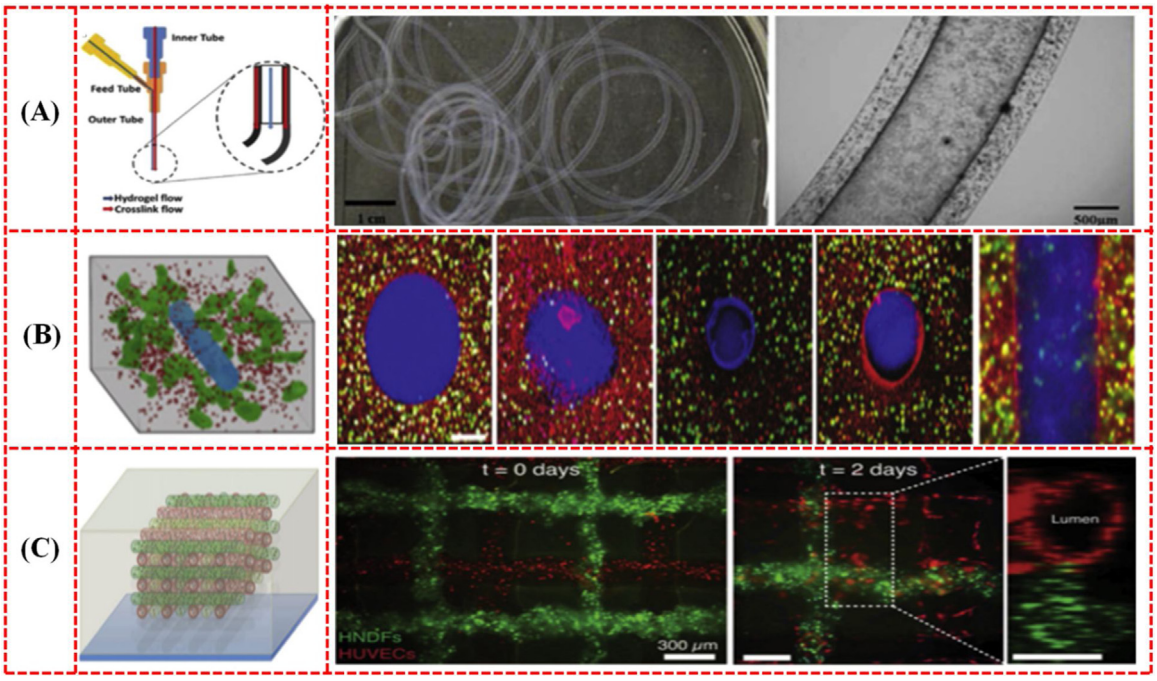

Fig. 3. Illustration of various bioprinting strategies for vascularization: (A) Fabrication of long vascular conduits using a coaxial nozzle system yielding internal lumen diameters below 1 mm, (B) utilization of carbohydrate glass to cast vascular features and demonstration of cellular growth in perfusable vessles, and (C) fabrication of open lumens (red) using Pluronic F127 bioink and demonstration of printed encapsulated cells around vessels (green).(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The figures have been reproduced from [108,120,154].

can potentially create graded macro-scale structures which mimic natural ECM and hence facilitate simultaneous adhesion and proliferation of multiple cell-types. Further, structural features such as ridges and modulated surfaces of these macro-scale structures can be manipulated by using material platforms with various dispending mechanism. Moreover, the mechanical and biochemical features of these structures can also be improved. Together, these modifications blessed by current developments in bioprinting technology effectively guide and improve cellular microenvironment, alignment, and differentiation [46].

Use of human fibroblasts and keratinocytes for bioprinting of human skin tissues have shown promising results [109,152]. Besides, several materials such as collagen or fibrin combined with cells have also been used as bioink for fabrication of skin tissues. Similarly, cells combined with collagen-elastin (MatriDerm®) composite have shown promising results and has shown to be more advantageous over hydrogels for bioprinting of skin cells to treat patients with facial burns [152]. Despite promising results shown by MatriDerm®, it has few discrepancies associated with it due to its animal origin, including growth factor contamination and batch-to-batch variation.

3.4. Bioprinting of blood vessels

Conventional bioprinting approaches have limited potency to construct vascular features in printed tissues. However, recent advancement in bioprinting technology has shown remarkable potential to bioprint synthetic blood vessels [153]. For example, a coaxial system developed by Dolati et al. was able to bioprint vascular conduits using CNTs reinforced alginate. The perfusable conduits possessed diameter in sub-millimeter range and were more than a meter long where human coronary artery smooth muscle cells were grown within the matrix [108] (Fig. 3A). However, the authors were unable to further reduce the diameter to match that of capillary blood vessels. This can be achieved by adding magnetically controlled nanoparticles (NPs) to bioink. Further, the position of vessels within the tissue can be controlled by allying the magnetic field [11]. Nevertheless, it is still at early stage of development and requires further extensive research to explore the efficacy of the strategy and potential benefits to viable cells and ECM bestowed by the magnetic NPs. Besides, several researchers have used sacrificial inks to reduce the diameter of vascular channels. This strategy involves direct introduction of vascular channels into the printed tissues and showed considerable success in reducing the diameter of channels. For example, as small as 150 μm seedable channels were formed by encapsulating and dissolving printed carbohydrate glass in various bulk ECMs [154] (Fig. 3B). In another study, small vascular channels with diameter 45 μm were printed using Pluronic F127 fugitive bioink which subsequently endothelialize them with HUVECs. This strategy assisted by printing fibroblasts encapsulated in a gelatin methacrylate bioink successfully prepared bioprinted multi-cellular constructs [120] (Fig. 3C). Bertassoni et al. further modified the strategy and casted hydrogels around printed agarose fibers rather dissolving the sacrificial material followed by aspiration or manual removal of fibers. The resulted lumen was perfusable and supported the growth of HUVECs that resulted in formation of an endothelial monolayer. These different studies demonstrate that such advanced sacrificial techniques have the potential to regulate pre-patterning of vascular features in bioprinted tissues and can provide base for fabrication of large tissue constructs.

3.5. Bioprinting of neuronal tissues

Bioprinting of neuronal tissues is immensely important breakthrough due to limited natural regeneration potential of neurons. Studies have explored the potential of bioprinting technology to print nervous tissues. Bioprinting of neuronal tissues works in two ways: it either bioprints new neuronal tissues or augment the innervation of already engineered tissue constructs which are subsequently implanted at target site where it should integrate with host nervous system to show its effect [11]. In an earlier

study, Owens et al. bioprinted a synthetic nerve graft composed of Schwann cell tubes enveloped by mouse bone marrow stem cell tubes by seeding these cells into the tubes of 500 μm diameter followed by loading into a bioprinter [155]. Later, successful bioprinting of neural cells was demonstrated by Lober et al. who bioprinted rat retinal ganglion cells and glia by using inkjet bioprinter [156]. In a more recent study by Pateman et al., PEG-based nerve guidance conduits were bioprinted using microsterolithographic technique which demonstrated effective nerve repair. These printed conduits exhibited fine resolution and demonstrated promising potential of bioprinting technology to print nerve grafts [157].

4. Challenges in current polymer-based bioprinting applications

Despite rapid and recent developments and advancements, and extensive advantages offered by bioprinting technology; there still exist some barriers to the typical bioprinting process that hinder its broad spectrum applications.

4.1. Complexity of bioink preparation

The efficacy of bioprinting is mainly compromised by the complex preparation procedures of bioink. This process usually takes few days to several weeks due to preparation of cell cultures and synthesis of different biomaterials [12]. Besides, limited shelf-life and storage difficulty of bioink is another major challenge. Extensive efforts have been made to overcome such barriers. For example, introduction of new features into bioprinter for preserving the newly printed regions, designing of more advanced parallel bioprinters, and refining the bioprinting process such as by introducing continuous liquid interface production (CLIP) [158] can help resolve the major issues associated with limited shelf-life of bioink.

4.2. Limited mechanical properties of 3D scaffolds

Although, various bioprinting techniques work on different principles, they use layer-by-layer strategy which generally faces the problem of printing complex hollow structures. A simple printing process using a single material requires that different layers remain connected and provide mechanical support to each other during bioprinting. However, introduction of voids in one layer results in collapsing of subsequent layers which result in a cascade of offset features and deformed geometry of the printed scaffold. This discrepancy can be overcome to some extent by incorporating sacrificial material which provides mechanical support to the subsequent layers during fabrication. Once the desired geometry is attained, sacrificial material is removed. Several suspended structures have been fabricated using this strategy such as microelectromechanical system (MEMS) devices [48,159]. For this purpose, several sacrificial materials have been used such as carbohydrate glass [154], Pluronic F-127 [120], and gelatin microparticles [160], etc. Although, addition of sacrificial materials has shown to be promising by several studies, their incorporation increases the complexity of printing process due to rapid exchange of materials during such process and addition of multiple nozzles for dispensing of different bioinks are required. Therefore, any sacrificial materials used should not only provide mechanical support, but should also be printable under the same experimental set up designed for bioprinting of non-sacrificial materials and viable cells. Further, its removal after completion of scaffold formation should be cyto-compatible. Such complexities caused by the addition of sacrificial materials are major barriers in the designing and application of novel sacrificial materials.

4.3. Bioprinting of complex tissue constructs and organs

Compared to conventional tissue engineering, bioprinting of complex tissue constructs and full-scale organs is more complex process. Unavailability of reliable printing techniques or limitations of existing strategies to print full-scale organ with highly complex metabolic demands at a relatively faster rates is a major challenge for current bioprinting technology. Unlike bioprinting of small-scale tissues where diffusion of nutrients and oxygen, etc. ensures their survival, a complex and embedded vasculature and mechanically vigorous conduits connected with host blood circulatory system are essential for growth and development of large- and full-scale organs and complex tissues. Similarly, compared to small-scale organs and tissues which are printed in several minutes to few hours, viability of bioprinted cells within the bioink and early printed regions is still a major hurdle in bioprinting of full-scale organs or tissue constructs [11]. Besides, bioprinting of large complex tissue constructs and full-scale organs is limited by less efficient and slow self-assembly of vascular features and high risk of necrosis during the early bioprinted segments or regions. Although, currently developed sacrificial techniques for bioprinting of small organs have demonstrated considerable reliability, further developments are required to improve fabrication of large tissue constructs and synthetic large-sized organs.

4.4. Tunable properties and selection of polymers for bioinks preparation

Selection of appropriate materials for bioprinting is a major concern for wide range applications of modern bioprinting practices. The conventional biomimetic materials such as dECM are lacking desired mechanical properties and hence cannot be used directly for printing of tissues, thus requiring a support but less-active materials such as PCL to impart it additional mechanical properties [161]. This problem can be resolved to some extent by using tunable bioinks possessing wide range of material properties. Such tunable bioinks can be prepared from novel composite materials with improved cross-linking and other desirable features without compromising the original properties of bioink. PEG has receive immense consideration owing to its tunable mechanics and proved to be a useful composite bioink [162]. For example, PEG:GelMA and CNTs incorporated photo-crosslinkable CNT:GelMA composites have demonstrated tunable degradation and mechanical properties for application in bioink [163]. Similarly, a composite mixture of low and high molecular weight PEG could mimic the anisotropy of heart valve leaflet moduli [164]. Another major challenge is the addition of multiple materials for preparation of bioinks in bulk where switching of materials during bioprinting involves changing to secondary preloaded reservoirs like separate syringe or bioink cartridge [11]. The simultaneous bioprinting of various materials make it hard or even impossible to create smooth gradient of cells or growth factors since it requires preparation of multiple independent solutions. This issue was addressed by Ober et al. by developing an efficient system comprised of an impeller for application in extrusion-based bioprinters [165]. The active mixing of several biomaterials effectively limits the quantity of required bioink solutions and controls the concentration of dispensing ingredients from mixture.

5. Future of bioprinting technology

Despite extensive reports on bioprinting of cells and maintaining their viability, there is no real report of cell functioning. Hence, one cannot determine the fate and potential of such bioprinted cells for tissues constructs and organ development. However, there

are few reports of bioprinted cells which mimic ECM and native tissues derived bioink has been proposed to stimulate *in vivo* microenvironment [9]. Besides, fabrication of tissues and organs containing an active network of functional blood vessels (veins, arteries, and capillaries) demonstrating supply of oxygen, nutrients, and cytokines besides removing of toxic wastes is still a major barrier towards practical applications of bioprinting technology. For example, bioprinting of skin is still at a very early stage of development; however, potential advantages of bioprinting technology are promising for various skin related issues such as treatment of facial burn wounds.

The main goal of future research of bioprinting technology is to optimize the materials required for bioprinting of cells, tissues, and organs. Ideally, a compromise between various properties of polymers should be achieved during selection of materials to ensure printing of constructs with high cell viability. Further, besides mimicking living tissues, the bioprinted constructs should remain stable and functionally active over longer time. Moreover, viscosity of bioinks should be moderate enough to allow bioprinting and bless structural stability to bioprinted constructs. Similarly, uniform distribution of cells within the polymer-matrix should be maintained without compromising on cell viability. Furthermore, swelling behavior of polymer-hydrogels should be closely monitored and controlled to ensure precise spatial distribution of biomaterials and cells and accurate conformation of bioprinted structures in order to obtain high resolution structures. The vascularization network formed within the bioprinted scaffolds should support cell infiltration and differentiation and maintain their viability for longer time in thick-engineered tissues.

Bioprinting technology can serve as a fabrication tool for development of synthetic organs owing to its micro-scale potential and controlled dispensing of cells [11]. It can be utilized where dispensing or assimilation of viable and active cells or living matter is required, for example, development of biosensors and stem cells based protein and DNA arrays have already been established using bioprinting technology [166]. Extensive development is required to characterize and assess the functionality of bioprinted tissues and organs. This should include the development of new tools, assays, functional markers, and animal models to investigate cell viability and cell tracking, and identification of new markers. Further, safety testing systems should be established to evaluate and monitor the bioprinted structures (i.e. tissues and organs). Current developments in bioprinting technology such as preparation of dynamic switchable hydrogels and oxygen producing hydrogels provide the base for establishing strategies to control cell microenvironment. However, it requires further developments such as increasing the bioprinting speed and rapid prototyping, improving the characteristics of polymers and bioinks, reducing cells and pre-polymer solution preparation time, development of vascularization in tissues, and controlling the scaffold cell maturation. Bioprinting can serve as a vital approach to fabricate human-on-a-chip systems and on-demand anatomically reasonable synthetic organs.

Several issues associated with current bioprinting technology can be resolved by adopting various strategies. For example, mechanical properties of polymeric materials can be improved by using microfiber reinforcement and multi-crosslinking methods. Similarly, photo-crosslinking and thermo-response strategies offer swift gelation. Current developments in micro-fluidics coupled with bioprinting open the gateways for creating vascularization networks within the fabricated tissue constructs. Similarly, co-printing and co-culturing might play a vital role in establishing successful tissue engineering and repair for longer time. Further, establishment of controlled bioprinting device able to deliver cells into tissues can be effective to treat craniofacial tissues. Moreover, enhancing self-repair ability of bioprinted tissues can also be promising for treating craniofacial tissues. The number of cells required for bioprinting can be reduced by exploring different sources of stem cells owing to their greater viability potential, short cell-cycle, and potential to differentiate into different cell types under appropriate growth conditions and microenvironment. At present, the potential of few types of stem cells has been evaluated to bioprint fabricated patches for repairing heart muscles. However, there is an increasing trend of using higher cell density for bioprinting which requires extensive *ex vivo* expansion, however, that can deteriorate the characteristic features and lower the potency of cells. This problem can be resolved by developing more advanced systems where a living body can serve as a bioreactor for *in vivo* growth of scaffolds seeded with viable cells which can be afterward implanted to the target site. Development of more robust high-resolution bioprinters will resolve several limitations of existing bioprinting technology. Use of composites material with tunable properties can further broaden the scope of bioprinting technology and bioprint several complex and biomimetic structures. Similarly, further development of active mixing systems may overcome the issues associated with preparation of cell suspensions for bioink formulation, development of pre-polymer solutions for preparation of hydrogels, balancing of growth factors and other ingredients in bioink as well as their storage in independently controlled reservoirs under optimized conditions. Bioprinting technology can bring revolution in pharmaceutical industry owing to its potential to accurately place biologics. Moreover, the development of physiologically relevant tissue models can be also be vital in pharmaceutical development. Similarly, conventional processes of drug development and screening can be improved by recent developments such as organ-on-a-chip models and microarrays for high-throughput screening (HTS). These potential broad spectrum applications demonstrate that although bioprinting technology is still at infancy, yet has great potential to serve as a promising solution for various biomedical issues especially in tissues and organ development, regenerated medicines, development of pharmaceutics, and several others.

6. Conclusions

Bioprinting is a fascinating technology that has revolutionized the biomedical research and industry. Currently, it has shown promising results at micro– and macro–levels and offer several merits in tissue engineering and regenerative medicines. Together with tissue engineering, bioprinting technology as the potential to serve as a strong fabrication tool for the establishment of micro- and macro-scale biomedical systems and devices with improved efficacy to better fulfill the requirements of natural ECM of cells, tissues, and organs, and offer broad range applications. It has grown as a promising technology with greater potential and hinted the fabrication of synthetic tissues constructs and organs as shown by considerable success in several *in vitro* and *in vivo* experiments. Despite extensive advantages it offers accomplished by advanced fabrication techniques, this technology at present faces several obstacles and challenges which overshadow its broad-spectrum applications. For example, selection of cells and materials for preparation of bioink, delivering of cells to form stable structures with appropriate mechanical and biological properties, vascularization within the fabricated structures, mimicking human-size constructs, successful co-printing and co-culturing of multiple cell types, and establishing a coordination between cells seeded on scaffolds and with the host tissues and ECM are still at early stage for organ development. Currently, bioprinting research is mainly focused to overcome the discrepancies associated with bioprintable biomaterials or bioinks and improves their structural, physico-mechanical, chemical, biological, rheological, and immunological properties

and we are expecting potential uses of this technology in biomedical, pharmaceutics, and several other fields in near future.

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