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Review

Unconventional Tissue Engineering Materials in Disguise

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Tissue engineering faces a recurring challenge in the transformation of biomaterials into 3D constructs that mimic the biological, chemical, and mechanical features of native tissues. Some of the conventional approaches can be sophisticated and involve extensive material processing and high-cost fabrication procedures. Despite tremendous strides in biomaterials discovery and characterization, the functional and manufacturing limitations have led to the innovation of novel biomimetic techniques that borrow from nature, human-made commodities, and other parts of life to overcome the challenges in tissue engineering and regenerative medicine. This review explores engineering strategies that involve unusual materials for improved functionality, scalability, sustainability, and cost-efficiency. The biomaterials discussed are globally accessible resources and can serve across a wide spectrum of biomedical research areas.

Highlights

Tissue engineering has demonstrated remarkable progress in facilitating regeneration in diseased or damaged tissues. The field suffers from lack of biomaterials that provide sufficient vascularization for proper integration with surrounding tissues. The development of functional materials can be an efficient approach to address this concern.

New strategies involve the rethinking of unconventional materials. Using materials such as plants, paper, ice, textiles, marine organisms, and edible products in modified fabrication techniques also adds the aspect of sustainability in these fields.

These approaches address the functional limitations in tissue engineering technologies and offer biological, chemical, and mechanical robustness. With increased utilization of abundant and sustainable resources, the potential of tissue engineering technologies can reach a global scale.

Current State of Tissue Engineering

The need for tissue and organ transplantation has exceeded the availability of tissue and organ donors and remains a global health disparity [1]. The engineering of clinically relevant 3D constructs (Figure 1, Key Figure) is a promising solution to appropriately and effectively respond to this unmet need [2–4]. Specifically, **tissue engineering** (see Glossary) aims to restore or enhance the functionality of tissues using **biomaterial** technologies that can integrate with the native microenvironment [1]. Recent advances in **biomimetic** materials demonstrate favorable properties such as porosity, swelling, degradation, **biocompatibility**, and mechanical strength [2,5]. Biomimetic materials offer promising approaches that often use polymers, metals, ceramics, and composites as basis for **scaffolds** [6–8]. The extensive characterization of these materials has enabled the tailoring of these scaffolds and cell culture substrates to specialized applications in bone, musculoskeletal, neural, cardiovascular, and pancreatic tissue engineering [2]. The material properties of these scaffolds usually possess facile tunability but often require complex manufacturing processes [7,9]. Moreover, the current *in vitro* and *in vivo* capabilities are not always commensurate to the needs of the specific tissue or organ. One major and recurring challenge in tissue engineering is the inability to scale biomaterials to 3D constructs that mimic the biological, chemical, and mechanical properties of the tissue microenvironment [7,10,11]. Biomaterial integration with the host vasculature *in vivo* or the vascularized network *in vitro* is vital for the maximized transport of nutrients and other essential molecules [3,11]. Moreover, the biomaterial must maintain its properties under physiological conditions without eliciting an immunological response in the host. Fundamentally, this aspect is crucial in clinical translation where patient safety and biomaterial efficacy are highly pertinent.

Emerging areas in tissue engineering reimagine the uses of readily available materials that are atypical in **regenerative medicine**. Materials such as plants, paper, ice, gauze, and fabrics have been recently employed as 3D matrices. These unconventional materials are promising alternatives that have demonstrated exceptional biomimetic capabilities that address the various challenges in tissue engineering and regenerative medicine. Across various areas of tissue engineering, there have been limitations in control over cell adhesion, stem cell differentiation, cell viability, and blood–material compatibility [12–15]. The conversion of simple and abundant items to advanced cell culture substrates addresses the modern challenges in tissue engineering while maintaining a holistic approach to the biological, chemical, and mechanical considerations. The departure from complex fabrication processes to the applications of unusual and ubiquitous materials provides another dimension to the engineering of viable multiscale tissue

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Key Figure

Schematic Diagram of a Tissue Engineering Approach that Incorporates Native Biological Molecules and Unconventional Materials

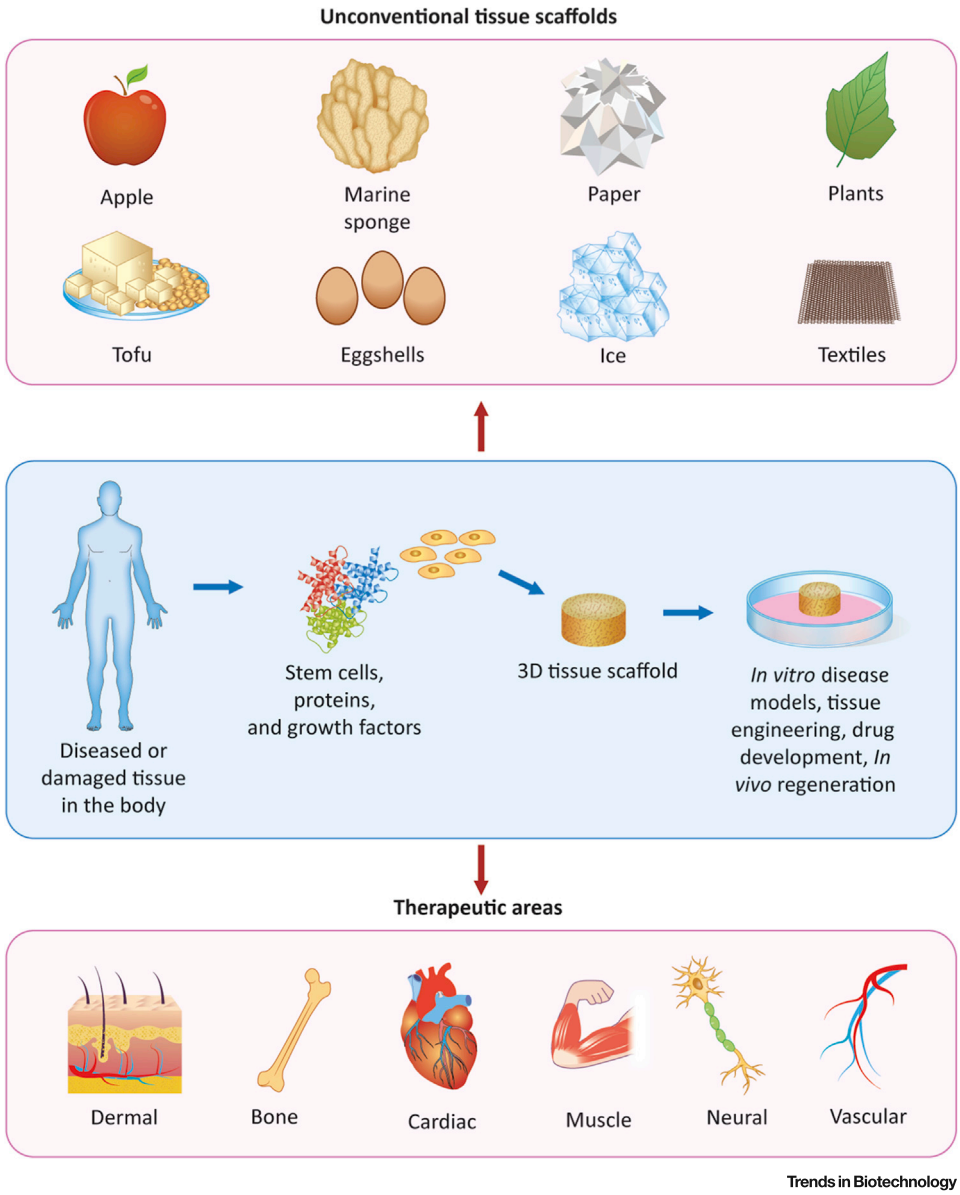


Figure 1. These approaches can cover a plethora of therapeutic and research areas including dermal, bone, cardiac, muscle, neural, and vascular tissues.

Glossary

Biocompatibility: a characteristic of biomaterials that allows a scaffold to perform its intended purpose without eliciting an adverse immune response.
Biofunctionalization: a surface modification that adds a biological molecule or chemical group for improved functionality of the biomaterial.
Biomaterial: a material comprising either synthetic or natural components and used for biomedical purposes such as tissue remodeling, therapeutics, or prosthetics.
Biomimetic: using a strategy that involves closely resembling or modeling a natural system to promote native or normal function in the human body.
Extracellular matrix (ECM): the structural and biological support of cells that includes molecules such as enzymes, fibers, polysaccharides, and proteins.
Regenerative medicine: a research area that develops translational approaches to engineer, repair, or regenerate tissues and organs.
Scaffolds: a structured form of a biomaterial that mimics a tissue environment and supports cell growth *in vitro* or *in vivo*.
Tissue engineering: the application of biomaterial technologies, cells, and other bioactive molecules to restore or improve the functionality of damaged tissues.
Vascularization: the physiological formation of new blood vessels.

Table 1. Summary of Unconventional Biomaterials and Their Applications

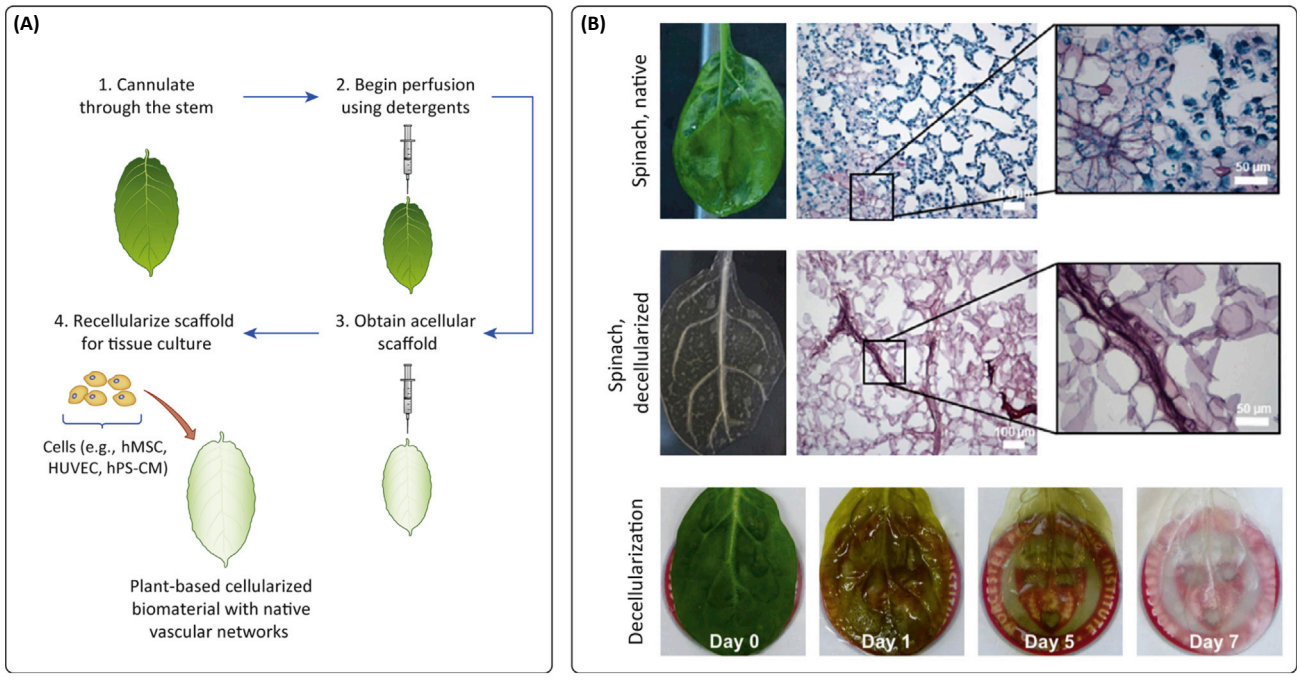
Biomaterial	Advantages	Disadvantages	Application	Refs
Decellularized plants	Natural vasculature networking, chemically modifiable for biofunctionalization, wide range of species for variety of scaffold geometries and networking	*In vivo* biocompatibility and performance have not been heavily investigated	Tissue-engineered cardiac valves, *in vitro* disease modeling, 3D tissue culture with hDF cells and hMSCs	[16,17]
Eggshells	High calcium carbonate ($CaCO_3$) content, sustainable, easily accessible and handled in preparation	No standardized protocol for processing and purifying eggshell particles for tissue engineering purposes	Nanoparticle-reinforced tissue constructs, osseous bone tissue engineering, 3D fibrous network structure for nerve tissue engineering	[22–24]
Apple pomace	Sustainable, cost-effective, natural, and nontoxic polysaccharides found in material	Purification of product after industrial processing	Extraction of cellulose to use as an additive in wound healing technologies and osteochondral tissue scaffolds	[20,21]
Ice	Well-characterized chemical behavior, easily handled, cost-effective	Requires optimization of conditions for spatial and temporal control over freezing process	Vascularized constructs, 3D ice printing for molding of intricate geometries, sacrificial molding, generation of anisotropic structures found in bone	[38,40]
Paper	Porous, accessible, low cost, foldable to generate complex structures, sustainable	Mechanical strength decreases dramatically under wet conditions, lacks biodegradability *in vivo*	*In vitro* disease modeling, screening of therapeutic targets, guided cell growth and mineralization in tissue construct	[31,35,37]
Textiles	Readily fabricated materials, chemically modifiable, wide range of material selections	Biodegradability under physiological conditions is limited or nonexistent in many manmade materials	*In vitro* disease modeling, 3D tissue culture, external wound dressings	[42,47]
Marine sponge	Highly porous, wide range of species enables variety of anisotropic structures, naturally occurring	Fabrication process can be time-consuming and includes sintering, heating, and cooling of scaffold	Sacrificial molding of bone tissue 3D scaffolds	[48,49]
Ulvan	Natural polysaccharide, prepolymer solution is in an injectable liquid form	Chemical crosslinking may be required in biomaterial fabrication	Additive in tissue constructs to support proliferation of PC12 cells *in vitro* and *in vivo*, additive in wound healing technologies, drug delivery technologies	[50,51]
Tofu and soy products	High protein content, porous, biodegradable *in vitro* and *in vivo* under physiological conditions	*In vivo* biocompatibility and performance have not been heavily investigated	Wound dressings for lacerations; integrated in composite sponges and bioactive glass biomaterials that are in contact with blood, *in vitro* and *in vivo* tissue models	[54,56,57]

constructs and regenerative technologies (Table 1). The use of sustainable constructs and novel fabrication strategies has the potential to increase access to tissue engineering technologies on a global scale. This review explores specific applications of unconventional materials used in tissue engineering and their potential implications looking forward in their areas of application.

Adopting Prevascularized Scaffolds from Nature

Plants have a unique vasculature system that allows efficient transport and delivery of nutrients which can conveniently provide functional benefits in tissue engineering. Decellularized plants allow the adoption of prevascularized systems that are comparable with organ-level sizes (Figure 2) [16]. The acellular plant scaffolds are further adapted through **biofunctionalization** [17]. In a previous report, this modification was achieved by coating the plants with a dopamine derivative. Specifically, RGD peptides were conjugated with dopamine to synthesize a product (RGDOPA) that modifies the scaffold with a functional group that supports strong human cell adhesion. In this study, several tropical plants, such as Bambusoideae (bamboo) and *Laelia anceps* (orchid) were biofunctionalized to promote human cell adhesion to the plant tissue [17]. The decellularized tropical plant stems conjugated with the RGDOPA were also mineralized using a modified simulated body fluid (mSBF). Then, the scaffolds were recellularized with human dermal fibroblast (hDF) cells and human mesenchymal stem cells (hMSCs) [13]. The results demonstrated enhanced adhesion of the hDFs in *in vitro* cell culture. In this application, the natural expansion of the plant tissue provides adequate space for cells to grow and proliferate [17]. As demonstrated in these studies, it is possible to support human cells in decellularized plant scaffolds. In addition to hDFs and hMSCs, human umbilical vein endothelial cells (HUVECs) and human pluripotent stem cell-derived cardiomyocytes (hPS-CMs) are potential options for *in vitro* tissue culture, especially for cardiac tissue engineering purposes.

Different species of plants have distinct geometries that can match the vasculature networking required in specific tissues. Tropical plant tissues tend to be porous, a commonly desired characteristic in scaffolding materials [2,5,7]. Other plant tissues have other features that are well suited for larger, organ-like structures. For instance, *Artemisia annua* (spinach) leaves were locally obtained



Trends in Biotechnology

Figure 2. Obtaining Acellular Plant Scaffolds.

(A) A schematic of the workflow in the decellularization of plant leaves using perfusion with detergents. Once the plant leaf is completely acellular, the remaining scaffold can be functionalized with peptides and recellularized with human cells for *in vitro* tissue culture. (B) Images of a native spinach leaf, a decellularized spinach leaf, and the progressive decellularization of the plant scaffold obtained over time. Bars, 100 μm and 50 μm. (B) Adapted, with permission, from [16].

for a cardiac tissue construct [16]. The spinach leaves were cannulated through the stems and treated with different reagents and surfactants over several days to obtain decellularized scaffolds. Then, hPS-CMs were seeded within the scaffold and cultured *in vitro*. The plant cell wall predominantly comprises cellulose, which is a naturally occurring polysaccharide that has been shown to promote cell attachment and proliferation [16,18,19]. Other components in the cell wall include pectin and hemicellulose, which have shown biocompatibility in bone tissue engineering and wound healing applications, respectively [10]. Plants conveniently provide these components that enhance the functionality of biomaterials. Although this green approach is promising, the proof-of-concept studies do not currently provide adequate support for clinical translation *in vivo*. With a plant-based scaffold, the chemical and mechanical capabilities of many plant species may not be compatible under physiological conditions.

Repurposing Sustainable Products for Regenerative Medicine

Other sustainable methods in tissue-engineered scaffolds utilize resources that are also considered byproducts in industrial processes. In the processing of foods, many materials are often disposed of despite their potential value in regenerative medicine. For example, in the manufacturing of apple purees, juice, or cider, apple pomace is the leftover solid residue after production. Instead of wasting the material, a study extracted biomaterial components such as pectin, chlorogenic acid, and caffeic acid from apple pomace [20]. In osteochondral tissue engineering, apple pomace is a promising resource in part because it offers a cost-effective resource for obtaining extracts that have been shown to support osteoblast and chondrocyte regeneration in *in vitro* 2D cell culture studies. In this study, viability assays demonstrate that the density of living cells can increase by up to approximately four times on these biomaterials between 7 to 14 days in culture [20]. The other motivation of repurposing is that the apple pomace provides an environmentally conscious approach with biofunctional benefits. Modulevsky *et al.* also observed this phenomenon using the apple's hypanthium tissue [21]. The study used apple-derived cellulose to fabricate scaffolds which were then subcutaneously implanted in mice [21]. The *in vivo* study demonstrated promising results in the regeneration of fibrous tissues, including the deposition of new **extracellular matrix (ECM)** in the scaffold.

Eggshells are also a form of waste from food processing that is not conventionally used in tissue engineering. The incorporation of eggshells in scaffolding materials has been successful in promoting osteoinduction and nerve tissue regeneration [22–25]. The eggshell is highly rich in calcium carbonate ($CaCO_3$), a strong basis for osteoblasts to deposit their calcium minerals into the matrix of the biomaterial [22,23]. In addition, the other components of the eggshell, such as hydroxyapatite (HA), are essential components of bone that can be easily incorporated to enhance the biocompatibility and functionality of the composite materials [22,23]. For example, eggshell microparticles (ESPs) reinforced conventional hydrogel constructs for improved biophysical properties that support the differentiation of pre-mature cells in osteoblasts [22]. In nerve tissue engineering, a composite material used the eggshell membrane (ESM) and polycaprolactone fumarate (PCLF) layer to fabricate a 3D fibrous network structure [24]. This vascularized scaffold supported PC12 cell spreading and proliferation. In all instances, the eggshell or the isolation of certain ESM constituents was prepared using simple techniques such as box furnace heating, acid treatment, and vacuum infiltration [23–25]. Simple purification and fabrication techniques can lend themselves to scalable and streamlined manufacturing processes, which can support the potential common use of eggshells in biomedical applications.

Ancient Technology in Modern Biomaterials

The use of paper in tissue engineering is a nontraditional application of a historically old and revolutionary technology [26–28]. Some paper applications are not as obvious as the typical printing material, writing canvas, and art forms that have been integrated into everyday life. Paper-supported cell culture substrates (Figure 3) are recent developments that involve stacking alternating layers of paper and cells encapsulated in hydrogels [29,30]. This strategy results in highly porous 3D tissue constructs and has seen success as a tissue model for monitoring lung cancer cells [29,31]. Similar to decellularized plant scaffolds, paper-based constructs can also be chemically modified for the addition of

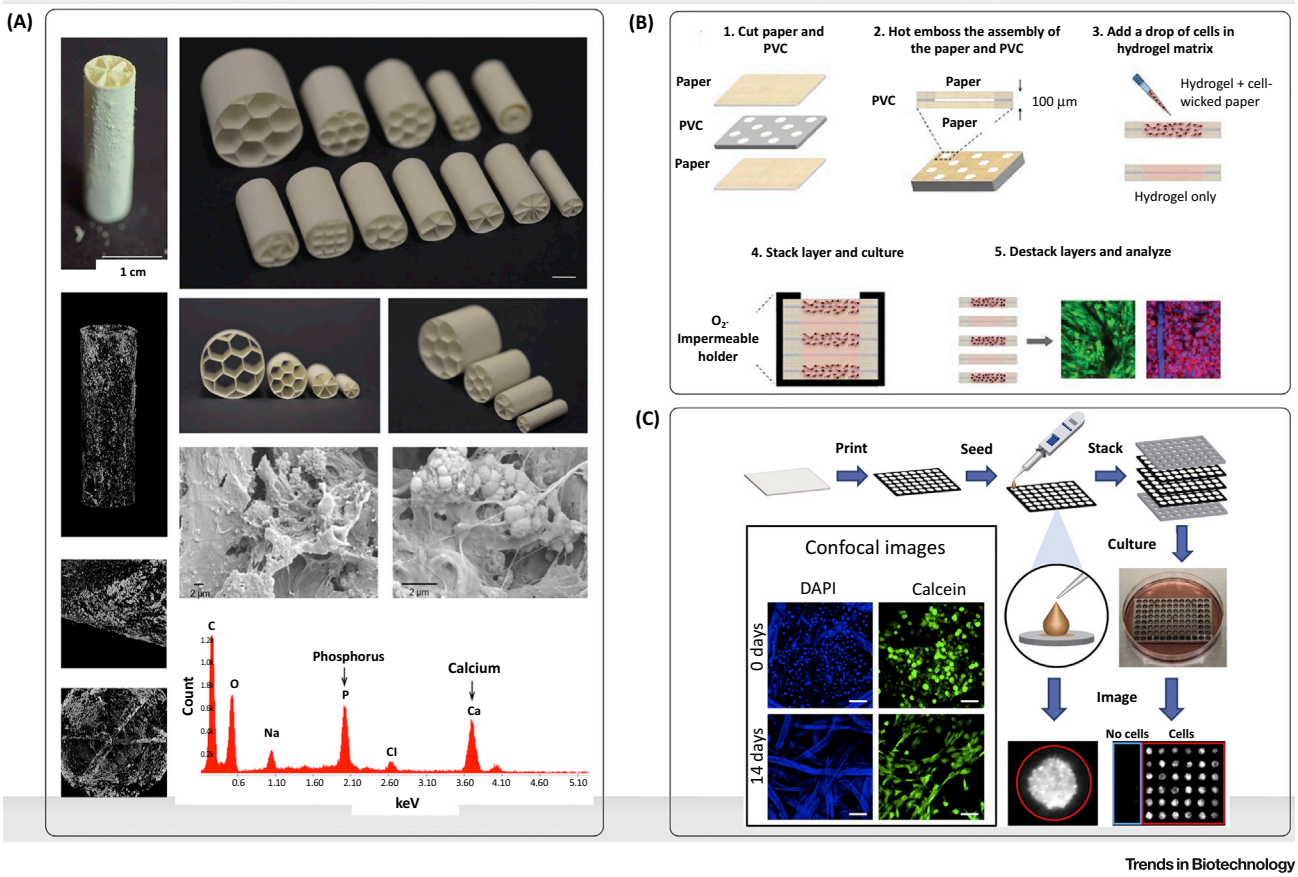


Figure 3. Paper-Based Tissue Constructs.

(A) Origami-inspired structures for tissue engineering and the generation of a wide spectrum of geometries. Mineralization in paper scaffolds revealed in scanning electron microscopy images. The elemental composition of the deposited minerals was determined using energy-dispersive X-ray spectroscopy (EDAX). (B) The fabrication of paper scaffolds with hot embossing and a multilayer-stacking strategy for coculturing of tumor cells and stromal cells. Destacking is conveniently performed for staining of different tissue sections in the construct. (C) Illustration of a similar paper-based strategy using 200-µm-thick filter-paper sheets that were patterned via wax printing in a 48-well-plate configuration. Confocal imaging shows 4′,6-diamidino-2-phenylindole (DAPI) and calcein staining for nuclei and cell viability. (A–C) Adapted, with permission, from [30,31,37].

functional groups [29,32]. A major advantage of using paper as a material is that its mechanical properties and porosity mimic the fibrous microarchitecture found in tissues [33,34]. These aspects are necessary to optimize mass transport of biochemical molecules such as oxygen and nutrients and integration with the host vasculature [2,5]. Other recent studies use paper's strength and foldable properties for origami- and kirigami-based 3D constructs for tissue engineering [33,35]. The transformation from art to cell culture substrates allows the design of a wide spectrum of geometries. In *in vitro* studies, template-guided biomineralization from osteoblasts has been successful, demonstrating potential tissue modeling applications to determine patient-specific treatments. Paper has also been recently utilized in microfluidic platforms [36]. The patterning and templating on paper can be conveniently achieved through wax printing or screen printing [37]. The advantages of using paper is that it has wicking and absorption properties and allows capillary action to occur within the material [36]. These features are applicable in fabricating viable tissue constructs and compact biosensors for detection of analytes.

In some ways, paper can address the mechanical shortcomings often found in hydrogel-based scaffolds. For example, it is easy to handle and manipulate hydrogels with high aspect ratios when

combined with paper [33]. While paper tensile strength can decrease considerably under wet conditions [35], it is possible to increase its mechanical strength by reinforcing the paper using premineralization approaches. Although paper is not biodegradable *in vivo*, it has proved useful as a biomaterial for applications that do not require degradation [37]. As a low-cost material, paper is widely available in different pore sizes, thicknesses, and chemical structures. Furthermore, paper allows the generation of gradients, complex 3D structures, multilayered personalized medicine platforms, high-throughput sample preparation and analysis, and origami-inspired tissue engineering. To date, the *in vitro* and *in vivo* success of paper shows advantageous technologies, especially in bone tissue engineering that requires guided growth and rigidity. However, drug development can potentially benefit from these tissue-engineered technologies. In early drug discovery, scouting for lead therapeutic targets under physiologically relevant conditions provides more translatability and predictability in the pharmacokinetics and immunogenicity of drug candidates *in vivo*. As a high-throughput model, these paper-based technologies can be integrated in these biophysical screenings to push lead targets forward efficiently.

Using Ice to Modify Material Processing Techniques

Templating and guided patterning in 3D tissue-engineered constructs can be achieved by using ice as a sacrificial material in fabrication processes. The freezing of aqueous solutions has been used for crystal formation and growth to fabricate anisotropic scaffolding templates [38]. During the freezing process, the solid particles in the solution concentrate in the interstitial spaces as the ice nucleates and grows. Afterwards, the ice is sublimed, leaving the shape of the scaffold walls. Anisotropic patterns are ubiquitous in native tissues such as bones, which can have significantly varied mechanical properties parallel and perpendicular to the axis of the bone [11,38,39]. As a drawback, anisotropic structures are not easily controlled, in part because of the nature of the freezing process. The freezing of the aqueous solution depends on several factors, such as the temperature and the solute content dissolved in the solvent [38]. These freezing parameters can affect the structural characteristics of the resulting scaffold [38]. Modification of the freezing process is not straightforward as directly modifying material composition or functionalizing surfaces in the conventional strategies.

Similarly, ice can be used to modify conventional 3D printing methods for molding of freestanding vascular structures (Figure 4). In ice printing, a 3D printer is customized with a printhead that includes a heating element and temperature sensor for the automated dispensing of distilled water under controlled thermal conditions [40]. The custom-modified 3D printer is operated at an ambient temperature of −30°C for the ejection of water [40]. As water is ejected from the printhead, the water freezes into ice in the shape of the desired sacrificial structure. The ice scaffolds are coated with well-characterized biocompatible materials to cast vascular structures for *in vitro* and *in vivo* cell culture. Some of these coatings include tropoelastin, polycaprolactone (PCL), polydimethylsiloxane (PDMS), and silk [40,41]. The sacrificial elements based on ice were then melted and removed leaving hollow, vascular structures. The 3D ice printing of freestanding vascular structures can be ideal for casting patient-specific thin- or thick-walled arteries, multifurcated structures, or aortas using materials that have been well characterized and are efficacious in tissue engineering.

Transforming Textiles into Biomaterial Fabrics

There are many possibilities of using mundane materials in tissue engineering, including fabrics such as cotton and meshes. Common textiles have been incorporated into biomaterials in regenerative medicine applications. In treating wounds, antibiotics are often applied in a topical form to prevent infection and facilitate wound healing [42]. However, excessive amounts of the antibiotics are easily applied, leading to increased risks of antibiotic misuse [42,43]. A strategy to control the optimal amount of administered antibiotics immobilized antimicrobial peptides on cotton gauze [42]. These antimicrobial agents were stacked in a polyelectrolyte multilayer, alternating between polycation and polyanion over the cotton gauze. The chitosan and alginic acid sodium salt served as the polycation and polyanion layers, respectively. Chitosan is bioactive and is naturally derived from shells of crustaceans [44,45]. Chitosan is also bacteriostatic and fungistatic, which inhibits replication of microbes [45]. The alginic acid sodium salt offers a gelling component that provides the necessary moisture for wound healing

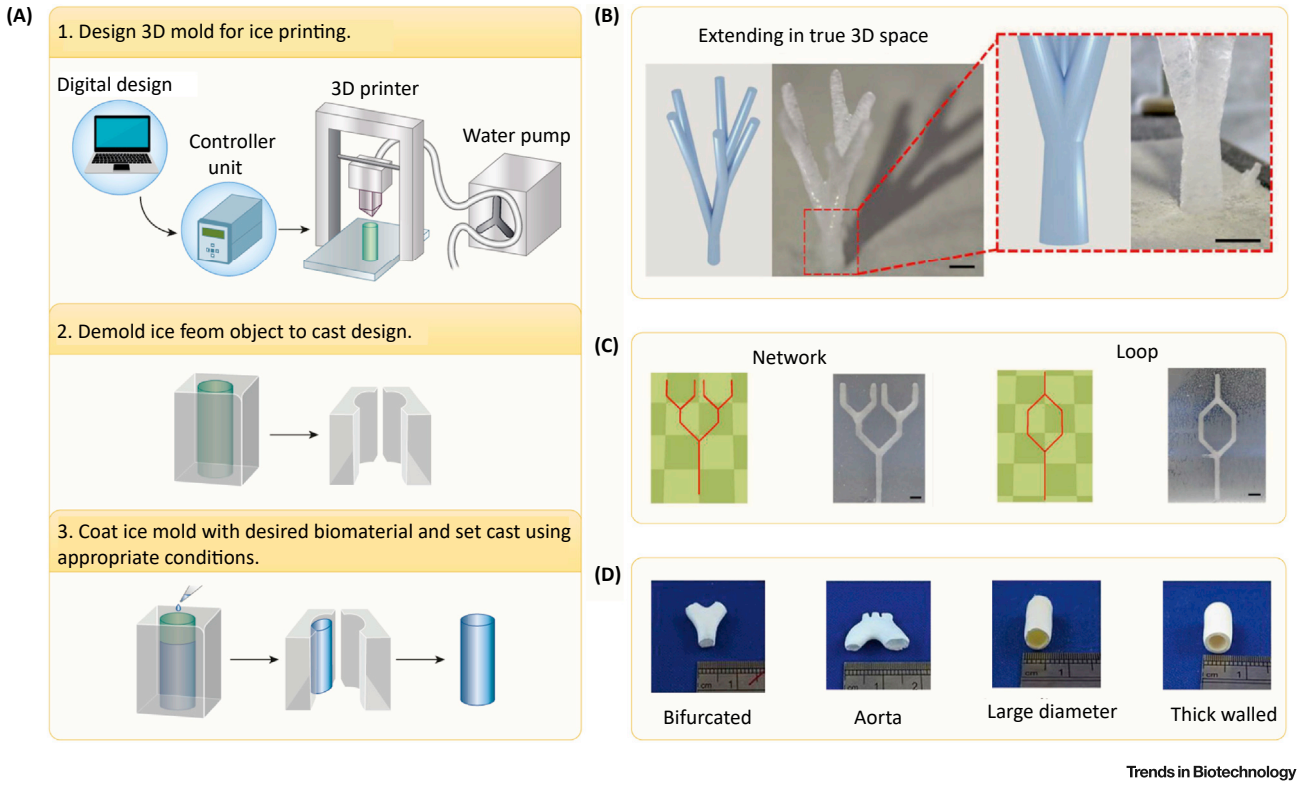


Figure 4. Using 3D Ice Printing to Generate Freestanding and Vascular Constructs.

(A) A general process for the 3D printing of sacrificial scaffolds of a variety of geometries. The desired construct is generated on computer-aided design (CAD) software. Once a mold is ice printed, a polymeric coating can be used to shape the biomaterial scaffold. Possible coatings include tropoelastin, tropoelastin/polycaprolactone (PCL), tropoelastin/polydimethylsiloxane (PDMS), silk, and silk/PDMS. (B) Spatial and temporal control of the ice-printing technology in 3D space. Bars, 4 mm. (C) Networks and loops with diameters that are ~1 mm. Bars, 2 mm. (D) A variety of biomaterial designs that are clinically relevant to geometries found in tissues and organs in the human body. Bars, 4 mm. (A–D) Adapted, with permission, from [40].

[42,44,45]. In another study, cotton wool was loaded with silver nanoparticles using a solution-dripping method that contained silver carbamate (CH_3AgNO_2) [43]. The silver in the cotton reacts with moisture from the skin or wound to release the silver ions, which damage bacterial DNA and RNA, preventing replication of the bacteria. The silver nanoparticle-loaded cotton demonstrated antimicrobial properties and improved blood clotting rates [43]. Both strategies achieve promising results in wound healing applications but they draw from different resources to modify traditional gauze for external use.

Adapting textiles such as polymeric meshes to 3D culture systems provides an efficient design approach because it involves materials that have been well characterized. A strategy called Cells-in-Gels-in-Mesh (CiGiM) uses the layering of polymeric mesh to support cells encapsulated in gels [46]. The layers were easily disassembled after MDA-MB-231 breast cancer cell culture studies, which allows the examination of *in vitro* cell cultures within layers and the development of future modifications. With this alternative approach, cell culture systems can be evaluated efficiently at different time points without the requirement for fixing or staining with reagents that may alter or convolute findings. The polymeric mesh system provides manipulatable tissue constructs for modeling analysis of 3D cell cultures. Since these meshes are often woven, current weaving technology in the textile industry can be applied in tissue engineering [47]. The potential blending of the two fields has been investigated in the weaving of a heart valve [47]. In this 3D tissue construct, the orientation of the yarns offered guided cell growth and ECM deposition. Mechanically, this is a robust approach to produce strong and anisotropic structures that can serve as precursors in bone tissue engineering.

Marine Life in Tissue Engineering

Other promising resources and inspiration from marine life have also progressed developments in tissue engineering and regenerative medicine. In bone tissue engineering, marine sponges were used as sacrificial casts to replicate the natural porosity found in the organisms (Figure 5) [48]. A heated slurry comprising polyvinyl alcohol (PVA) in deionized water was used to mix Bioglass® powder into the suspension [48,49]. The sponges were submerged in the slurry a few times with removal of excess slurry between drying and additional dip coatings. Once this is completed, a heat treatment is performed to remove the sacrificial template and sinter the scaffold. The product was a bioactive glass scaffold that provided effective diffusion of oxygen, mechanical strength (2–4 MPa), and porosity (68–76%). The sponge template generated decreased porosity, which improved the

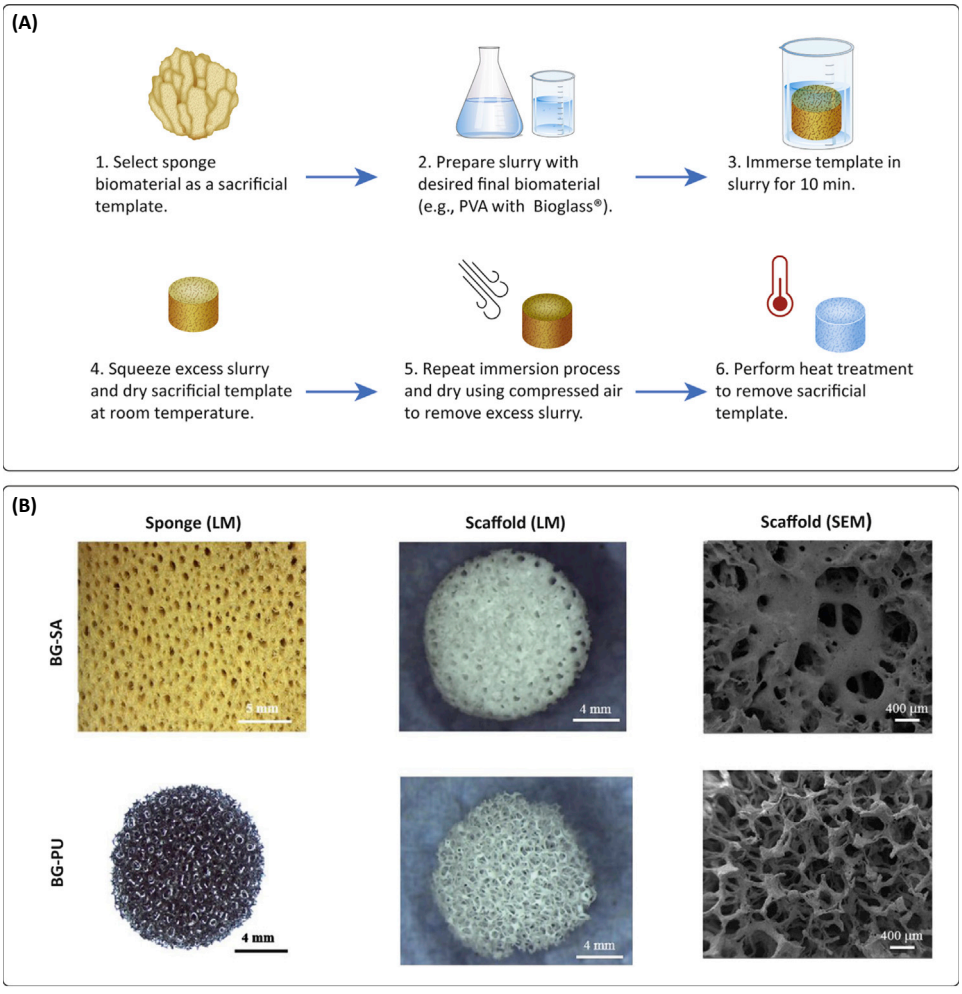


Figure 5. Porous Tissue Constructs Using Marine Sponges.

(A) The fabrication of porous tissue constructs. The process begins with an initial biomaterial templating selection using a marine sponge. These sponges naturally possess an anisotropic structure, which is a valuable precursor for bone tissue engineering. The marine sponge is a sacrificial biomaterial that is removed at the final step. (B) Various scaffolds with distinctive physical properties were generated using different species of marine sponges and bioactive glass (BG) *Spongia agaricina* (BG-SA) and *Spongia lamella* (BG-SL). These structures were compared with a scaffold generated using polyurethane foam (BG-PU). Bars, 5 mm and 4 mm. Light microscopy (LM) and scanning electron microscopy (SEM) reveal the porosity found in these scaffolds. Each source of sponge yielded a distinctive porosity profile in the resulting scaffold. Bars, 400 µm. Adapted, with permission, from [48].

mechanical strength but did not maximize oxygen diffusion. By comparison, the porosity found in bioactive glass scaffolds shaped by a polymeric foam using the same process had limited mechanical strength but maximized oxygen diffusion. Similar to decellularized plants, different species of sponges, such as *Spongia agaricina* and *Spongia lamella*, can yield distinct geometries in the resulting tissue constructs [48,49]. However, sponge geometry can lead to variable results, which in effect influences the reproducibility of the generation of a certain structure [49].

Ulvan is another polysaccharide found in marine life that can be isolated from green algae [50,51]. In cell delivery applications, ulvan can be used to fabricate 3D *in vitro* and *in vivo* tissue constructs. One study demonstrated that the scaffold can support the proliferation of PC12 cells, which are derived from neuroendocrine tumors of rats. However, this injectable polymer strategy is applicable in minimally invasive procedures, such as the implantation of cardiac patches, that utilize catheter-based approaches [52]. Studies have also utilized ulvan for wound healing applications [53]. Ulvan can be processed in the form of fibers and nanoparticles, which is compatible with various hydrogel fabrication techniques [50,51]. In wound healing applications, rapid release of a model drug (dexamethasone) *in vitro* was measured at 49% in the first hour and 75% for up to 14 days [53]. Ulvan-based wound dressings are promising vehicles for sustained drug delivery of biological factors that support wound healing. Ulvan can be further tailored by chemical modification to render hydrogels thermostable or temperature or light responsive through the addition of chemical functional groups [53]. Interestingly, ulvan is also commonly included in dietary consumption in Eastern countries [50]. This aspect of ulvan challenges other consumable items that are also valuable in tissue engineering.

Edible Items in Tissue Engineering

From soy products to essential oils, there are a variety of foods that have been introduced in tissue engineering. Edible items can function as scaffolding material or be integrated in additive manufacturing techniques. For example, tofu was applied as a porous scaffold to address limitations in current tissue engineering strategies [54–57]. Huang and colleagues fabricated two types of tofu scaffolds using its conventional food processing technique and another one that involved an additional covalent crosslinking step (Figure 6) [54]. The tofu strategy used soymilk and a coagulant (Nigari) to gel the scaffold in a wooden mold lined with cloth and plastic sheet. Then, the tofu is pressed, cut, washed, and lyophilized to obtain the final scaffold. The two conditions provided similar results in porosity, cell proliferation, and biocompatibility in *in vivo* mouse models. Histological evaluation through staining of the explanted tofu and soybean protein scaffolds that were subcutaneously implanted in the submucosal layer revealed integration with native tissues, with some blood vessels formed around the biomaterial–tissue interface. As a soybean-based product, tofu scaffolds are rich in proteins, support oxygen supply, degrade under physiological conditions, and promote cell adhesion [54,57,58]. These aspects are physiologically relevant in early stages of wound healing. Therefore, tofu-based biomaterials are potentially promising candidates for wound dressing materials. In addition, tofu has been also integrated into composite sponges and bioactive glass biomaterials that are in contact with blood or as tissue scaffolds [56,58,59].

Other methodologies involve modifying current approaches as discussed in 3D ice printing [40]. For example, a 3D-printer head was modified to heat and dispense a mixture of glucose, sucrose, and water to yield in temporary casts for vascularized engineered tissues [60]. Another application of sugar is to use it in a pellet form to manufacture porous metallic scaffolds [61]. The pellets act as biocompatible space holders in the manufacturing of the material. This strategy has potential in hard tissue engineering or fabrication of load-bearing constructs that also possess tunable porosity. In orthopedic areas of interest, these types of constructs can be found in common medical conditions such as hip joint deterioration or major bone trauma that eventually requires replacement of bone with an implanted metal support. Other forms of additive manufacturing use the therapeutic benefits of essential oils such as grapeseed oil and honey or propolis [62]. In a wound healing application, a mixture of honey, royal jelly, and olive oil-propolis extract demonstrated accelerated wound healing in diabetic mice [63]. With a similar combination of essential oils and polyurethane in an electrospinning platform, the resulting scaffold demonstrated promising blood biocompatibility and cell viability rates [62].

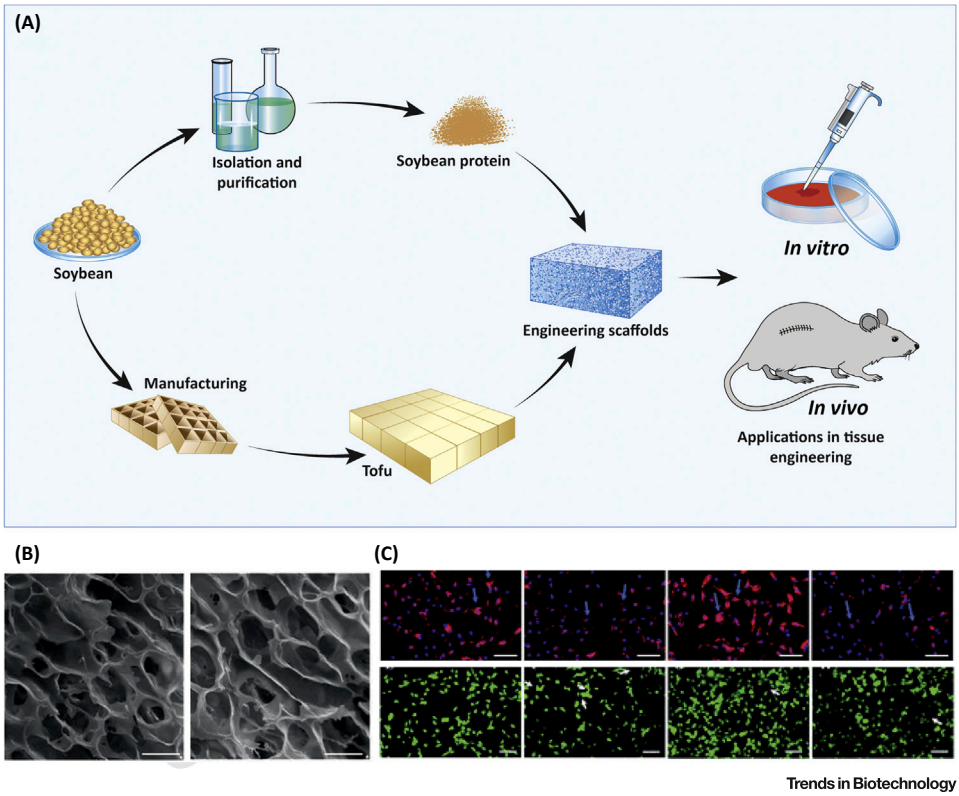


Figure 6. Biomimetic Protein Scaffolds from Tofu.
(A) A schematic diagram illustrating the fabrication process from soybean to tofu-based engineered scaffold. The scaffold was seeded with 3T3 cells and cultured *in vitro*. The 3D construct was also implanted into mice for *in vivo* testing, which did not elicit any significant immune response, demonstrating biocompatibility with the host organism. (B) Scanning electron microscopy images that reveal the porosity achieved in tofu and soybean-protein scaffolds. As shown, similar physical properties were achieved using two different soy-based derivatives. Bars, 20 μm. (C) A 4′,6-diamidino-2-phenylindole (DAPI) staining of 3T3 cells seeded on these scaffolds and live/dead staining of these tissue constructs. Blue arrows indicate good cell morphology and white arrows point to dead cells shown in the assay after various time points in culture. High cell viability and compatibility were achieved using these scaffolds. Bars, 50 μm. (A–C) Adapted, with permission, from [54].

Concluding Remarks and Future Prospects

The plethora of mundane materials opens a wealth of opportunity in tissue engineering and regenerative medicine (Table 1). The use of plants, textiles, art, food, and other common materials from everyday life have shown promising results in proof-of-concept studies. Borrowing from nature, the plant- and marine sponge-based materials offer optimal **vascularization** for applications such as cardiovascular, liver, and musculoskeletal tissue engineering, where supply of oxygen and nutrients through transportation of blood is essential for tissue and organ functionality. However, vascularization in 3D constructs is not always the central component in tissue engineering applications, including in the repair of some other, avascular tissues and organs such as the bladder and cartilage. As discussed, the unconventional tissue engineering scaffolds that are readily available and adapted from nature exhibit biomimetic characteristics including porosity, structure, and bioactivity. It is, therefore, possible to fabricate physiologically relevant constructs utilizing these biomaterials. The use of existing naturally derived materials for tissue engineering provides an inexpensive and sustainable approach that benefits the economy and environment while providing unique advantages. Many of these biomaterials are overlooked and under-studied for biomedical applications, partially for their simplicity as mundane items. However, as we continue studying their physical, chemical, and biological properties, we expect to uncover additional functionalities of these materials.

Outstanding Questions

Conventional hydrogel-based approaches in tissue engineering have robust and tunable properties. Can the use of unconventional scaffolds such as decellularized plants offer the same control over biological, chemical, and mechanical tunability found in conventional hydrogel-based strategies?

Are the vascularization strategies in these discussed approaches scalable for future fabrication of whole 3D organs?

How reproducible are the results from these strategies that utilize unconventional materials or borrow scaffolds from the outer matrix of plants and other organisms?

In terms of regulatory approval, how will these approaches affect the guidelines for characterizing and approving unconventional materials for clinical applications?

The clinical translation of some of the unconventional biomaterials, such as plants and paper, can be challenging. Some of these studies are still in their infancy, with promising results mainly in *in vitro* cell culture (see Outstanding Questions). Given the successes *in vitro*, the plant- and paper-based tissue constructs can lend themselves as meaningful personalized models for disease understanding or modalities for predicting potential immunological responses *in vivo*. These biomaterials can serve across myriad complex diseases such as cancers, muscular dystrophies, and cardiovascular diseases as well as common treatable conditions such as skin lacerations and bone fractures. The *in vitro* and *in vivo* tissue models can be translated into customized treatments for the patient. Moreover, adapting current technologies such as 3D printing and weaving to incorporate readily available biomaterials can enhance tissue engineering capabilities. As discussed, 3D-printed and freestanding structures have incorporated edible items and commercial textiles for fabrication of clinically relevant scaffolds. These scaffolds can play a dual role as implantable tissue constructs and as models for clinicians to understand a patient-specific profile for a disease. In doing so, the increased use of these unconventional materials can bring forward tissue engineering technologies and advance biomedical research breakthroughs at a global scale.

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