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Tubular Bioartificial Organs: From Physiological Requirements to Fabrication Processes and Resulting Properties. A Critical Review

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Regenerative medicine · Tubular organs · 3D bioprinting · Solution electrospinning · Melt electrowriting

Abstract
In this featured review manuscript, the aim is to present a critical survey on the processes available for fabricating bioartificial organs (BAOs). The focus will be on hollow tubular organs for the transport of anabolites and catabolites, i.e., vessels, trachea, esophagus, ureter and urethra, and intestine. First, the anatomic hierarchical structures of tubular organs, as well as their principal physiological functions, will be presented, as this constitutes the mandatory requirements for effectively designing and developing physiologically relevant BAOs. Second, 3D bioprinting, solution electrospinning, and melt electrowriting will be introduced, together with their capacity to match the requirements imposed by designing scaffolds compatible with the anatomical and physiologically relevant environment. Finally, the intrinsic correlation between processes, materials, and cells will be critically discussed, and directives defining the strengths, weaknesses, and opportunities offered by each process will be proposed for assisting bioengineers in the selection of the appropriate process for the target BAO and its specific required functions.

Introduction, Approach and Objectives

Bioengineering is a discipline in which engineering principles are applied to biological systems and biomedical technologies. One of the main goals of bioengineering is to reproduce, repair, or recapitulate tissues and organs, or their functions. In bioengineering, geometries are directly inspired by anatomy, while properties closely follow physiological functions. From an anatomical point of view, there are 5 fundamental levels of organization in the human body, from the simplest one to the most complex: (i) the cellular level, (ii) the tissue level, (iii) the organ level, (iv) the organ-system level, and (v) the organism level [Góra et al., 2016]. Each tissue is a complex structure composed by multiple cell types immersed in multiple sets of proteins dispersed in an extracellular matrix (ECM) [Chen and Liu, 2016]. The cells in a tissue work together in an orchestrated manner to accomplish specific functions. An organ is made of various types of tissues, and intrinsically, of several types of cells. Each organ is characterized by complex structural, mechanical, and motility patterns responsible for one or more specific physiological functions [Del Gaudio et al., 2014; Mandrycky et al., 2015].

Diseases, injuries, and malfunctions of one (or more than one) of the organs affect and decrease the patient's

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quality of life, and in the worst case, lead to death [Leberfinger et al., 2019]. The type of clinical treatment depends on the severity of the injury, the type of disease, and the medical history of the patient. As a first option, drug therapy and/or other noninvasive therapeutic treatments are privileged. However, when the progression of the disease advances, surgical intervention, including tissue transplantation or substitution, is unavoidable. Current transplantation and substitution techniques are based on the use of (i) autologous, or (ii) heterologous tissues, or (iii) synthetic prostheses, but these do not always represent a viable option [Hodges and Atala, 2013; Holland et al., 2018]. Substitution or transplantation of autologous tissues is not possible in case of previous harvesting and/or pathological degenerative conditions. As for heterologous tissues, the main limitation is a shortage of suitable and available tissues [Atala, 2005; Del Gaudio et al., 2014; Chen and Liu, 2016; Leberfinger et al., 2019]. In the past decades, synthetic prostheses were developed in the hope of facing the abovementioned shortcomings. However, there is an important mismatch between anatomical and mechanical requirements (MRs), and other issues can be found in the required biological properties and long-term expected patency [Holland et al., 2018]. Therefore, although organ shortage is already addressed by reparative [Stock and Vacanti, 2001; Ratner et al., 2004; Vacanti and Vacanti, 2014] (through implants, artificial organs and devices) or regenerative [Mozafari et al., 2019] (cell-containing structures or cell-based therapies) medicine, clinical complications still limit the success of the implantation. In an attempt to improve this success rate and increase the overall clinical performance, tissue engineering and regenerative medicine (TERM) aim to restore the functional and structural properties of diseased or damaged tissue, while maintaining and/or improving tissue performance [Shafiee and Atala, 2017]. Different approaches have been explored, all relying on the use of cells, scaffolds, or their combination [Furth and Atala, 2013; Hodges and Atala, 2013; Del Gaudio et al., 2014;]. Through further process engineering, the resulting constructs are expected to mimic the structure (i.e., the internal architecture) and the complex cellular microenvironment of native tissues [Chen and Liu, 2016; Barbosa and Martins, 2018]. In particular, bioartificial organs (BAOs) constitute the expected outcome of designing and developing functional organs from regenerative medicine strategies. In order to be able to mimic the native organs to the greatest extent possible, researchers have to look in detail into the anatomical hierarchy of tissues [Nerem and Schutte, 2014] and their biological and mechanical properties [Nichol and Khademhosseini, 2010; Moffat et al., 2014; Marx, 2015; Chen and Liu, 2016].

To better understand the rich complexity (issued by millions of years of biological evolution), that can be found in various tissues and organs, Atala et al. [2012] have proposed 4 levels of classification according to a defined scale of increasing complexity: (i) flat tissue structures, (ii) tubular structures, (iii) hollow, non-tubular, viscous structures, and (iv) complex solid organs. Despite the available knowledge (both on the engineering and the biology side) and the accessible technologies (both the standard and the more advanced ones), there are still plenty of challenges in designing and developing more complex structures. Therefore, this review will point out the current situation considering these challenges, and can hopefully open up a new path for future studies. More precisely, this review will focus on the second group, namely the tubular structures. The human body is composed of several organ systems, including the respiratory, digestive, urinary, and circulatory system, each one containing tubular organs [Góra et al., 2016; Holland et al., 2018]. Their main function is to transport fluids, metabolites, and gases from, to, and through organs [Atala et al., 2012; Del Gaudio et al., 2014]. In order to engineer these tubular systems, biomaterials are processed into a tubular structure that is used as such or combined with cells and allowed to mature in vitro, before implantation. Various processing techniques to fabricate tubular constructs have already been proposed [Holland et al., 2018]. Such processing techniques can be grouped into (i) conventional and (ii) advanced techniques. Some examples of conventional laboratory techniques are gas foaming, molding, solvent casting, dip coating, and a few others. More advanced techniques, for reproducible results and adapted to clinical transfer, include three-dimensional bioprinting (3DBP), solution electrospinning (sES), and melt electrowriting (MEW) [Mandrycky et al., 2015; Dutta et al., 2017; Pedde et al., 2017; Holland et al., 2018]. Each of them has its own pros and cons – they will be discussed here below – which will influence the resulting properties of the fabricated tubular construct. Likewise, the choice of the processing technique depends on the specific requirements for which each BAO has been designed for. These biological requirements (BRs) and MRs depend, in their turn, on the anatomical hierarchical structure of the different tissues and on the physiological functions related to the anatomy of a specific organ. Consequently, there is an underlying correlation between (i) the requirements to match

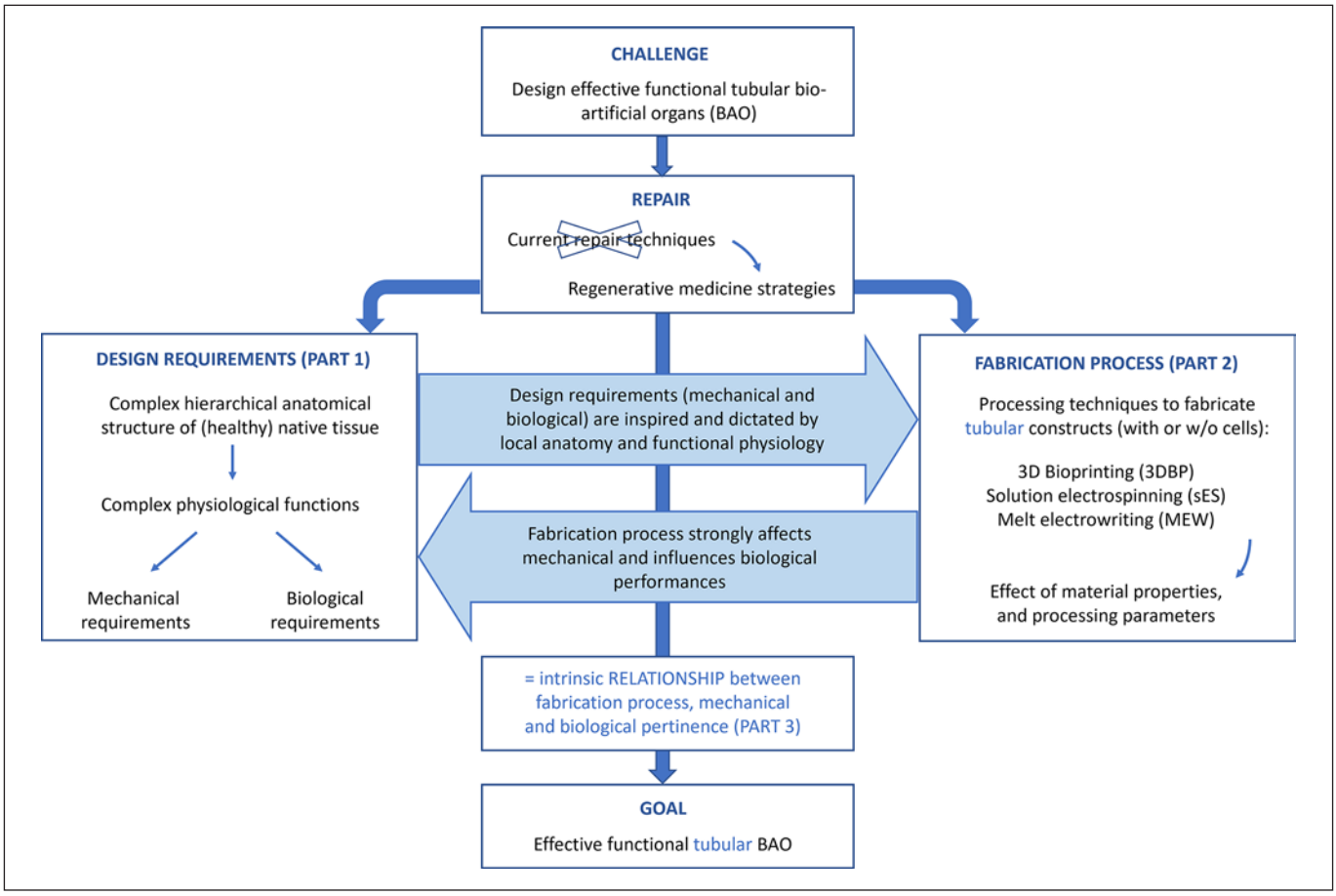


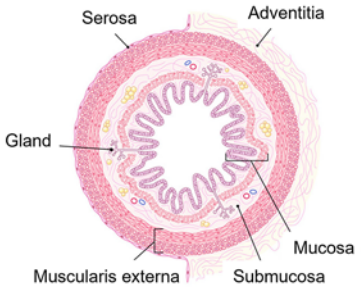
Fig. 1. Flow chart. Part 1: Requirements dictated by anatomical and physiological concerns. Part 2: Strategies for the fabrication of tubular constructs for the regeneration of tubular organs. Part 3: Relationship between the process, cells, mechanical and biological performance.

in order to restore the physiological functions, (ii) the various processing techniques to fabricate a tubular construct, and (iii) the obtained properties of the fabricated construct.

In this work, the development of functional tubular constructs from biomaterials and/or cells was reviewed (as depicted in the flow chart, Fig. 1). More specifically, the hierarchical anatomical structure of the 4 hollow tubular organs will be described (Part 1), together with the complex physiological functions and the MRs and BRs of each one. The state-of-the-art (SOTA) of processing techniques to develop tubular constructs (Part 2) will be reviewed as well. In the final part, the effect of processing techniques on the mechanical and biological aspects (Part 3), and thus the existing correlation between process, mechanical and biological pertinence will be discussed.

From Organs to Hierarchical Structure of Hollow Tubular Organs: Design Requirements Dictated by Anatomical Structure and Physiological Functions

As introduced above, requirements for TERM applications are defined considering the organ anatomy and physiology. The wall of all tubular organs is composed of different layers. In general, 4 layers can be distinguished including (i) mucosa, (ii) submucosa, (iii) muscularis externa, and (iv) adventitia and/or serosa layer (Fig. 2, left) [Góra et al., 2016]. A comparison between the 4 basic layers of each tubular system (i.e., trachea, esophagus, intestines, urethra and ureter, and blood vessels) is shown in Figure 2. These 4 layers consist of various cell types and ECM, which are organ specific. Each kind of cell and ECM component has a specific role to perform individually, but also as a multilayered structure in its whole, in



	Trachea	Esophagus	Intestines	Urethra and ureter	Blood vessels
Mucosa	Pseudostratified ciliated epithelium	Pluristratified, squamous epithelium, lamina propria and muscularis mucosa	Simple epithelium, lamina propria and muscularis mucosa	Epithelium and lamina propria	Epithelium (endotelium)
Submucosa	Connective tissue with seromucous glands	Connective tissue with branched tubular glands	Connective tissue with glands		
Muscularis externa	Smooth muscle and connective tissue reinforced with hyaline cartilage	Alternation of smooth and striated muscle cells	Connective tissue with peristaltic smooth muscles	Inner longitudinal and outer circular muscle layer	Connective tissue with smooth muscle
Adventitia and/or serosa		Connective tissue	Vascularized connective tissue	Connective tissue	Connective tissue

Fig. 2. Anatomical structure of tubular organs. Left: General structure of tubular organs (Image adapted from UNIFAL-MG, Histologia interatva; https://www.unifal-mg.edu.br).Right: comparison of the wall structure of the trachea, esophagus, intestines, urethra, ureter, and blood vessels.

such a way that they enable the physiological functions of the tubular organ.

Depending on the physiological functions that each tubular organ has to fulfil, each layer of the tubular wall will have its own biological and mechanical properties, resulting in great differences in the hierarchical structure of the different tissues. Thus, it is important to look in detail into the different layers of the tubular wall and into their physiological functions, taken individually and as a whole (i.e., 4-layered wall structure). Moreover, it is important to investigate the correlations existing between the anatomy (hierarchical structure), the physiological function, and the mechanical and biological properties of a specific tubular organ. The main challenge when engineering a BAO with specific physiological functions is to meet the MRs and BRs. Table 1 gives an overview on (i) anatomical hierarchical structure, (ii) physiological functions, and (iii) MRs and BRs for each of the previously mentioned tubular organs.

Strategies for Processing Constructs for the Regeneration of Tubular Organs

In this section, 3 processing techniques (i.e., 3DBP, sES, and MEW) that enable the development of hollow tubular constructs will be introduced. An overview of the SOTA of each processing technique used for engineering one of the 4 tubular organs discussed above will be given. In particular, the correlations between processing, mechanical and biological performances will be discussed. Then, the potential of clinical translation of these tubular constructs will be evaluated.

Processing Techniques for the Development of Tubular Constructs to Regenerate Hollow Tubular Organs

Three-Dimensional Bioprinting

3DBP is a fabrication method that, starting from a computer-aided design model, creates a 3D construct in a layer-by-layer manner [Murphy and Atala, 2014]. As the "bio" term suggests, it involves biologically derived materials and/or cells [Moroni et al., 2018]. This technique allows the creation of constructs made of multiple materials and cell types in the same process, following a design-specific distribution. 3DBP techniques are usually classified into 3 categories, depending on the working principle of the layer-by-layer deposition process. They can be distinguished in (i) microextrusion-based, (ii) inkjet-based, and (iii) laser-assisted bioprinting (Fig. 3). For detailed information on the working principles of each bioprinter type, the authors suggest the reviews of Murphy and Atala, [2014], Holland et al. [2018], Van Hoorick et al. [2019], and Jeong et al. [2020].

Many advantages have been reported in literature on the 3DBP technique. One of them is the precise control at the micrometric scale of the biomaterial deposition. This allows to obtain a controlled porosity, in terms of both geometry and size, and to accurately mimic the physio-

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Table 1. Anatomy, physiolocial functions and requirements per system

	Anatomical key points	Physiological functions	Construct design: Mechanical requirements (MR)	Construct design: Biological requirements (BR)	References
Respiratory system (Trachea)	- Semiflexible tube, outer diameter (D) = [1.5-2] cm, length (L) of [10-13] cm - It is composed of several layers, including (1) mucosa layer: composed of a pseudostratified ciliated epithelium containing ciliated cells, goblet cells, basal cells and neuroendocrine cells, (2) submucosa layer: is a connective tissue layer rich in elastin deep to the mucosa and contains seromucous glands and smooth muscle, and (3) the submucosa is supported by 15 to 20 horseshoe-shaped rings of hyaline cartilage, which is in turn encased by the adventitia layer (i.e. the outermost layer of connective tissue)	- It conducts air between the larynx and the bronchi - It lengthens and widens during inhalation, shortens and narrows during exhalation - It is a conduit for ventilation, clears secretions, and warms, moistens and cleans the air from the respiratory system - It has an intrinsic defensive mechanism - Mucosa: plays a role in production of mucus and thus in moistening, cleaning and protecting the air - Submucosa: maintain the trachea open while adjusting lumen diameter during respiration - Adventitia: enables movement within the neck and thorax	1. Necessity of an airtight lumen 2. It should have elastic elements to make it flexible enough to stretch and move inferiorly during inspiration, and recoil during expiration (elastic modulus: [1-20] MPa, compliance [40-60] %/45 mmHg) 3. It should keep the airway open and should not collapse, despite pressure changes occurring during breathing (max. stress [0.25-7] MPa, max. strain [5-40] %)	1. Necessity of an uninterrupted lining of ciliated epithelium 2. It should mimic the submucosa and/or adventitia layer 3. It should be able to self-repair, remodel, revascularize and regenerate without the risk of rejection	SYS: [Ott et al., 2011; Brand-Saberi and Schäfer, 2014; Hamilton et al., 2014; Haykal et al., 2014; Kojima and Vacanti, 2014; Crowley et al., 2015; Chiang et al., 2016; Law et al., 2016; Safshekan et al., 2016; Siddiqi, 2017; Boazak and Auguste, 2018; Raja et al., 2018; Udelsman et al., 2018; Dhasmana et al., 2020] MR: [Rains et al., 1992; Trabelsi et al., 2010; Safshekan et al., 2017; Eskandari et al., 2018]
Digestive system (Esophagus and intestines)	- Gastrointestinal (GI) tract is approx. 5 m long. The esophagus = muscular tubular structure (L = approx. 25 cm), small intestine = convoluted tube with D = [2.5-4] cm, L = [2-4] m, large intestine: D = approx. 7 cm, L = 1.5 m - It consists of 4 layers: (1) mucosa layer: most inner layer, has an epithelium, lamina propria and muscularis mucosae, contains gland cells, endocrine cells, small blood vessels, nerve fibers and lymphatic cells, (2) submucosa layer: external to mucosa, contains areolar connective tissue, blood and lymphatic vessels, and nerve fibers, (3) muscularis externa layer: surrounds the submucosa, is a thick muscle layer consisting of an inner and outer longitudinal layer and a nervous system in between these 2 layers, (4) serosa layer = the visceral peritoneum, formed of areolar connective tissue covered with 1 layer of epithelial cells (i.e. mesothelium)	- It conveys food from the pharynx to the pharynx (esophagus) - It enhances the absorption of nutrients, transits food and excretes waste (intestines) - Mucosa: helps in production of mucus, and helps in absorption and secretion - Submucosa: supports the mucosa and joins it to the muscular layer - Muscularis externa: contributes to the gut mobility (i.e. contractions of smooth muscles in the GI tract wall) - Serosa: connects the GI tract to the abdominal wall and neighboring structures - The GI function is mainly controlled by the enteric nervous system	1. It should not leak 2. It should be able to be exposed to repeated cycles of stretching, and should have a high degree of compliance; Should consider different muscle types and their orientation: stronger in longitudinal than in radial direction (elastic modulus: [1-3] MPa, shear modulus [5-180] kPa, ultimate strength [1-3] MPa, compliance [4-8] mm^2/mmHg) 3. Other important parameters: viscoelasticity, dilation and intraluminal pressure for rupture (max. stress [2-5] MPa, max. strain [15-30] %, burst pressure [30-55] kPa)	1. Formation of mucosal epithelium 2. It should mimic the other layers of the GI tract tissue & several complex cell types 3. It should resist gastric acid, and no stenosis should occur	SYS: [Egorov et al., 2002; Marieb and Hoehn, 2010; Bitar et al., 2014; Luc et al., 2014; Maghsoudlou et al., 2014; Fedoruk and Hong, 2014; Londono and Badylak, 2015; Jensen et al., 2015; Poghosyan et al., 2016; Arakelian et al., 2018; Urbanska et al., 2018; Noh, 2018; Dosh et al., 2018; Hussey et al., 2018; Kanetaka et al., 2018; Kanetkar and Ekenseair, 2019; Kovler and Hackam, 2019; Jones et al., 2019; Qi et al., 2020] MR: [Lomholt, 1992; Habib et al., 1994; Gregersen and Kassab, 1996; Rao et al., 1996; Takeda et al., 2002; Vanags et al., 2003; Yang et al., 2004; Bhrany et al., 2006; Bleier et al., 2008; Baiguera et al., 2012; Schleifenbaum et al., 2016; Bu et al., 2017]

Table 1 (continued)

	Anatomical key points	Physiological functions	Construct design: Mechanical requirements (MR)	Construct design: Biological requirements (BR)	References
Urinary system (Ureters and urethra)	- Ureters: L = [25-30] cm, D = [3-4] mm, urethra: L = [18-23] cm (men), and L = approx. 4 cm (women) - Ureters: (1) lined by an urothelium layer (i.e. urothelial cells), and a smooth muscle layer in the more one-third distal part, (2) lamina propria: made up of loose connective tissue with many elastic fibers, blood vessels, veins and lymphatics, (3) two muscular layers (i.e. inner longitudinal layer and outer circular layer of muscle) surround ureter lumen; lower third of the ureter has a 3rd muscular layer, (4) adventitia layer: contains blood vessels, veins and lymphatic vessels - Urethra: (1) mucosa layer: stratified columnar epithelium, (2) submucosa: surrounds the mucosa layer, (3) muscular layers (adventitia layer): inner longitudinal muscle layer and outer circular muscle layer, and (4) adventitia layer: connective tissue	- It transports urine from kidneys to bladder (ureters) and from bladder out of the body (urethra) for excretion (women and men), additional function of urethra in men: ejaculation - Mucosa and submucosa: respond to stretches and contractions; protects the stroma from urine; is an effective permeability barrier; helps in production of mucus - Muscular layers: combination of longitudinal and circular muscles provides strong contraction power - Adventitia layer: foresees blood supply	1. It should not leak 2. It should withstand fluid shear stress and radial pressure (i.e. occurring during urine storage and transport) (max. stress [1-10] MPa, failure stretch [1.2-1.9], burst pressure [500-550] mmHg) 3. It should be able to restore the peristaltic waves on the reconstructed segment (elastic modulus: [1-10] MPa, tensile strength [4-9] MPa)	1. It should enable generation of a functional urothelium, and regenerate the smooth muscle cell layer 2. It should be resistant to the toxic environment (i.e. contact with urine) & should protect the underlying tissue from urine (i.e. function as an efficient barrier) 3. It should include vascularization in smooth muscle cell layers, and nerve regeneration	SYS: [Sloff et al., 2014; de Jonge et al., 2015; De Kemp et al., 2015; Engel et al., 2015; Kloskowski et al., 2015; Versteegden et al., 2017; Sievert, 2017; Singh et al., 2017; Davis et al., 2018; Zou and Fu, 2018; Adamowicz et al., 2019; Orabi, 2019] MR: [Yin and Fung, 1971; Nakagawa, 1989; Spirka et al., 2013; Shilo et al., 2014; Yao et al., 2015; Sokolis et al., 2017; de Jonge et al., 2018; Petsepe et al., 2018; Sokolis, 2019; Natali et al., 2020]
Circulatory system (Blood vessels)	- Arteries: D = [5-10] mm and T = 1 mm, veins: D = [5-20] mm and T = 0.5 mm - It consist of 3 layers: (1) tunica intima, most inner layer, in direct contact with blood, that consists of 1 layer of endothelial cells aligned in the direction of the blood flow and an underlying basal lamina, (2) tunica media, composed out of different layers of mostly circularly arranged smooth muscle cells in an ECM of collagen, elastin and proteoglycans, (3) tunica adventitia, composed of a dense network of collagen fibers that include fibroblasts and fibrocytes, this layer is infiltrated with nerve fibers, lymphatic vessels, and sometimes a network of elastic fibers and the vasa vasorum - The tunica media is separated from the tunica intima and tunica adventitia by an internal and external elastic lamina	- Arteries: carry blood away from the heart, veins: carry blood towards the heart - 3 layers: repairing, remodeling and maintaining the blood vessel structure and function (i.e. transport of oxygen, nutrients, hormones and cellular waste products throughout the body) - Tunica intima: critical role in tissue homeostasis, thrombo-resistant barrier to enable laminar blood flow, regulates transport of substances across endothelium, controls vessel tone, platelet activation, adhesion and aggregation, and leukocyte adhesion - Tunica media: regulates circulatory dynamics by providing contractile and relaxation response, and muscle tone, produces 'active tension' under vasomotor stimulation, alters the total tension, synthesizes and organizes ECM of the vascular wall - Tunica adventitia: reinforces the vessel and enables anchoring to surrounding tissue, prevents vessel rupture and pulsatile deformation, responds to vascular stresses	1. It should not leak 2. It should withstand physiological pressures; Should be non-linear elastic, characterized by stiffening with increased pressure to protect the vessel wall from rupture (elastic modulus: [1-2] MPa, burst pressure: [2031-4225] mmHg, compliance: [4.5 - 6.2] %/100 mmHg, max. stress: [1-2] MPa, max. strain: [0.25-0.75] MPa) 3. It should by highly resilient, a large proportion of energy input during systolic inflation should be recovered by elastic recoil; Should induce low hysteresis during inflation - deflation cycle	1. It should consist of a smooth, friction-reducing and semi-permeable membrane (i.e. endothelium, tunica intima) that is in contact with blood; Should be non-thrombogenic 2. It should also mimic the tunica media and tunica adventitia 3. It should respond to vasomotricity	SYS: [Holzapfel and Ogden, 2003; Zhang et al., 2007; Wagenseil and Mecham, 2009; Martinez-Lemus et al., 2009; Naito et al., 2011; Ait-Oufella et al., 2012; Nemeno-Guanzon et al., 2012; Cleary et al., 2012; Seifu et al., 2013; Xu and Shi, 2014; Catto et al., 2014; Fernandez et al., 2014; Benrashid et al., 2016; Pashneh-Tala et al., 2016; Tuan-Mu et al., 2016; Chen and Kassab, 2016; Elliott and Gerecht, 2016; Wissing et al., 2017; Song et al., 2018] MR: [Dobrin, 1973; Karimi et al., 2013; Chen and Kassab, 2016]

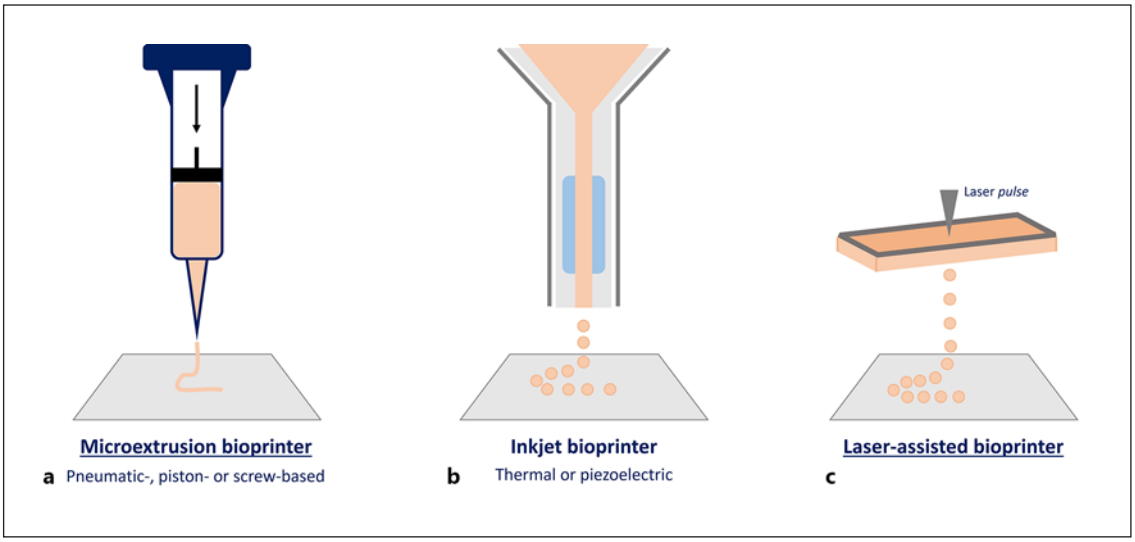

Fig. 3. 3DBP process: bioprinters classification based on the working principle. **a** Microextrusion bioprinter, **b** Inkjet bioprinter, **c** Laser-assisted bioprinter. Image adapted from Murphy and Atala [2014].

logical structure of the native organs [Li et al., 2016]. Moreover, the possibility to combine multiple materials and cell types in the same process, with specific arrangements, allows to overcome the limitations of conventional fabrication techniques and it brings TERM closer to the complexity of native tissues. Finally, despite not yet used in clinical practice, in a future perspective, 3DBP will allow the fabrication of patient-specific BAOs, starting from the patient's medical images (e.g., magnetic resonance imaging) [Sahai and Gogoi, 2020]. This customization would improve the SOTA of regenerative medicine.

However, the formulation of biomaterials and cell components responding to the bioprinting requirements is the main challenge of this technique, and the final construct accuracy strongly depends on it [Panwar and Tan, 2016]. Additional drawbacks are (i) the possible cellular damage due to the stress applied during the process, and (ii) the use in some cases of temperatures or light wavelengths incompatible with cell survival. Table 2 shows an overview of the SOTA on 3DBP of tubular organs.

Solution Electrospinning

sES is a versatile processing technique that relies on the application of a high voltage electrical force to enable the production of micro- and nano-scale fibers from a polymer solution and deposit these fibers on a suitable collector. The high voltage (within a range of several kV, typically between 5 and 20 kV) generates electric charges on the polymer solution. These electric charges accumulate on the polymer surface until they eventually overcome the surface tension and form a Taylor cone. This results in an electrically charged polymer jet that is drawn from the tip of the Taylor cone and stretches in the electric field towards the oppositely charged collector such as a plate, a rotating mandrel, etc. As the polymer moves towards the collector, the solvent evaporates, and the jet solidifies, forming solid micro- and nano-scaled fibers. A schematic representation of the sES process and the different elements constituting the sES set-up are illustrated in Figure 4. A detailed description of the fundamentals of sES can be found in the book of Bosworth and Downes [2011].

Various factors influence the sES process, including solution parameters (i.e., polymer concentration and molecular weight, solution viscosity and conductivity, surface tension, solvents), process parameters (i.e., applied voltage, flow rate, collecting electrode, needle tip-to-collector distance, diameter of the needle tip), and environmental parameters (i.e., temperature, humidity). All these factors have been described in detail by Ibrahim and Klingner [2020] in a review on electrospun polymeric nanofibers and will not be discussed further in this review.

The main advantage of using sES as a processing technique for TERM is the production of fibrous networks that resemble those of the natural ECM in terms of hierarchical organization and properties. Other advantages include the high surface-to-volume ratio of the fibers, high aspect ratio, tunable porosity, flexibility to tailor sur-

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Table 2. 3D Bioprinting as a fabrication technique

3D bioprinting for regeneration of	References/study	Material choice	Cell source	Design idea and focus on anatomical key points/ physiological functions in the study	Mechanical and biological pertinence							
					MR 1	MR 2	MR 3	BR 1	BR 2	BR 3	VIT	VIV
Respiratory system	[Bae et al., 2018]	Poly(ε-caprolactone) (PCL) + sodium alginate	Rabbit bone marrow derived mesenchymal stem cells (MSCs), rabbit epithelial cells (ECs)	In vivo implantation of a multilayered PCL-sodium alginate artificial trachea with separate layers of chondrogenic differentiated MSCS and ECs	N	N	N	E	E	S	n	y
	[Chang et al., 2014]	PCL + fibrin	Rabbit bone marrow derived MSCs	3D printing of a half-pipe-shaped PCL scaffold for tracheal defect covering, seeded with MSCs embedded in fibrin. In vivo implantation in rabbit tracheal defect	N	N	N	E	S	N	y	y
	[Kaye et al., 2019]	PCL + alginate/collagen hydrogel	Chondrocytes isolated from cartilage	In vivo implantation of a PCL partial ring segment with multiple empty channels filled with alginate/collagen hydrogel containing chondrocytes	N	N	N	N	S	N	n	y
	[Pan et al., 2019]	PCL	Rabbit bone marrow derived MSCs	Optimization of a cellularized PCL scaffold: Study of the effects of pore size (from 200 μm to 600 μm) and of surface modification (hydrolysis/amination/nano silicon dioxide-NSD treatment) on mechanical and biological properties	N	E	E	S	S	S	y	y
	[Park et al., 2019]	PCL + sodium alginate hydrogel	Rabbit nasal ECs, rabbit auricular cartilage cells	Multilayered tubular construct, with alternating PCL and alginate. Separation of epithelial and cartilage layer. In vivo study up to 12 months	N	N	N	E	S	N	y	y
	[Ke et al., 2019]	PCL + hyaluronan-based commercial hydrogel	Human mesenchymal stem cells (hMSCs)	Patient-specific design of a printed trachea, cellularized with human derived MSCs. Optimization of pore shape and size for cell viability and post-printing differentiation	N	E	N	N	S	N	y	n
	[Gao M. et al., 2017]	PCL	Rabbit chondrocytes from auricular cartilage	Development of a scaffold for the whole-segment tracheal repair, resembling the rabbit trachea shape. In vivo implantation in rabbits	N	N	N	S	E	S	y	y
	[Machino et al., 2019]	Cellular spheroids	Human Knee articular chondrocytes, human dermal fibroblasts, human bone marrow-derived MSCs, human umbilical vein endothelial cells (HUVECs)	Development of a scaffold-free tracheal structure, based on multicellular spheroids. In vitro biological and mechanical characterization and in vivo implantation in rats	N	E	S	N	S	N	y	y
	[Taniguchi et al., 2018]	Cellular spheroids	Rat rib cartilage chondrocytes, bone marrow-derived MSCs and lung endothelial cells	Development of a scaffold-free tracheal structure, based on multicellular spheroids. In vitro mechanical characterization and in vivo implantation in rats	N	S	N	S	N	S	y	y
	[Hsieh et al., 2018]	Waterborne biodegradable polyurethanes (PUs)	Human umbilical cord and placenta-derived MSCs, human induced pluripotent stem cell-derived MSCs	Optimization of PU bioinks based on mechanical properties and degradation rate, in order to promote cell proliferation and chondrogenic differentiation. Use of liquid-frozen deposition manufacturing (LFDM) as BP technique. Assessment of mechanical properties	E	E	N	N	S	N	y	y
Digestive system	[Takeoka et al., 2019]	Cellular spheroids	Human dermal fibroblasts, esophageal smooth muscle cells (SMCs), bone marrow-derived MSCs, umbilical vein endothelial cells	Development of a scaffold-free esophagus based on multicellular spheroids. In vitro optimization of spheroids composition and mechanical characterization; in vivo implantation in rats	S	N	S	E	S	S	y	y
	[Kim et al., 2019]	PU and PCL	Human adipose-derived MSCs	Combination of electrospun nanofibers and 3D printed strands to obtain adequate both biological and mechanical properties	N	S	S	E	S	S	y	y
	[Chung et al., 2018]	PCL	NIH 3T3	Combination of electrospinning and 3D printing to obtain a reinforced tubular construct for in vivo implantation in rat animal model	N	S	S	S	N	N	y	y

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Table 2 (continued)

3D bioprinting for regeneration of	References/study	Material choice	Cell source	Design idea and focus on anatomical key points/ physiological functions in the study	Mechanical and biological pertinence							
					MR 1	MR 2	MR 3	BR 1	BR 2	BR 3	VIT	VIV
Urinary system	[Zhang et al., 2017]	PCL and Poly(lactide-co-caprolactone) (PLCL)	Rabbit bladder urothelial cells (UCs) and SMCs	Optimization of a co-polymer formulation with mechanical properties (tensile stress, strain, Young's modulus) comparable to those of native rabbit urethra. Separate cellularized layers of UCs (internal side) and SMCs (external side)	N	E	N	E	N	N	y	n
	[Pi et al., 2018]	Gelatin methacryloyl (GelMA) + alginate + poly(ethylene glycol) (PEG) acrylate with tripentaerythritol core (PEGOA)	Human urothelial cells (HUCs) and human bladder smooth muscle cells (HBdSMCs)	Development of multichannel coaxial extrusion system (MCCES) for microfluidic bioprinting of circumferentially multilayered tubular tissues in a single step	N	N	N	S	N	N	y	n
Circulatory system	[Freeman et al., 2019]	Gelatin + fibrinogen	Neonatal human dermal fibroblasts (HDF-n)	Strategy based on blending fibrinogen for collagen synthesis promotion and gelatin for rheological properties. Innovative tubular construct fabrication through a rotating mandrel approach	N	E	N	N	S	N	y	n
	[Gao G. et al., 2017]	Vascular-tissue-derived decellularized extracellular matrix (VdECM) and alginate	Endothelial progenitor cells (EPCs)	Bioprinting using a co-axial strategy, for delivering EPCs and proangiogenic drugs, loaded poly(lactic-co-glycolic) acid microspheres, for the treatment of ischemic injuries	N	N	N	S	N	N	y	y
	[Itoh et al., 2015]	Multicellular spheroids	HUVECs, human aortic SMCs, human normal dermal fibroblasts	Scaffold-free fabrication of small diameter vessels by using multicellular spheroids, printed in needle-arrays. In vivo implantation in rats to explore the remodeling and cell migration/arrangement	N	N	N	S	S	N	y	y
	[Gao Q. et al., 2017]	Sodium alginate	L929 mouse fibroblasts, MOVAS mouse smooth muscle cells, HUVECs	Fabrication of a vessel-like structure with multilevel fluidic channels, using a coaxial nozzle-assisted bioprinting. The hollow sodium alginate filaments are deposited in spiral shape on a rotating rod. Possibility of both chemical and mechanical loading	N	S	N	S	E	N	y	n
	[Gao G. et al., 2019]	Pluronic F127, VdECM from porcine aorta	HUVECs, human aortic SMCs	Fabrication of a biomimetic small diameter vessel with separate tunica intima-like and tunica media-like layers, using a triple coaxial nozzle	N	S	N	S	S	S	y	y
	[Jang et al., 2020]	PCL and sodium alginate	Canine bone marrow-derived MSCs	Triple layer printed vessel for (i) enable materials exchange, (ii) promote differentiation into endothelial-like cells and (iii) protect from blood leakage	S	N	N	S	N	N	y	y
	[Li L. et al., 2020]	Gelatin, sodium alginate and carbon nanotubes	Mouse epidermal fibroblasts	Use of carbon nanotubes for improving mechanical strength of natural hydrogels in tubular vascular constructs. Fabrication through extrusion and rotating mandrel combined approach	S	E	N	N	S	N	y	n
	[Xu et al., 2018]	Silicone elastomer SE1700 as scaffold material, decellularized extracellular matrix	HUVECs, human aortic vascular SMCs, human dermal fibroblasts–neonatal	Multistep approach based on a silicone porous scaffold for 3 layers tubular construct, mimicking the physiological multilayered structure of the blood vessel wall	N	N	N	S	E	N	y	n

MR, mechanical requirements (see Table 1); BR, biological requirements (see Table 1); ECs, epithelial cells; SMCs, smooth muscle cells; S, studied; E, explored; N, not assessed; VIT, in vitro; VIV, in vivo; y, yes; n, no.

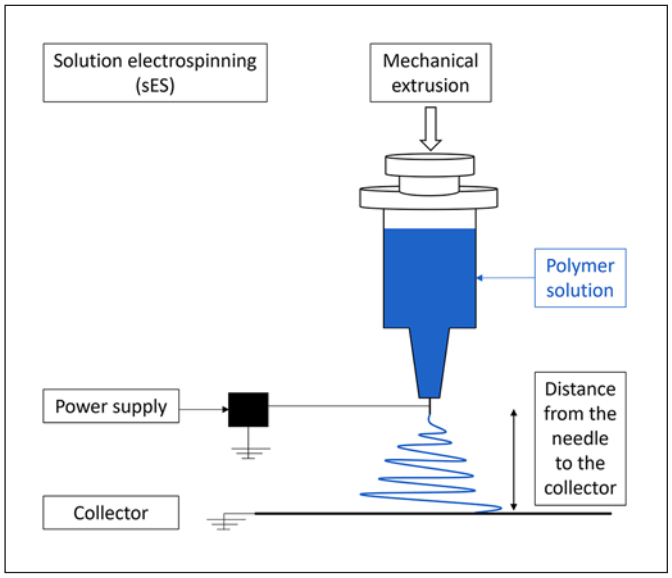

Fig. 4. sES process: different elements required and overall schematic.

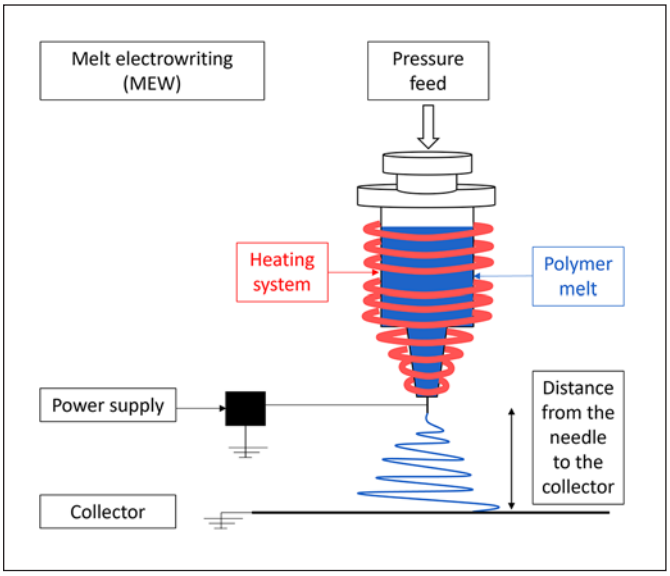

Fig. 5. MEW process: different elements required and overall schematic.

face properties, and the possibility to produce fibers from a large variety of materials. Electrospun scaffolds are known to provide a good microenvironment for cell adhesion, proliferation, and differentiation [Mo et al., 2019; Oprea et al., 2019].

Even though the sES process has been known since the 1930s, it gained renewed interest in the last decades due to the inception of advanced electrospinning set-ups (e.g., side-by-side ES and coaxial ES). These advanced set-ups have the ability to produce scaffolds with multiple layers, made of multiple materials, with gradients, with fiber alignment, with multiphasic fibers, with core-shell fibers, with drug-loaded fibers, etc [Subbiah et al., 2005; Moghe and Gupta, 2008; Sill and von Recum, 2008; Bhardwaj and Kundu, 2010]. Therefore, it has been extensively used in the research focusing on the development of scaffolds for various TERM applications [Lelkens et al., 2008; Sell et al., 2010; Jin et al., 2012; Jiang et al., 2014; Erdem et al., 2016; Kennedy et al., 2016; Pien et al., 2021]. In Table 3, a summary of recent research studies using sES for the fabrication of tubular scaffolds for the regeneration of the 4 tubular organs described in Part 1 is given.

Melt Electrowriting

MEW process is similar to sES, except that in MEW a polymer melt is used instead of a polymer solution [Willerth, 2017; Yang et al., 2018]. Therefore, an extra heating system to heat up the polymer is needed in the MEW setup (Fig. 5). As in sES, an electrostatically ejected jet is drawn as a polymer jet which then cools down and solidifies either in air or on the collector. A low variation in fiber diameter can be obtained due to the high viscosity and low charge of these polymer melts. In combination with a moving collector, the MEW process enables (i) to directly write a 3D scaffold, and (ii) the rational design of scaffolds with control over pore size and pore interconnectivity [Jin et al., 2020]. More specifically, MEW allows to fabricate scaffolds with high reproducibility using a computer-controlled layer-by-layer approach (similar to fused deposition modelling technologies including 3DBP). In other words, MEW fibers can be precisely deposited to generate constructs with predefined architectures [Hochleitner et al., 2015]. Another advantage of MEW compared to sES is that it has no solvent evaporation, and thus, toxicity issues associated with solvents can be avoided [Dalton et al., 2015; Muerza-Cascante et al., 2015; Brown et al., 2016].

The MEW technique and its use in TERM applications have already been extensively reviewed by Dalton et al. [2013], Muerza-Cascante et al. [2015], and Afghah et al. [2019]. The most recent literature has been summarized last year by Robinson et al. [2019] and will therefore not be described in detail in this review. In addition to the optimization of general processing parameters, research has also focused on the optimization of the MEW process with the aim to fabricate hollow tubular constructs (and

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Table 3. Solution electrospinning as a fabrication technique

ES for regeneration of	References/study	Material choice	Biological model	Design idea and focus on anatomical key points/ physiological functions in the study	Mechanical and biological pertinence							
					MR 1	MR 2	MR 3	BR1	BR 2	BR 3	VIT	VIV
Respiratory system	[Townsend et al., 2018]	PCL	Acellular	Design combining electrospun fibers to promote tissue integration, while remaining air-tight when wet and 3D printed rings to hold the airway open and provide external strength	E	N	E	S	N	S	n	y
	[Ott et al., 2016]	PCL and poly-lactic-co-glycolic acid (PLGA)	Acellular	Effect of the design of a fibrous, polymeric scaffold (organized in monolayers, blends, gradient, bilayers, and with or w/o 3D printed structural ring supports) on maintaining a patent airway	N	S	S	N	N	N	n	n
	[Hinderer et al., 2012]	PCL and gelatin, with decorin (structural and functional proteoglycan)	Human primary airway epithelial cells (hPAECs)	Generation of functional 3D scaffolds with low immunogenicity for hPAECs expansion, and the feasibility to include proteoglycans	N	N	N	S	N	E	y	n
	[O'Leary et al., 2020]	PCL and chitosan, and all-*trans* retinoic acid (atRA)	CALU3 bronchial EC line	Development of a nanofibrous scaffold loaded with a signaling molecule (atRA) to increase mucociliary gene expression	N	N	N	S	N	N	y	n
	[Townsend et al., 2020]	PCL and poly(L-lactide-co-caprolactone) (PLACL) blend, cell adhesion peptide or antimicrobial compound	Acellular	Design of an electrospun construct, that includes a cell adhesion peptide or an antimicrobial compound for enhanced cell adhesion and antimicrobial activity, respectively and its effect on re-epithelialization, lumen volume and tissue (in-)growth	E	N	E	S	N	S	y	y
	[Bridge et al., 2015]	Polyethylene terephthalate (PET)	CALU3 epithelial cells, MRC5 fibroblasts and ASM cells	Design of a co-cultured model mimicking the three main micro-environments of the airway bronchial wall	N	N	N	Y	Y	N	y	n
	[Dharmadhikari et al., 2020]	PET and PU	Bone marrow- derived mononuclear cells (BM-MNCs)	Defining the role of cell seeding, the mechanism of respiratory epithelialization and proliferation and the role of inflammatory immune response in trachea regeneration using electrospun scaffolds	N	N	N	Y	N	N	y	y
	[Clark et al., 2016]	PET and PU	Bone marrow-derived mononuclear cells	Study of the effect of cell seeding on neotissue formation, and the seeding efficiency on normal porosity versus high porosity electrospun tubular constructs	N	N	N	S	E	N	n	y
	[Kang et al., 2019]	Polylactide (PLA)	Fibroblasts L929	Design of multileveled (antibacterial) structural fibrous membranes by patterned electrospinning for better cell infiltration and promotion of tissue growth	N	S	S	N	N	N	y	y

Table 3 (continued)

ES for regeneration of	References/study	Material choice	Biological model	Design idea and focus on anatomical key points/ physiological functions in the study	Mechanical and biological pertinence							
					MR 1	MR 2	MR 3	BR1	BR 2	BR 3	VIT	VIV
	[Wu et al., 2017]	poly(L-lactide-co-caprolactone) (P(LLA-CL) and collagen	Autologous tracheal ECs and chondrocytes	Design of a bilayered tubular scaffold via electrospinning, the effect of cell-seeding and pre-vascularization of the scaffold, and its potential for chondrocyte activity and tracheal EC adhesion and proliferation	N	N	N	S	S	E	n	y
Digestive system	[Yekrang et al., 2016]	PU	Acellular	Design of a bilayered construct in which the nanofibrous layer is developed to mimic the thin elastic tissues in the lamina propria and thin elastic fibers in the muscularis mucosae (submucosa)	E	S	S	N	N	N	n	n
	[Soliman et al., 2019]	PU	Porcine adipose-derived MSCs	Regeneration of an epithelium on the luminal surface, and a muscle layer on the exterior surface by design of a multilayered tubular scaffold	N	N	E	S	S	N	y	n
	[La Francesca et al., 2018]	PU	Autologous adipose-derived mesenchymal stem cells (aMSCs)	Study the effect of seeding aMSCSs on a synthetic electrospun construct on the regrowth of endogenous esophageal tissue (and the different layers)	S	E	E	S	S	N	y	y
	[Wu et al., 2019]	PU	Bone marrow-derived hMSCs	Design of a double-layered tubular scaffold, and by mechanical stimuli simultaneous differentiation into epithelial and muscle lineages	E	E	N	S	S	N	y	n
	[Kim et al., 2020]	PU	Human adipose-derived stem cells (hMSCs)	Design of a two-layered tubular construct (PU electrospun layer with PCL support), seeded with hMSCSs to obtain superior initial epithelialization and muscle regeneration	S	S	E	S	S	N	y	y
	[Chung et al., 2015]	PCL and silk fibroin	Acellular	Assessment of the feasibility of a three-layered scaffold and the regeneration of mucosa and soft tissue	N	N	S	N	E	N	y	y
	[Kuppan et al., 2016]	PCL, poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), gelatin	Non-keratinized, stratified, squamous ECs	Study on the cell-matrix interaction using polymeric random and aligned fibrous tubular constructs and their potential to regenerate the mucosal layer	N	N	N	S	N	N	y	n
	[Boomer et al., 2014]	PCL, PU, poly(L-lactic acid) (PLLA), poly(D-lactic acid-co-glycolic acid) (PDLGA), poly(glycolic acid) (PGA)	Acellular	Study on various electrospun tubular constructs and their potential use for tissue engineering the intestine: tissue infiltration and mechanical characteristics	N	E	E	E	N	N	y	y
	[Barron et al., 2018]	PCL, PLGA, PU, polydioxanone (PDS), poly(D,L-lactide-co-glycolide)	Pig oesophageal-derived mucosal cells	Investigation of the regeneration of GI tissue, including epithelial, submucosal and skeletal muscle layers with vascularization using a seeded electrospun graft	N	E	E	S	S	N	y	y

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Table 3 (continued)

ES for regeneration of	References/study	Material choice	Biological model	Design idea and focus on anatomical key points/ physiological functions in the study	Mechanical and biological pertinence							
					MR 1	MR 2	MR 3	BR1	BR 2	BR 3	VIT	VIV
Urinary system	[Kloskowski et al., 2014]	PLACL	Acellular	Study on the use of an acellular tubular construct and its potential in regenerating the urothelium layer and the smooth muscle layer	E	N	N	S	N	N	y	y
	[Lv et al., 2018]	PLLA and PEG	Human amniotic mesenchymal cells (hAMSCs) and acellular	Study on the influence of pre-seeding hAMSCSs on the tubular electrospun constructs prior to implantation and the resulting effects on urethral epithelium repair, urethral morphology, tissue regeneration, luminal patency and complication incidence	N	E	E	S	N	N	y	y
	[Wei et al., 2015]	PCL, silk fibroin, collagen	Oral mucosal ECs	Study on the use of an electrospun construct to regenerate mucosa for urethral repair	N	N	N	E	N	N	y	n
Circulatory system	[Tan et al., 2017]	PCL	Acellular	Design of a bilayered fibrous scaffold with a thin internal layer of longitudinally aligned fibers and a highly porous external layer to promote cell proliferation, collagen-fiber deposition and the ingrowth of SMCs (media layer) and endothelial cells (endothelium)	E	N	N	E	E	N	y	y
	[Huang et al., 2018]	PCL	Acellular	Design of a triple-layered fibrous construct to promote cell growth and infiltration, focusing on the functions of lumen surface and media layer	E	N	N	S	N	N	y	y
	[Wu et al., 2018]	PCL	Acellular	Study on the long-term performance of a macro-porous electrospun construct in a rat model, with regeneration of neotissue composed of a complete endothelial layer and several layers of SMCs	S	N	E	S	E	E	n	y
	[Abdal-hay et al., 2018]	PCL and PU	Acellular	Design of biphasic tubular electrospun scaffolds to improve the mechanical properties of a vascular graft scaffold: suture retention, burst pressure and compliance	S	E	N	E	N	N	y	n
	[Joy et al., 2019,2020]	PCL, polytrimethylene carbonate (PTMC) and gelatin	Acellular	Fabrication of an electrospun tubular scaffold as media layer (PTMC and gelatin) or as adventitia layer (PCL and gelatin) for blood vessel regeneration	E	N	N	N	N	E	y	y
	[Shi et al., 2019]	PCL and gelatin	Acellular	Design of a hybrid PCL/gelatin vascular graft, functionalized with heparin to improve hemocompatibility with the aim to promote rapid endothelialization and regulate smooth muscle regeneration	E	N	N	S	E	N	n	y

Table 3 (continued)

ES for regeneration of	References/study	Material choice	Biological model	Design idea and focus on anatomical key points/ physiological functions in the study	Mechanical and biological pertinence							
					MR 1	MR 2	MR 3	BR1	BR 2	BR 3	VIT	VIV
	[Li X. et al., 2020]	PCL, poly (D, L-lactide-co-glycolide) and gelatin	SMCs and endothelial cells	Development of a dual-oriented/bilayered electrospun scaffold aiming at cell-specific orientation of SMCs and endothelial cells to mimic the multi-layered, cell-specific oriented spatial structure of the native blood vessels	E	N	N	E	E	N	y	n
	[Ju et al., 2017]	PCL and collagen	Endothelial cells and autologous SMCs	Development of a cellularized vascular construct based on a bilayered electrospun scaffold and autologous cells, and evaluation of the construct on endothelialization and SMC layer	S	N	E	S	S	E	y	y
	[Wang et al., 2017]	PCL, class I hydrophobin (HGFI) and vascular endothelial growth factor (VEGF)	Acellular	Fabrication of electrospun vascular grafts modified with the fusion protein (VEGF-HGFI) to enhance cellularization, endothelium formation, smooth muscle regeneration and capillary formation	S	N	E	S	E	E	y	y
	[Pan et al., 2017]	PCL and PDS	Acellular	Design of a co-electrospun construct and the effect of improved mechanical properties and hydrophilicity to the coverage of endothelial cells and SMC regeneration	S	N	E	S	E	E	n	y
	[Zhou et al., 2017]	PLGA loaded with Val-Ala-Pro-Gly (VAPG) peptide and microRNAs	Acellular	Design of a functional electrospun PLGA construct, loaded with specific adhesive peptides and microRNAs to modulate the phenotype and proliferation of SMCs and prevent intimal hyperplasia	N	N	S	S	E	S	y	y
	[Wu et al., 2018]	PLCL/collagen	Acellular	Fabrication of a bilayered vascular scaffold mimicking the luminal and medial layers, including heparin and anti-CD133 antibody to contribute for lumen anticoagulation functionality and promote development of neo-intima	E	N	N	S	E	N	y	y
	[Kuang et al., 2019]	PLGA, collagen, nanoparticles and PU	Human umbilical vein endothelial cells	Design of a composite bilayered electrospun graft to promote cell proliferation and improve blood compatibility, resulting in a regeneration of an endothelium and smooth muscle	N	N	N	S	E	N	y	y
	[Wen et al., 2020]	Poly(ethylene glycol)-b-poly(L-lactide-co-ε-caprolactone) (PELCL), Arg-Glu-Asp-Val (REDV) peptide	Acellular	Development of a bioactive tri-layered vascular graft encapsulating dual microRNAs to enhance endothelialization, contractile SMC regeneration, and promoting normal extracellular matrix formation	E	N	E	S	E	E	y	y

For abbreviations, see Table 2.

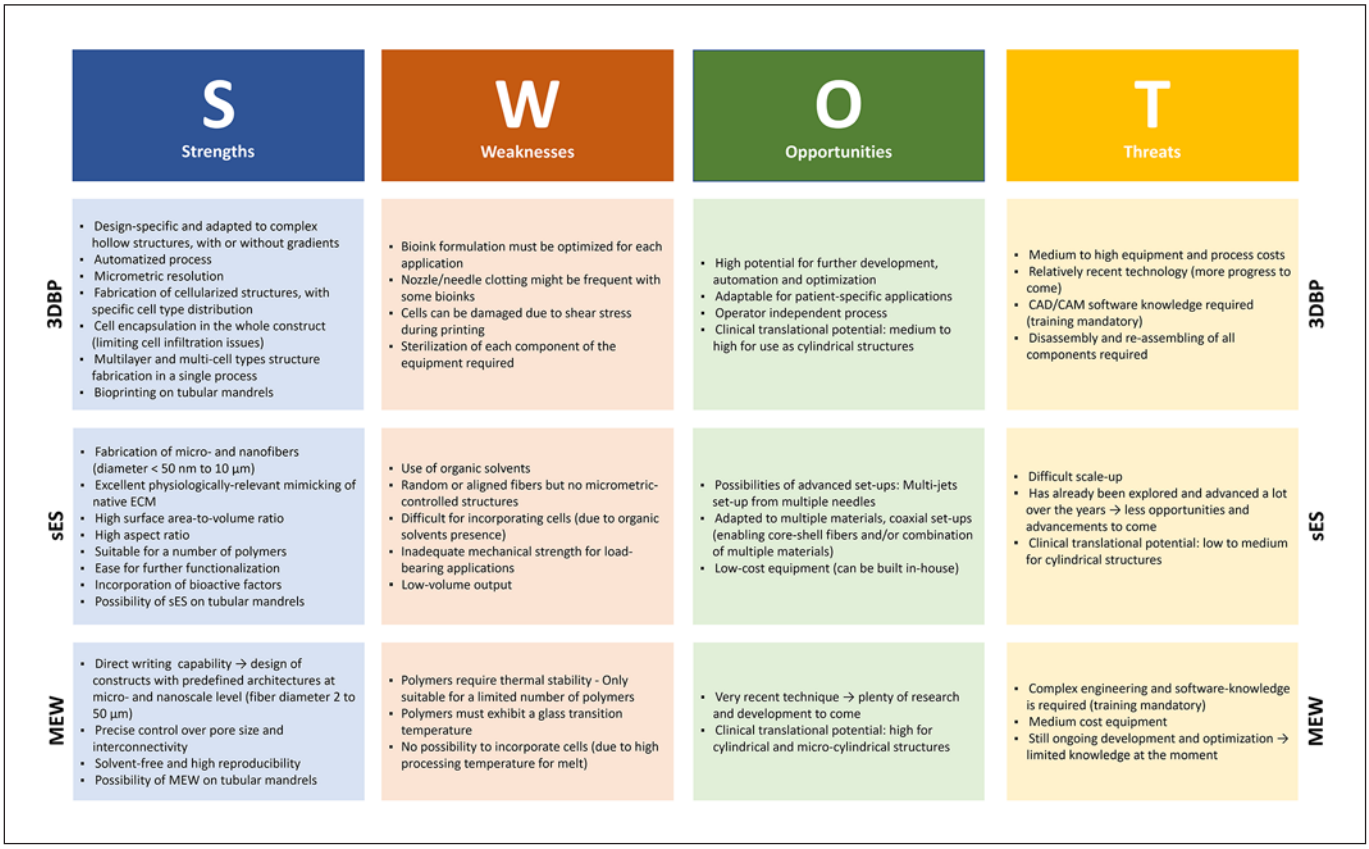

Fig. 6. Strengths, weaknesses, opportunities and threats (SWOT) of the 3 advanced processing techniques discussed in this review. 3DBP, 3D bioprinting; sES, solution electrospinning; MEW, melt electrowriting.

thus, on the fabricating process onto a rotating mandrel). For more details on MEW onto rotating mandrels, and the MEW design parameters of tubular constructs for TERM applications in general, the authors would like to refer to the work of Jungst et al. [2015], Brown et al. [2016], McColl et al. [2018], Ibrahim et al. [2019], and Paxton et al. [2020]. The focus of this review goes to the use of MEW to fabricate tubular constructs for the regeneration of the introduced 4 hollow tubular organs (Table 4).

Strengths, Weaknesses, Opportunities, and Threats

Each one of the presented fabrication techniques has specific advantages and limitations that should be considered when scientists want to develop a BAO. Strengths, weaknesses, opportunities, and threats (SWOT) of each technique are summarized in Figure 6 in a parallel SWOT analysis of the 3 mentioned techniques.

Correlation between Processing, Mechanical and Biological Performances

As discussed above (Part 1), the anatomical hierarchical structure of healthy native tissues (Fig. 2) and their corresponding complex physiological functions result in very specific mechanical and biological design requirements when engineering a BAO (Table 1). On the one hand, the MRs and BRs for the construct design influence the process selection. It is worth noting that when looking into the SOTA of the fabrication, and more precisely into the advanced processing techniques (Part 2), a wide variety of materials and biological models have been investigated (Tables 2, 3, 4). Engineering a bioartificial tubular organ not only depends on the choice of the applied processing technique, its corresponding processing parameters and the construct design, but also on the material properties and on the biological model (i.e., cells and biological cues) selected for the fabrication. This means that a first correlation can be found within the fabrication pro-

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Table 4. Melt electrowriting as a fabrication technique

MEW for regeneration of	References/study	Material choice	Biological model	Design idea and focus on anatomical key points/ physiological functions in the study	Mechanical and biological pertinence							
					MR 1	MR 2	MR 3	BR1	BR 2	BR 3	VIT	VIV
Respiratory system	None on tubular constructs											
Digestive system	None on tubular constructs											
Urinary system	None on tubular constructs											
Circulatory system	[Mazalevska et al., 2013]	PLA and polypropylene (PP)	None	Preliminary study on the design of small diameter vascular prostheses with a multilayered structure; effect of the processing parameters on the structural properties	N	N	N	N	N	N	n	n
	[Chrzanowska et al., 2014]	PLGA and PP	None	Study on the possible sterilization techniques and their effect on the microstructure of MEW tubular constructs for vascular prostheses	N	N	N	N	N	N	n	n
	[Jungst et al., 2019]	PCL	Mesenchymal stromal cells (MSCs) and endothelial colony forming cells (ECFCs)	Guide the neotissue to enable formation of an intraluminal endothelial cell monolayer, while recapitulating the stacking and orientation of vascular SMCs to mimic the tunica media	E	N	N	S	E	E	y	n
	[Pennings et al., 2020]	PCL	Multipotent MSCSs and ECFCs	Evaluation of the simultaneous layer-specific (i.e. tunica intima and tunica media) maturation of cells in a physiologically relevant environment, and establishment of cell phenotypes of endothelial cells and vascular SMCs as well as matrix production	N	N	N	S	E	E	y	n

MEW, melt electrowriting. For further abbreviatons, see Table 2.

cess itself: (i) material choice, (ii) biological model, and (iii) processing technique (including process parameters and construct design). On the other hand, the selection of the fabrication process (i.e., processing, materials, cells) when engineering a BAO influences the resulting mechanical and biological properties of the developed construct. These resulting properties can now be linked back to check if the requirements have been met, and to evaluate the mechanical and biological pertinence of the processing technique. In other words, there is also a correlation between (i) the construct requirements to match (depending on anatomy and physiology) and (ii) the resulting properties obtained (depending on the fabrication process).

These intrinsic correlations are discussed based on examples from literature, in the paragraphs below, and aim at showing the advancements and limitations per technique and/or per tubular organ.

Cellularization of a BAO

As shown in Table 1, some of the physiological functions of each organ rely on the presence of the proper cell types of each layer. For this reason, the cellularization of the scaffold is an important step in engineering BAOs. Because of process-related limitations [Dalton et al., 2015; Hong et al., 2019], both MEW and sES mainly provide a tubular "skeleton", which acts as a mechanical structural support for (i) cell seeding prior to implantation or (ii) to trigger cell migration after implantation. Lv et al. [2016] reported on a bioengineered construct produced by sES for urethral repair, in which they compared (i) a cell-based model [i.e., mesenchymal stem cells (MSCs) seeded prior to implantation] with (ii) an acellular model. Results pointed out that the cell-based models outperformed the acellular models, for urethral defect repair in rabbits. However, the long production time of a cell-based model (i.e., for cell seeding and maturation) and the vast biological expertise required for its fabrication are some of the reasons why acellular models are still widely investigated.

In contrast to MEW and sES, 3DBP has the possibility to directly incorporate cells and/or biological molecules in the construct during its fabrication. Different cell types can be printed in the same process, with the desired spatial distribution, in order to reproduce the physiological multilayered structure of tubular organs. Using this strategy, Bae et al. [2018] were able to print epithelial cells in the inner layer of their trachea construct, well separated from the layer of MSCs. After in vivo implantation in rabbits, this allowed the formation of a ciliated respiratory epithelium, thus fulfilling one of the BRs (BR1 in Table 1).

Regarding the source for the BAO cellularization, Tables 2, 3, 4 show a large use of MSCs as a cell source for the construct cellularization. These multipotent stem cells can be easily harvested from different sources, including bone marrow and adipose tissue, and many studies have demonstrated the possibility to differentiate them into different cell types through biochemical and mechanical cues [Huang and Li, 2008]. The use of MSCs is convenient from a clinical perspective, thanks to the possibility to use an autologous source in the construct fabrication. This is true both at the animal and human trial level, and it is well represented in the tables, where most of the animal in vivo studies have been conducted using autologous MSCs. However, the use of MSCs also implies that at the time of its fabrication, the construct is not able to reproduce the physiological functions shown in Table 1, and thus it does not satisfy the BRs. After a transition period for cell differentiation, the construct should be able to fulfil the BRs and thus should be able to replace the organ functions.

Finally, it is important to consider that 3DBP offers an interesting and unique opportunity to print cellular spheroids, without the support of any additional material [Murata et al., 2020]. This possibility has been further explored and developed in a technique, known as Kenzan method, to create hollow tubular structures starting from needle arrays of cellular spheroids [Moldovan et al., 2017]. The absence of structural biomaterials can be seen as a significant advantage in bioprinting where the bioink formulation is challenging. However, the absence of biomaterials also makes the resulting mechanical properties more variable and unpredictable, and the fabrication process is long and complex. This technique has been explored in almost all applications of TERM of tubular organs, as shown in Table 2. While the early focus was mainly on the biological outcomes of cellular spheroids [Itoh et al., 2015], the development of this technique over the years also allowed to improve and further investigate the mechanical properties. Recently, Takeoka et al. [2019] validated this method for the esophagus. They showed that both excellent biological properties and satisfactory mechanical properties could be achieved both in vitro and in vivo.

Impact of the Processing Technique on Material Structure and Geometry

Both MEW and sES are techniques that enable micro- and nano-scale fiber production. Working at the fiber level constitutes a significant advantage in mimicking natural ECM in terms of hierarchical organization and

properties. However, the fiber deposition in sES is random (or aligned in the direction of rotation when sES is performed with a high-speed rotating mandrel) [Eslamian et al., 2019; Niu et al., 2019] and cannot be controlled in specific, complex patterns. In this direction, MEW opened a new era by enabling the precise control of fiber deposition and alignment in specific 3D patterns [Jungst et al., 2015; Brown et al., 2016; McColl et al., 2018]. These patterns can direct physiological tissue-like cell organization and differentiation. Of note, cell orientation is important to recapitulate the physiological functions of the different layers, individually and as a whole (Table 1). As an example, when bioengineering blood vessels, it is possible to guide the orientation of smooth muscle cells in order to enable vasodilation and vasoconstriction [Jungst et al., 2019]. This has been studied by Jungst et al. [2019], who guided the cell orientation in the media layer (i.e., smooth muscle cells) by varying the angle of the deposited MEW fibers. As suggested by this study and as shown in Table 4, research on MEW mainly focuses on matching the BRs, but not (yet) on the MRs.

3DBP allows to control the material deposition down to the micron level [Li et al., 2016]. Moreover, the 3DBP approach can rely on cell-mediated matrix remodeling, thanks to the possibility to incorporate cells inside the construct. Matrix rearrangement can require a variable period of initial growth and further maturation in vivo, which may take up to months, to achieve a physiologically relevant construct. Freeman et al. [2019] reported the effect of maturation of a bioprinted vascular construct over 45 days in vitro. Volumetric reduction over time was observed, and histology revealed significant matrix changes and fiber alignment. Interestingly, this correlated with the evolution of mechanical properties. At day 0, the constructs did not fulfil the MRs, such as elastic modulus, burst pressure, and ultimate tensile strength. However, maturation and remodeling allowed to withstand a burst pressure of 1,110 mm Hg, which is a promising result in the cardiovascular tissue engineering scenario.

Some researchers also exploited the possibility given by 3DBP to control the direction of the material deposition to obtain layers with different functions (i.e., permeability, cell interaction), starting from the same material. This way, they demonstrated the possibility to obtain multilayered constructs with layer-specific functions. For instance, Jang et al. [2020] alternated poly (ε-caprolactone) (PCL) and sodium alginate layers to obtain a vascular construct. Diagonal cross-striping of PCL allowed to achieve good nutrient exchange between the layers, while helix deposition ensured protection against blood leakage. A similar approach has been shown also by Bae et al. [2018], but in this case for the generation of a tracheal construct. They used PCL diagonal grid patterns with micro-pores for the exchange of growth factors between cells and the surrounding ambient and helical form without pores to keep the different cell lines separated. Like this, they were able to respect the multilayered structure shown in Table 1, in particular, the epithelial layer separated from the other layers.

Impact of the Processing Technique on Material Properties

When comparing the 3 processing techniques, only sES and 3DBP enable the processing of natural materials [Wang et al., 2020], which is not feasible using MEW because of the high thermal stability required for this technique [Muerza-Cascante et al., 2015]. However, when bioengineering one of the 4 presented tubular organs, sES and 3DBP combine natural with synthetic polymers in order to attain the required mechanical properties [Lee et al., 2008]. Since most of the biological macromolecules are also sensitive to degradation or denaturation at higher temperatures, they are widely processed by sES and 3DBP, and seldom by MEW. The synergistic advantages of combining natural and synthetic materials have been shown by Wu T. et al. [2018a]. They have fabricated a bilayered vascular scaffold by combining a synthetic and natural material, and incorporated biomolecules in them. This way, they achieved better compliance performance than the commercial expanded polytetrafluoroethylene and matched compliance with the human saphenous vein, while promoting rapid endothelialization and attaining a similar organization to the native blood vessel [Wu T. et al., 2018b].

The analysis of the SOTA revealed that PCL is the most used synthetic material for 3DBP, sES and MEW applications, thanks to its low melting point and good thermoplastic properties that make it simple to be processed. Moreover, PCL does not degrade into toxic products, and it has been approved by the Food and Drug Administration (FDA; https://www.fda.gov). The study of Pan et al. [2019] clearly shows that it is possible to tune and optimize the properties of bare PCL to obtain excellent mechanical properties. Similarly, Zhang et al. [2017] combined 2 synthetic polymers, PCL and poly (lactide-co-caprolactone), to comply with the MRs of their engineered urethra. However, in many studies dealing with the use of synthetic polymers, despite the application in animal trials, the MRs were not checked, leaving a big lack of information.

Impact of the Hierarchical Structure and Physiological Functions in the Design of BAOs

Despite the importance of the multilayered organization in tubular organs and its role in organ functions, the SOTA reveals only a few studies reproducing the different layers of native tissues. Many groups focus on a single- or double-layered approach, which clearly cannot satisfy all BRs illustrated in Table 1. It is important to consider the whole life of the tubular construct. It is worth noting that after in vitro maturation or in vivo implantation, cell infiltration and/or differentiation have an impact on the biological properties of the construct. As an example, Kim et al. [2019] obtained 80% of mucosal epithelium regeneration in their tissue-engineered esophagus 2 weeks post-implantation in rats. While at day 0, the BR1 was not satisfied, due to the presence in the construct of MSCs only, the implantation allowed to attain the desired biological characteristics in a relatively short time. However, in vivo implantation may also cause inflammation or stenosis, thus adversely affecting the properties of the construct [Kaye et al., 2019].

When designing a BAO, the complex geometry is one of the fundamental requirements. One of the important innovations brought by 3DBP (and also MEW) is the possibility to design complex geometries through computer-aided design models [Paxton et al., 2020; Sahai and Gogoi, 2020]. This is relevant in TERM, since today's technology provides tools to convert medical image data into printable information, allowing for the fabrication of patient-specific designs. Ke et al. [2019] were able to design a trachea based on a CT scan from human patients. This combined with the use of human MSCs, which can be used as an autologous cell source, constitutes the proof-of-concept for clinical translation.

Impact of the Synergetic Combination of Multiple Processing Techniques for BAO Design

An interesting approach is the combination of 2 different techniques, in a multistep process for the final tubular construct fabrication. In this context, the sES and 3DBP techniques have been combined for optimal mechanical and biological properties. Chung et al. [2018] focused on the improvement and control of mechanical performance of their artificial esophagus. They 3D printed sequential reinforcement rings of PCL, which were then combined with a tubular electrospun PCL layer. This allowed increasing the mechanical properties, while keeping a good structure for cell infiltration. Kim et al. [2019] combined electrospun PU nanofibers in the inner layer with 3D-printed PCL strands in the outer layer. The hypothesis of the study was to provide topographical cues for the mucosal layer on the inner part and to give mechanical strength and flexibility to the external layer, thus achieving both biological and mechanical good performance. sES has also been combined with MEW. In this regard, Pennings et al. [2020] used this combination with the aim to induce and maintain multiple cell phenotypes within a biomimetic structure. The sES was used for a randomly oriented layer on the luminal side, whereas the deposition of oriented MEW fibers served as a guidance for MSCs. This way, they have succeeded in inducing layer-specific cell differentiation with a blood-vessel native-like cell organization.

In vivo Studies Involving Tubular BAOs

Several works reported in vivo testing with animal models, both on 3DBP and sES-based constructs. As a general trend, the goal of in vivo testing was to assess the biological response to the tubular construct implantation, while mechanical properties after implantation were rarely reported. The animal model was generally selected based on the tubular organ to be implanted, regardless of the used fabrication technique, i.e., rabbit for trachea.

As example, Gao et al. [2019] performed a complete biological characterization of a 3D bioprinted vessel after implantation in a rat model. In this study, all 3 BRs for bioengineered blood vessels were validated, as reported in Table 1. Ultrasonography was used to assess the non-thrombogenicity and immunohistochemistry to check the multilayer composition and the endothelium integrity. They showed a great potential of the co-axial nozzle technique for the fabrication of artificial vessels. As in this study, in general, immunohistochemistry was widely used by all research groups to assess the biological properties after explantation.

When looking at the SOTA of sES-based constructs for tubular BAO (Table 3), it can be concluded that most research was mainly focused on the study of either biological or mechanical properties. Wu et al. [2017] studied the effect of cell-seeding and pre-vascularization on their bilayered tubular construct in a rat model. Based on this in vivo evaluation, they concluded that pre-cellularized and pre-vascularized constructs resulted in higher capillary regeneration, and in lower immunogenicity, while improving tracheal tissue regeneration. However, they did not assess the mechanical performances. Nevertheless, in some recent studies, research groups have started exploring both biological and mechanical performances. Townsend et al. [2020] mainly focused on studying the BRs in depth in a rabbit model, but in addition, they also

started exploring some of the mechanical properties required to design a functional BAO. The explanted tracheas were studied for the lumen volume, minimum cross-sectional area and the tracheal patency, enabling better fine-tuning of the developed tubular constructs for future studies.

As shown in Table 4, no in vivo testing has yet been reported on MEW-based tubular constructs, due to the very recent introduction of this technique. Research is currently focusing on attaining more in vitro insights, before being able to step into the animal trial phase.

In conclusion, there are important consequences considering the intrinsic correlation between (i) the construct requirements to meet, i.e., the MRs *and* BRs (depending on anatomy and physiology) and (ii) the resulting properties obtained (depending on the fabrication process), i.e., the mechanical *and* biological properties of the final construct.

Clinical Translational Potential for Tubular Constructs Processed by 3DBP, sES and MEW

As previously stated, in a scenario in which heterologous organ transplantation is burdened by the shortage of donor tissue and currently available synthetic grafts show issues in terms of biological and mechanical properties (especially on the long term), bioengineered artificial tissues certainly represent a viable solution. The development of physiologically relevant tubular tissues for regenerative medicine purposes can be used to correct defects, restore functions, or substitute damaged tissues in patients suffering from life-threatening conditions [Holland et al., 2018].

Tissue engineering-based constructs, in their journey from the lab bench to clinical use, are subjected to strict regulation. As stated by the U.S. FDA, the process of development for new medical products and devices can be divided in 5 stages: (1) discovery and concept; (2) preclinical research, comprehensive of in vitro and in vivo testing, and prototype; (3) pathway to approval; (4) FDA device review, and (5) FDA post-market device safety monitoring (U.S. FDA). sES and 3DBP to design, develop and optimize tubular organs have already been reported, while MEW, despite its novelty, is rapidly gaining attention in this field (Tables 2, 3, 4). Interestingly, contrarily to more conventional tissue engineering strategies such as decellularization [Elliott et al., 2012; Gonfiotti et al., 2014], all hereby presented studies are at the preclinical research level according to the FDA subdivision.

The current advanced TERM strategies (such as 3DBP, sES, and MEW) are still affected by some limitations that impeach their successful translation into clinic. Despite the promising results and achievements obtained in the past years, the produced devices are still hampered by a mismatch in functionality (both at the mechanical and biological level) with the native tissues they are intended to substitute [Holland et al., 2018]. Hunsberger et al. [2016] reported that major drawbacks in the clinical transfer of advanced TERM strategies are related to the precise mapping of cells in the developed tissues (their placement, organization, phenotype, and function), reliable sources for cells, immunosuppression, prosthetic tissue integration with the host and vascularization.

Finally, these new technologies evolve in a specific and precise regulatory structure allowing the scaling-up and marketing of tubular BAOs [Mason et al., 2016; Holland et al., 2018]. Although regulatory processes may appear to limit their development, which might be true in some cases, it should also be noted that this constitutes a unique moment for regenerative medicine specialists, including scientists, engineers, industrials, and clinicians, to seed the basics of future regulations.

Regulating a new BAO is a long and complex procedure, which requires time, investment, and collaborations. On the one hand, the International Standards Organization (ISO) has to be involved, mainly because quality control will require testing and evaluation of the final products. ISO is open to extend and add new standards, specific to testing and assessing the mechanical performance, the stability, and the degradability of tubular BAOs. On the other hand, contrarily to what is (sometimes) mentioned in some manuscripts, FDA does not approve biomaterials, nor processes. The FDA is responsible for protecting public health by regulating medical devices (and a panoply of other industrial products, including drugs, tobacco products, food for humans and animals, cosmetics, and radiation-emitting electronic products). Future commercialized BAOs, after having been developed and fully tested in laboratories, must be proven safe and effective to FDA's satisfaction before companies can market them in the interstate American commerce. Future manufacturers must also prove they are able to make the product according to federal quality standards. The FDA does not develop or test products before approving them. Instead, FDA experts review the results of laboratory (in vitro), animal (in vivo), and human preclinical and clinical testing done by the manufacturers. If FDA grants an approval, it means the agency has determined that the benefits of the product outweigh the known risks for the intended use. FDA, and all other country-specific regulatory bodies, will require to be con-

vinced that the proposed BAOs will not present risks for its population. An interesting example is constituted by the recent effort between FDA and the National Institute of Standard Technology, for the collaboration on standards development activities supporting innovation and translation of regenerative medicine products [Arcidiacono et al., 2018]. Standards development can accelerate product development cycles and broaden market opportunities in innovative fields such as regenerative medicine. Standardization provides a forum for the convergence of diverse scientific approaches; standardized approaches to address common scientific challenges can enable broader application of innovative products without stifling continuing innovation. Standardization efforts made by national standards regulatory bodies, industry, and academia can lead to international harmonization and global marketing of regenerative medicine products. Regulation and standardization, together have the potential to facilitate the development and the translation of regenerative medicine products, such as BAOs.

Despite the above considerations, the advancements achieved at the preclinical level by the above-detailed strategies, and the rapid development of processing we witnessed in the last decade, foresee that the gap separating them from the clinic will shortly be filled. In particular, we are convinced that the clinical translational potential of 3DBP of degradable scaffolds with living (including autologous) cells is unique and very high. 3DBP clinical translation would open the era of personalized medicine. For example, from medical images acquired from the patient during the preoperative diagnostic phase, a 3DBP-personalized process could be implemented for developing the required BAO to regenerate the diseased tissue or organ. If on one side this constitutes a confined application, it is on the other side important to highlight the high impact that this would have in some specific clinical cases. The clinical translation potential of sES and MEW for polymeric scaffolds (not cellularized at the time of implantation but able to attract and interact with a patient's surrounding cells all along the implantation time) will be in high demand for local and long-term support for hollow tubular BAOs partially affected by localized diseases (i.e., cancers or inflammatory processes).

Conclusions and Perspectives

Injury, diseases, and malfunctioning of hollow tubular organs represent a unique challenge for bioengineers and clinicians. A multidisciplinary approach needs to be applied in order to successfully develop functional bioartificial organs. The main efforts in addressing the challenge are summarized in the following key points:

i. The MRs and BRs should be the dictating factors during the design phase of a BAO, being the key point to address the anatomical i. structure and physiological functions. This is true for all tissues and organs, but it is particularly challenging in the case of tubular ones, due to the complex hierarchical structure;
ii. Construct cellularization is a key point for replacing diseased or damaged tissues and organs. On the one hand, 3DBP enables the incorporation of cells directly in the construct. On the other hand, sES and MEW rely on post-processing seeding or on cell migration and infiltration after implantation. In both cases, cell integration and cell-mediated remodeling are fundamental for a successful outcome of engineered BAOs;
iii. The main advanced techniques for the fabrication of tubular BAOs are 3DBP, sES, and MEW. Although they are not all at the same level of technological maturity, they all have the potential for clinical translation. While 3DBP presents the unique advantage to process materials and cells together, this also raises the question of which cell source to use to ensure the best outcome. Autologous outsourcing of cells looks like an attractive possibility, but its clinical feasibility for personalized medicine remains low, due to possible autocontamination issues, regulatory processes, and ethical concerns. 3DBP, sES, and MEW all present unique advantages to process materials leading to high reproducibility at the micrometric level, nano- and microfibers production mimicking the ECM, and precise spatial deposition at fiber level, respectively;
iv. In the current research on the fabrication of functional tubular BAOs, there is a missing link that focuses on the correlation between (i) the MRs and BRs of the construct design dictated by the anatomical structure and physiological functions, (ii) the fabrication process, and (iii) the resulting mechanical and biological properties of the developed tubular BOA. Even though the development of functional tubular BAOs using the presented processing techniques is still at the preclinical level, the advancements in the last decade look promising and speculate great potential for clinical translation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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References

Abdal-hay A, Bartnikowski M, Hamlet S, Ivanovski S. Electrospun biphasic tubular scaffold with enhanced mechanical properties for vascular tissue engineering. Mater Sci Eng C Mater Biol Appl. 2018;82:10–8.

Adamowicz J, Kuffel B, Van Breda SV, Pokrwczynska M, Drewa T. Reconstructive urology and tissue engineering: Converging developmental paths. J Tissue Eng Regen Med. 2019; 13(3):522–33.

Afghah F, Dikyol C, Altunbek M, Koc B. Biomimicry in bio-manufacturing: Developments in melt electrospinning writing technology towards hybrid biomanufacturing. Appl Sci. 2019;9(17):3540.

Ait-Oufella H, Maury E, Lehoux S, Guidet B, Offenstadt G. The endothelium: Physiological functions and role in microcirculatory failure during severe sepsis. Appl Physiol Intensive Care Med. 2 Physiol. Rev. Ed. 2012:237–49.

Arakelian L, Kanai N, Dua K, Durand M, Cattan P, Ohki T. Esophageal tissue engineering: from bench to bedside. Ann N Y Acad Sci. 2018;1434(2):156–63.

Arcidiacono JA, Bauer SR, Kaplan DS, Allocca CM, Sarkar S, Lin-Gibson S. FDA and NIST collaboration on standards development activities supporting innovation and translation of regenerative medicine products. Cytotherapy. 2018 Jun;20(6):779–84.

Atala A. Tissue engineering, stem cells and cloning: current concepts and changing trends. Expert Opin Biol Ther. 2005;5(7):879–92.

Atala A, Kasper FK, Mikos AG. Engineering Complex Tissues. Sci Transl Med. 2012; 4(160):160rv12.

Bae SW, Lee KW, Park JH, Lee JH, Jung CR, Yu JJ, et al. 3D bioprinted artificial trachea with epithelial cells and chondrogenic-differentiated bone marrow-derived mesenchymal stem cells. Int J Mol Sci. 2018;19(6):1624.

Baiguera S, Del Gaudio C, Jaus MO, Polizzi L, Gonfiotti A, Comin CE, et al. Long-term changes to in vitro preserved bioengineered human trachea and their implications for decellularized tissues. Biomaterials. 2012; 33(14):3662–72.

Barbosa MA, Martins MCL. Peptides and Proteins as Biomaterials for Tissue Regeneration and Repair. Woodhead Publishing; 2018.

Barron MR, Blanco EW, Aho JM, Chakroff J, Johnson J, Cassivi SD, et al. Full-thickness oesophageal regeneration in pig using a polyurethane mucosal cell seeded graft. J Tissue Eng Regen Med. 2018;12(1):175–85.

Benrashid E, McCoy CC, Youngwirth LM, Kim J, Manson RJ, Otto JC, et al. Tissue engineered vascular grafts: Origins, development, and current strategies for clinical application. Methods. 2016;99:13–9.

Bhardwaj N, Kundu SC. Electrospinning: A fascinating fiber fabrication technique. Biotechnol Adv. 2010;28(3):325–47.

Bhrany AD, Beckstead BL, Lang TC, Farwell DG, Giachelli CM, Ratner BD, et al. Development of an Esophagus Acellular Matrix Tissue Scaffold. Tissue Eng. 2006 Feb;12(2):319–30.

Bitar KN, Raghavan S, Zakhem E. Tissue engineering in the gut: Developments in neuromusculature. Gastroenterology. 2014;146(7): 1614–24.

Bleier BS, Gratton MA, Leibowitz JM, Palmer JN, Newman JG, Cohen NA. Laser-welded endoscopic endoluminal repair of iatrogenic esophageal perforation: An animal model. Otolaryngol Head Neck Surg. 2008;139(5):713–7.

Boazak EM, Auguste DT. Trachea Mechanics for Tissue Engineering Design. ACS Biomater Sci Eng. 2018;4(4):1272–84.

Boomer L, Liu Y, Mahler N, Johnson J, Zak K, Nelson T, et al. Scaffolding for challenging environments: Materials selection for tissue engineered intestine. J Biomed Mater Res A. 2014;102(11):3795–802.

Bosworth LA, Downes S. Electrospinning for tissue regeneration. 1st ed. Woodhead Publishing; 2011.

Brand-Saberi BEM, Schäfer T. Trachea: Anatomy and physiology. Thorac Surg Clin. 2014; 24(1):1–5.

Bridge JC, Aylott JW, Brightling CE, Ghaemmaghami AM, Knox AJ, Lewis MP, et al. Adapting the electrospinning process to provide three unique environments for a tri-layered in vitro model of the airway wall. J Vis Exp. 2015;2015(101):e52986–11.

Brown TD, Dalton PD, Hutmacher DW. Melt electrospinning today: An opportune time for an emerging polymer process. Prog Polym Sci. 2016;56:116–66.

Bu R, Balakrishnan S, Iftimia N, Price H, Zdanski C, Oldenburg AL. Airway compliance measured by anatomic optical coherence tomography. Biomed Opt Express. 2017;8(4):2195.

Catto V, Farè S, Freddi G, Tanzi MC. Vascular Tissue Engineering: Recent Advances in Small Diameter Blood Vessel Regeneration. ISRN Vascular Med. 2014;2014:1–27.

Chang JW, Park SA, Park J, Choi JW, Kim Y, Shin YS, et al. Tissue-Engineered Tracheal Reconstruction Using Three-Dimensionally Printed Artificial Tracheal Graft : Preliminary Report. Artif Organs. 2014;38(6):E95–E105.

Chen H, Kassab GS. Microstructure-based biomechanics of coronary arteries in health and disease. J Biomech. 2016;49(12):2548–59.

Chen FM, Liu X. Advancing biomaterials of human origin for tissue engineering. Prog Polym Sci. 2016;53:86–168.

Chiang T, Pepper V, Best C, Onwuka E, Breuer CK. Clinical Translation of Tissue Engineered Trachea Grafts. Ann Otol Rhinol Laryngol. 2016;125(11):873–85.

Chrzanowska O, Struszczyk MH, Krucinska I, Puchalski M, Herczyńska L, Chrzanowski M. Elaboration of small-diameter vascular prostheses-Selection of appropriate sterilisation method. J Appl Polym Sci. 2014;131(18):1–10.

Chung EJ, Ju HW, Park HJ, Park CH. Three-layered scaffolds for artificial esophagus using poly(caprolactone) nanofibers and silk fibroin: An experimental study in a rat model. J Biomed Mater Res A. 2015;103(6):2057–65.

Chung EJ, Ju HW, Yeon YK, Lee JS, Lee YJ, Seo YB, et al. Development of an omentum-cultured oesophageal scaffold reinforced by a 3D-printed ring: feasibility of an in vivo bioreactor. Artif Cells Nanomed Biotechnol. 2018;46(Suppl 1):885–95.

Clark ES, Best C, Onwuka E, Sugiura T, Mahler N, Bolon B, et al. Effect of cell seeding on neotissue formation in a tissue engineered trachea. J Pediatr Surg. 2016;51(1):49–55.

Cleary MA, Geiger E, Grady C, Best C, Naito Y, Breuer C. Vascular tissue engineering: The next generation. Trends Mol Med. 2012; 18(7):394–404.

Crowley C, Birchall M, Seifalian AM. Trachea transplantation: From laboratory to patient. J Tissue Eng Regen Med. 2015;9(4):357–67.

Dalton PD, Vaquette C, Farrugia BL, Dargaville TR, Brown TD, Hutmacher DW. Electrospinning and additive manufacturing: Converging technologies. Biomater Sci. 2013;1(2):171–85.
Dalton PD, Muerza-Cascante ML, Hutmacher DW. Design and Fabrication of Scaffolds via Melt Electrospinning for Applications in Tissue Engineering.In: Mitchell GR, editor. Electrospinning: Principles Practice and Possibilities. The Royal Society of Chemistry; 2015. p. 100–20.
Davis NF, Cunnane EM, O'Brien FJ, Mulvihill JJ, Walsh MT. Tissue engineered extracellular matrices (ECMs) in urology: Evolution and future directions. Surgeon. 2018;16(1):55–65.
de Jonge PKJD, Simaioforidis V, Geutjes PJ, Oosterwijk E, Feitz WFJ. Recent Advances in Ureteral Tissue Engineering. Curr Urol Rep. 2015;16(1):465.
De Jonge PKJD, Sloff M, Janke HP, Versteegden LRM, Kortmann BBM, De Gier RPE, et al. Ureteral Reconstruction in Goats Using Tissue-Engineered Templates and Subcutaneous Preimplantation. Tissue Eng Part A. 2018;24(11–12):863–72.
De Kemp V, De Graaf P, Fledderus JO, Ruud Bosch JL, De Kort LM. Tissue engineering for human urethral reconstruction: Systematic review of recent literature. PLoS One. 2015;10(2):e0118653.
Del Gaudio C, Baiguera S, Ajalloueian F, Bianco A, Macchiarini P. Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs? J Biomed Mater Res A. 2014;102(7):2427–47.
Dharmadhikari S, Liu L, Shontz K, Wiet M, White A, Goins A, et al. Acta Biomaterialia Deconstructing tissue engineered trachea : Assessing the role of synthetic scaffolds, segmental replacement and cell seeding on graft performance. Acta Biomater. 2020;102:181–91.
Dhasmana A, Singh A, Rawal S. Biomedical grafts for tracheal tissue repairing and regeneration „Tracheal tissue engineering: an overview". J Tissue Eng Regen Med. 2020;14(5):653–72.
Dobrin PB. Stress gradients in the walls of large arteries. J Biomech.1973;6(6):631–9.
Dosh RH, Jordan-Mahy N, Sammon C, Le Maitre CL. Tissue Engineering Laboratory Models of the Small Intestine. Tissue Eng Part B Rev. 2018;24(2):98–111.
Dutta RC, Dey M, Dutta AK, Basu B. Competent processing techniques for scaffolds in tissue engineering. Biotechnol Adv. 2017;35(2):240–50.
Egorov VI, Schastlivtsev IV, Prut EV, Baranov AO, Turusov RA. Mechanical properties of the human gastrointestinal tract. J Biomech. 2002;35(10):1417–25.
Elliott MJ, De Coppi P, Speggiorin S, Roebuck D, Butler CR, Samuel E, et al. Stem-cell-based, tissue engineered tracheal replacement in a child: a 2-year follow-up study. Lancet. 2012;380(9846):994–1000.
Elliott MB, Gerecht S. Three-dimensional culture of small-diameter vascular grafts. J Mater Chem B. 2016;4(20):3443–53.
Engel O, Rink M, Fisch M. Management of iatrogenic ureteral injury and techniques for ureteral reconstruction. Curr Opin Urol. 2015;25(4):331–5.
Erdem R, Yüksek M, Sancak E, Atak O, Erginer M, Kabasakal L, et al. Electrospinning of single and multilayered scaffolds for tissue engineering applications. J Text Inst. 2016;108(6):935–46.
Eskandari M, Arvayo AL, Levenston ME. Mechanical properties of the airway tree: Heterogeneous and anisotropic pseudoelastic and viscoelastic tissue responses. J Appl Physiol (1985). 2018;125(3):878–88.
Eslamian M, Khorrami M, Yi N, Majd S, Abidian MR. Electrospinning of highly aligned fibers for drug delivery applications. J Mater Chem B. 2019;7(2):224–32.
Fedoruk MJ, Hong S. Gastrointestinal System Springer; 2014.
Fernandez CE, Achneck HE, Reichert WM, Truskey GA. Biological and engineering design considerations for vascular tissue engineered blood vessels (TEBVs). Curr Opin Chem Eng. 2014;3(3):83–90.
Freeman S, Ramos R, Alexis Chando P, Zhou L, Reeser K, Jin S, et al. A bioink blend for rotary 3D bioprinting tissue engineered small-diameter vascular constructs. Acta Biomater. 2019;95:152–64.
Furth ME, Atala A. Tissue Engineering: Future Perspectives Princ.4th ed. Tissue Eng Elsevier; 2013. p. 83–123.
Gao G, Lee JH, Jang J, Lee DH, Kong J-S, Kim BS, et al. Tissue Engineered Bio-Blood-Vessels Constructed Using a Tissue-Specific Bioink and 3D Coaxial Cell Printing Technique: A Novel Therapy for Ischemic Disease. Adv Funct Mater. 2017;27(33):1700798.
Gao G, Kim H, Kim BS, Kong JS, Lee JY, Park BW, et al. Tissue-engineering of vascular grafts containing endothelium and smooth-muscle using triple-coaxial cell printing. Appl Phys Rev. 2019;6(4):41402.
Gao Q, Liu Z, Lin Z, Qiu J, Liu Y, Liu A, et al. 3D Bioprinting of Vessel-like Structures with Multilevel Fluidic Channels. ACS Biomater Sci Eng. 2017;3(3):399–408.
Gao M, Zhang H, Dong W, Bai J, Gao B, Xia D, et al. Tissue-engineered trachea from a 3D-printed scaffold enhances whole-segment tracheal repair. Sci Rep. 2017;7(1):5246.
Gonfiotti A, Jaus MO, Barale D, Baiguera S, Comin C, Lavorini F, et al. The first tissue-engineered airway transplantation: 5-year follow-up results. Lancet. 2014;383(9913):238–44.
Góra A, Pliszka D, Mukherjee S, Ramakrishna S. Tubular Tissues and Organs of Human Body--Challenges in Regenerative Medicine. J Nanosci Nanotechnol. 2016;16(1):19–39.
Gregersen H, Kassab G. Biomechanics of the gastrointestinal tract. Neurogastroenterol Motil. 1996;8(4):277–97.
Habib RH, Chalker RB, Suki B, Jackson AC. Airway geometry and wall mechanical properties estimated from subglottal input impedance in humans. J Appl Physiol (1985). 1994;77(1):441–51.
Hamilton N, Bullock AJ, Macneil S, Janes SM, Birchall M. Tissue engineering airway mucosa: A systematic review. Laryngoscope. 2014;124(4):961–8.
Haykal S, Salna M, Waddell TK, Hofer SO. Advances in tracheal reconstruction. Plast Reconstr Surg Glob Open. 2014;2(7):e178–11.
Hinderer S, Schesny M, Bayrak A, Ibold B, Hampel M, Walles T, et al. Engineering of fibrillar decorin matrices for a tissue-engineered trachea. Biomaterials. 2012;33(21):5259–66.
Hochleitner G, Jüngst T, Brown TD, Hahn K, Moseke C, Jakob F, et al. Additive manufacturing of scaffolds with sub-micron filaments via melt electrospinning writing. Biofabrication. 2015;7(3):035002.
Hodges SJ, Atala A. Tissue-Engineered Organs. 4th ed. Elsevier; 2013. p. 1765–77.
Holland I, Logan J, Shi J, McCormick C, Liu D, Shu W. 3D biofabrication for tubular tissue engineering. Biodes Manuf. 2018;1(2):89–100.
Holzapfel GA, Ogden RW. Biomechanics of Soft Tissue in Cardiovascular Systems [Internet]. Springer-Verlag Wien GmbH; 2003.
Hong J, Yeo M, Yang GH, Kim G. Cell-Electrospinning and Its Application for Tissue Engineering. Int J Mol Sci. 2019;20(24):6208.
Hsieh C-T, Liao C-Y, Dai N-T, Tseng C-S, Yen BL, Hsu S-h. 3D printing of tubular scaffolds with elasticity and complex structure from multiple waterborne polyurethanes for tracheal tissue engineering. Applied Materials Today. 2018;12:330–41.
Huang NF, Li S. Mesenchymal stem cells for vascular regeneration. Regen Med. 2008;3(6):877–92.
Huang R, Gao X, Wang J, Chen H, Tong C, Tan Y, et al. Triple-Layer Vascular Grafts Fabricated by Combined E-Jet 3D Printing and Electrospinning. Ann Biomed Eng. 2018;46(9):1254–66.
Hunsberger J, Neubert J, Wertheim JA, Allickson J, Atala A. Bioengineering Priorities on a Path to Ending Organ Shortage. Curr Stem Cell Rep. 2016;2(2):118–27.
Hussey GS, Cramer MC, Badylak SF. Extracellular Matrix Bioscaffolds for Building Gastrointestinal Tissue. Cell Mol Gastroenterol Hepatol. 2018;5(1):1–13.
Ibrahim YS, Hussein EA, Zagho MM, Abdo GG, Elzatahry AA. Melt Electrospinning Designs for Nanofiber Fabrication for Different Applications. Int J Mol Sci. 2019;20(10):1–17.
Ibrahim HM, Klingner A. A review on electrospun polymeric nanofibers : Production parameters and potential applications. Polym Test. 2020;90:106647.

Itoh M, Nakayama K, Noguchi R, Kamohara K, Furukawa K, Uchihashi K, et al. Scaffold-Free Tubular Tissues Created by a Bio-3D Printer Undergo Remodeling and Endothelialization when Implanted in Rat Aortae. PLoS One. 2015;10(9):e0136681–15.
Jang EH, Kim JH, Lee JH, Kim DH, Youn YN. Enhanced biocompatibility of multi-layered, 3D bio-printed artificial vessels composed of autologous mesenchymal stem cells. Polymers (Basel). 2020;12(3).
Jensen T, Blanchette A, Vadasz S, Dave A, Canfarotta M, Sayej WN, et al. Biomimetic and synthetic esophageal tissue engineering. Biomaterials. 2015;57:133–41.
Jeong HJ, Nam H, Jang J and Lee SJ. 3D bioprinting strategies for the regeneration of functional tubular tissues and organs. Bioengeneering (Basel).2020;7(2):32.
Jiang T, Carbone EJ, Lo KW-H, Laurencin CT. Electrospinning of Polymer Nanofibers for Tissue Regeneration. Prog Polym Sci. 2014; 46:1–24.
Jin L, Wang T, Zhu ML, Leach MK, Naim YI, Corey JM, et al. Electrospun fibers and tissue engineering. J Biomed Nanotechnol. 2012;8(1): 1–9.
Jin Y, Gao Q, Xie C, Li G, Du J, Fu J. Fabrication of heterogeneous scaffolds using melt electrospinning writing : Design and optimization. Mater Des. 2020;185:108274.
Jones E, Jensen T, Sharma I, Wanczyk H, Mitchell A, Foster C, et al. Scaffolds for esophageal tissue engineering. Handb. Tissue Eng. Scaffolds, Vol. Two Elsevier Ltd; 2019. p. 565–92.
Joy J, Pereira J, Aid-Launais R, Pavon-Djavid G, Ray AR, Letourneur D, et al. Electrospun microporous gelatin-polycaprolactone blend tubular scaffold as a potential vascular biomaterial. Polym Int. 2019;68(7):1367–77.
Joy J, Aid-Launais R, Pereira J, Pavon-Djavid G, Ray AR, Letourneur D, et al. Gelatin-polytrimethylene carbonate blend based electrospun tubular construct as a potential vascular biomaterial. Mater Sci Eng C Mater Biol Appl. 2020;106:110178.
Ju YM, Ahn H, Arenas-Herrera J, Kim C, Abolbashari M, Atala A, et al. Electrospun vascular scaffold for cellularized small diameter blood vessels: A preclinical large animal study. Acta Biomater. 2017;59:58–67.
Jungst T, Muerza-Cascante ML, Brown TD, Standfest M, Hutmacher DW, Groll J, et al. Melt electrospinning onto cylinders: Effects of rotational velocity and collector diameter on morphology of tubular structures. Polym Int. 2015;64(9):1086–95.
Jungst T, Pennings I, Schmitz M, Rosenberg AJWPWP, Groll J, Gawlitta D. Heterotypic Scaffold Design Orchestrates Primary Cell Organization and Phenotypes in Cocultured Small Diameter Vascular Grafts. Adv Funct Mater. 2019;29(43).
Kanetaka K, Kobayashi S, Eguchi S. Regenerative medicine for the esophagus. Surg Today. 2018;48(8):739–47.
Kanetkar NS, Ekenseair AK. Scaffolds for intestinal tissue engineering. Handb Tissue Eng Scaffolds. 2019. Vol. 2. Elsevier Ltd; p. 593–632.
Kang Y, Wang C, Qiao Y, Gu J, Zhang H, Peijs T, et al. Tissue-Engineered Trachea Consisting of Electrospun Patterned sc-PLA/GO- g-IL Fibrous Membranes with Antibacterial Property and 3D-Printed Skeletons with Elasticity. Biomacromolecules. 2019;20(4):1765–76.
Karimi A, Navidbakhsh M, Shojaei A, Faghihi S. Measurement of the uniaxial mechanical properties of healthy and atherosclerotic human coronary arteries. Mater Sci Eng C Mater Biol Appl. 2013;33(5):2550–4.
Kaye R, Goldstein T, Grande DA, Zeltsman D, Smith LP. A 3-dimensional bioprinted tracheal segment implant pilot study: Rabbit tracheal resection with graft implantation. Int J Pediatr Otorhinolaryngol. 2019 Feb;117:175–8.
Ke D, Yi H, Est-Witte S, George S, Kengla C, Lee SJ, et al. Bioprinted trachea constructs with patient-matched design, mechanical and biological properties. Biofabrication. 2019;12(1): 015022.
Kennedy KM, Bhaw-Luximon A, Jhurry D. Cell-matrix mechanical interaction in electrospun polymeric scaffolds for tissue engineering: implications for scaffold design and performance. Acta Biomater. 2016;50:41–55.
Kim IG, Wu Y, Park SA, Cho H, Choi JJ, Kwon SK, et al. Tissue-Engineered Esophagus via Bioreactor Cultivation for Circumferential Esophageal Reconstruction. Tissue Eng Part A. 2019;25(21-22):1478–92.
Kim IG, Wu Y, Park SA, Cho H, Shin JW, Chung EJ. Tissue-engineered graft for circumferential esophageal reconstruction in rats. J Vis Exp. 2020;2020(156):1–7.
Kloskowski T, Jundziłł A, Kowalczyk T, Nowacki M, Bodnar M, Marszałek A, et al. Ureter regeneration-The proper scaffold has to be defined. PLoS One. 2014;9(8):e106023.
Kloskowski T, Pokrywczyńska M, Drewa T. Artificial urinary conduit construction using tissue engineering methods. Cent European J Urol. 2015;68(1):109–14.
Kojima K, Vacanti CA. Tissue engineering in the trachea. Anat Rec (Hoboken). 2014;297(1): 44–50.
Kovler ML, Hackam DJ. Generating an Artificial Intestine for the Treatment of Short Bowel Syndrome. Gastroenterol Clin North Am. 2019;48(4):585–605.
Kuang H, Yang S, Wang Y, He Y, Ye K, Hu J, et al. Electrospun bilayer composite vascular graft with an inner layer modified by polyethylene glycol and haparin to regenerate the blood vessel. J Biomed Nanotechnol. 2019; 15(1):77–84.
Kuppan P, Sethuraman S, Krishnan UM. Fabrication and investigation of nanofibrous matrices as esophageal tissue scaffolds using human non-keratinized, stratified, squamous epithelial cells. RSC Adv. 2016;6(31):26461–73.
La Francesca S, Aho JM, Barron MR, Blanco EW, Soliman S, Kalenjian L, et al. Long-term regeneration and remodeling of the pig esophagus after circumferential resection using a retrievable synthetic scaffold carrying autologous cells. Sci Rep. 2018;8(1):4123–16.
Law JX, Liau LL, Aminuddin BS, Ruszymah BH. Tissue-engineered trachea: A review. Int J Pediatr Otorhinolaryngol. 2016;91:55–63.
Leberfinger AN, Dinda S, Wu Y, Koduru SV, Ozbolat V, Ravnic DJ, et al. Bioprinting functional tissues. Acta Biomater. 2019;95:32–49.
Lee SJ, Liu J, Oh SH, Soker S, Atala A, Yoo JJ. Development of a composite vascular scaffolding system that withstands physiological vascular conditions. Biomaterials. 2008;29(19): 2891–8.
Lelkens P, Li M, Perets A, Lin L, Han J, Woerdeman D. Electrospinning of natural proteins for tissue engineering scaffolding. Nat Polym Biomed Appl. Woodhead Publishing; 2008. p. 446–82. (Woodhead Publishing Series in Biomaterials).
Li J, Chen M, Fan X, Zhou H. Recent advances in bioprinting techniques: approaches, applications and future prospects. J Transl Med. 2016;14(1):271.
Li X, Huang L, Li L, Tang Y, Liu Q, Xie H, et al. Biomimetic dual-oriented/bilayered electrospun scaffold for vascular tissue engineering. J Biomater Sci Polym Ed. 2020;31(4):439–55.
Li L, Qin S, Peng J, Chen A, Nie Y, Liu T, et al. Engineering gelatin-based alginate/carbon nanotubes blend bioink for direct 3D printing of vessel constructs. Int J Biol Macromol. 2020;145:262–71.
Lomholt N. Tracheal models which simulate the compliance of the adult male trachea. Br J Anaesth. 1992;69(1):98–100.
Londono R, Badylak SF. Regenerative Medicine Strategies for Esophageal Repair. Tissue Eng Part B Rev. 2015;21(4):393–410.
Luc G, Durand M, Collet D, Guillemot F, Bordenave L. Esophageal tissue engineering. Expert Rev Med Devices. 2014;11(2):225–41.
Lv X, Guo Q, Han F, Chen C, Ling C, Chen W, et al. Electrospun poly(L-lactide)/poly(ethylene glycol) scaffolds seeded with human amniotic mesenchymal stem cells for urethral epithelium repair. Int J Mol Sci. 2016;17(8):1262.
Lv L, Tang Y, Zhang P, Liu Y, Bai X, Zhou Y. Biomaterial Cues Regulate Epigenetic State and Cell Functions-A Systematic Review. Tissue Eng Part B Rev. 2018;24(2):112–32.
Machino R, Matsumoto K, Taniguchi D, Tsuchiya T, Takeoka Y, Taura Y, et al. Replacement of Rat Tracheas by Layered, Trachea-Like, Scaffold-Free Structures of Human Cells Using a Bio-3D Printing System. Adv Healthc Mater. 2019;8:e1800983.
Maghsoudlou P, Eaton S, De Coppi P. Tissue engineering of the esophagus. Semin Pediatr Surg. 2014;23(3):127–34.
Mandrycky C, Wang Z, Kim K, Kim DH. 3D bioprinting for engineering complex tissues. Biotechnol Adv. 2015;34(4):422–34.

Marieb EN, Hoehn K Human anatomy & physiology [Internet]. 8th ed Pearson; 2010.
Martinez-Lemus LA, Hill MA, Meininger GA. The Plastic Nature of the Vascular Wall: A Continuum of Remodeling Events Contributing to Control of Arteriolar Diameter and Structure. Physiology. 2009;24(1):45–57.
Marx V. Tissue engineering: Organs from the lab. Nature. 2015;522:373.
Mason JE, Traoré I, Woungang I. Measured Performance. CADTH Issues Emerg Heal Technol. 2016:175.
Mazalevska O, Struszczyk MH, Krucinska I. Design of vascular prostheses by melt electrospinning-structural characterizations. J Appl Polym Sci. 2013;129(2):779–92.
McColl E, Groll J, Jungst T, Dalton PD. Design and fabrication of melt electrowritten tubes using intuitive software. Materials & Design. 2018;155:46–58.
Mo X, Sun B, Wu T, Li D. Electrospun Nanofibers for Tissue Engineering. Electrospinning Nanofabrication Appl Elsevier Inc.; 2019. p. 719–34.
Moffat KL, Neal RA, Freed LE, Guilak F. Engineering Functional Tissues. 4th ed. Princ Tissue Eng. Elsevier; 2014. p. 237–59. Engineering Functional Tissues: In Vitro Culture Parameters [Internet].
Moghe AK, Gupta BS. Co-axial electrospinning for nanofiber structures: Preparation and applications. Polym Rev. 2008;48(2):353–77.
Moldovan NI, Hibino N, Nakayama K. Principles of the Kenzan Method for Robotic Cell Spheroid-Based Three-Dimensional Bioprinting. Tissue Eng Part B Rev. 2017;23(3):237–44.
Moroni L, Boland T, Burdick JA, De Maria C, Derby B, Forgacs G, et al. Biofabrication: A Guide to Technology and Terminology. Trends Biotechnol. 2018;36(4):384–402.
Mozafari M, Sefat F, Atala A. Handbook of tissue engineering scaffolds. Vol. One. Woodhead Publishing; 2019. p. 1–759.
Muerza-Cascante ML, Haylock D, Hutmacher DW, Dalton PD. Melt Electrospinning and Its Technologization in Tissue Engineering. Tissue Eng Part B Rev. 2015;21(2):187–202.
Murata D, Arai K, Nakayama K. Scaffold-Free Bio-3D Printing Using Spheroids as "Bio-Inks" for Tissue (Re-)Construction and Drug Response Tests. Adv Healthc Mater. 2020;9(15):1–18.
Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol. 2014;32(8):773–85.
Naito Y, Shinoka T, Duncan D, Hibino N, Solomon D, Cleary M, et al. Vascular tissue engineering: Towards the next generation vascular grafts. Adv Drug Deliv Rev. 2011;63(4):312–23.
Nakagawa Y. Mechanical property of the human ureter (in Japanese). Nihon Hinyokika Gakkai Zasshi. 1989;80(10):1481–8.
Natali AN, Fontanella CG, Carniel EL. Biomechanical analysis of the interaction phenomena between artificial urinary sphincter and urethral duct. Int J Numer Method Biomed Eng. 2020;36(3):e3308.
Nemeno-Guanzon JG, Lee S, Berg JR, Jo YH, Yeo JE, Nam BM, et al. Trends in tissue engineering for blood vessels. J Biomed Biotechnol. 2012;2012:956345.
Nerem RM, Schutte SC. The Challenge of Imitating Nature [Internet]. 4th ed. Princ. Tissue Eng. Elsevier; 2014. p. 9–24.
Nichol JW, Khademhosseini A. Modular tissue engineering: engineering biological tissues from the bottom up. Soft Matters. 2010;5(7):1312–9.
Niu Z, Wang X, Meng X, Guo X, Jiang Y, Xu Y, et al. Controllable fiber orientation and nonlinear elasticity of electrospun nanofibrous small diameter tubular scaffolds for vascular tissue engineering. Biomed Mater. 2019;14(3):035006.
Noh I. Biomimetic Medical Materials: From Nanotechnology to 3D Bioprinting. Springer; 2018.
O'Leary C, Soriano L, Fagan-Murphy A, Ivankovic I, Cavanagh B, O'Brien FJ, et al. The Fabrication and in vitro Evaluation of Retinoic Acid-Loaded Electrospun Composite Biomaterials for Tracheal Tissue Regeneration. Front Bioeng Biotechnol. 2020;8:190.
Oprea AE, Ficai A, Andronescu E. Chapter 4. Electrospun nanofibers for tissue engineering applications [Internet]. Mater Biomed Eng Nanobiomaterials Tissue Eng: Elsevier Inc. 2019. p. 77–96.
Orabi H. Scaffolds for tissue engineering of the urethra.Vol. Two. Handb Tissue Eng Scaffolds. Elsevier Ltd; 2019. p. 549–61.
Ott LM, Weatherly RA, Detamore MS. Overview of tracheal tissue engineering: Clinical need drives the laboratory approach. Ann Biomed Eng. 2011;39(8):2091–113.
Ott LM, Zabel TA, Walker NK, Farris AL, Chakroff JT, Ohst DG, et al. Mechanical evaluation of gradient electrospun scaffolds with 3D printed ring reinforcements for tracheal defect repair. Biomed Mater. 2016;11(2):025020.
Pan S, Zhong Y, Shan Y, Liu X, Xiao Y, Shi H. Selection of the optimum 3D-printed pore and the surface modification techniques for tissue engineering tracheal scaffold in vivo reconstruction. J Biomed Mater Res A. 2019 Feb;107(2):360–70.
Pan Y, Zhou X, Wei Y, Zhang Q, Wang T, Zhu M, et al. Small-diameter hybrid vascular grafts composed of polycaprolactone and polydioxanone fibers. Sci Rep. 2017;7(1):3615–1.
Panwar A, Tan LP. Current status of bioinks for micro-extrusion-based 3D bioprinting. Molecules. 2016;21(6):685.
Park JH, Yoon JK, Lee JB, Shin YM, Lee KW, Bae SW, et al. Experimental Tracheal Replacement Using 3-dimensional Bioprinted Artificial Trachea with Autologous Epithelial Cells and Chondrocytes. Sci Rep. 2019;9(1):2103.
Pashneh-Tala S, MacNeil S, Claeyssens F. The Tissue-Engineered Vascular Graft-Past, Present, and Future. Tissue Eng Part B Rev. 2016;22(1):68–100.
Paxton NC, Lanaro M, Bo A, Crooks N, Ross MT, Green N, et al. Design tools for patient specific and highly controlled melt electrowritten scaffolds. J Mech Behav Biomed Mater. 2020;105:103695.
Pedde RD, Mirani B, Navaei A, Styan T, Wong S, Mehrali M, et al. Emerging Biofabrication Strategies for Engineering Complex Tissue Constructs. Adv Mater. 2017.
Pennings I, Van Haaften EE, Jungst T, Bulsink JA, Rosenberg AJWP, Groll J, et al. Layer-specific cell differentiation in bi-layered vascular grafts under flow perfusion. Biofabrication. 2020;12(1):015009.
Petsepe DC, Kourkoulis SK, Papadodima SA, Sokolis DP. Regional and age-dependent residual strains, curvature, and dimensions of the human ureter. Proc Inst Mech Eng H. 2018;232(2):149–62.
Pi Q, Maharjan S, Yan X, Liu X, Singh B, van Genderen AM, et al. Digitally Tunable Microfluidic Bioprinting of Multilayered Cannular Tissues. Adv Mater. 2018;30(43):e1706913.
Pien N, Peeters I, Deconinck L, Van Damme L, De Wilde L, Martens A, et al. Design and development of a reinforced tubular electrospun construct for the repair of ruptures of deep flexor tendons. Mat Sci Eng C Mater Biol Appl. 2021;119:111504.
Poghosyan T, Catry J, Luong-Nguyen M, Bruneval P, Domet T, Arakelian L, et al. Esophageal tissue engineering: Current status and perspectives. J Visc Surg. 2016;153(1):21–9.
Qi D, Shi W, Black AR, Kuss MA, Pang X, He Y, et al. Repair and regeneration of small intestine: A review of current engineering approaches. Biomaterials. 2020;240:119832.
Rains JK, Bert JL, Roberts CR, Paré PD. Mechanical properties of human tracheal cartilage. J Appl Physiol (1985). 1992;72(1):219–25.
Raja TI, Mozafari M, Milan PB, Samadikuchaksaraei A, Sefat F. Nanoengineered biomaterials for tracheal replacement [Internet]. Nanoeng Biomater Regen Med. Elsevier Inc.; 2018. p. 285–303.
Rao SS, Gregersen H, Hayek B, Summers RW, Christensen J. Unexplained chest Pain: The hypersensitive, hyperreactive, and poorly compliant esophagus. Ann Intern Med. 1996;124(11):950–8.
Ratner BD, Hoffman AS, Schoen FJ, Lemons JE. Biomaterial Science - An Introduction to Materials in Medicine [Internet]. 2nd ed. Elsevier Academic Press; 2004.
Robinson TM, Hutmacher DW, Dalton PD. The Next Frontier in Melt Electrospinning: Taming the Jet. Adv Funct Mater. 2019;29(44).
Safshekan F, Tafazzoli-Shadpour M, Abdouss M, Shadmehr MB. Mechanical characterization and constitutive modeling of human trachea: Age and gender dependency. Materials (Basel). 2016;9(6):456.
Safshekan F, Tafazzoli-Shadpour M, Abdouss M, Shadmehr MB. Viscoelastic Properties of Human Tracheal Tissues. J Biomech Eng. 2017;139(1):1–9.

Sahai N, Gogoi M. 3D tissue scaffold library development form medical images for bioprinting application. Materials Today: Proceedings. 2020;26:399–404.
Schleifenbaum S, Prietzel T, Aust G, Boldt A, Fritsch S, Keil I, et al. Acellularization-Induced changes in tensile properties are organ specific - An In-Vitro mechanical and structural analysis of porcine soft tissues. PLoS One. 2016;11(3):e0151223.
Seifu DG, Purnama A, Mequanint K, Mantovani D. Small-diameter vascular tissue engineering. Nat Rev Cardiol. 2013;10(7):410–21.
Sell SA, Wolfe PS, Garg K, McCool JM, Rodriguez IA, Bowlin GL. The use of natural polymers in tissue engineering: A focus on electrospun extracellular matrix analogues. Polymers. 2010;2(4):522–53.
Shafiee A, Atala A. Tissue Engineering: Toward a New Era of Medicine. Annu Rev Med. 2017;68:29–40.
Shi J, Chen S, Wang L, Zhang X, Gao J, Jiang L, et al. Rapid endothelialization and controlled smooth muscle regeneration by electrospun heparin-loaded polycaprolactone/gelatin hybrid vascular grafts. J Biomed Mater Res B Appl Biomater. 2019;107(6):2040–9.
Shilo Y, Pichamuthu JE, Averch TD, Vorp DA. First prize: Evaluation of the tensile strength of the human ureter-preliminary results. J Endourol. 2014;28(12):1470–3.
Siddiqi S. Tissue Engineering of the Trachea: What is the Hold-up?. MOJ Cell Sci Rep. 2017;4(1):13–7.
Sievert KD. Tissue Engineering of the Urethra: Solid Basic Research and Farsighted Planning are Required for Clinical Application. Eur Urol. 2017;72(4):607–9.
Sill TJ, von Recum HA. Electrospinning: Applications in drug delivery and tissue engineering. Biomaterials. 2008;29(13):1989–2006.
Singh A, Lee D, Sopko N, Matsui H, Sabnekar P, Liu X, et al. Biomanufacturing Seamless Tubular and Hollow Collagen Scaffolds with Unique Design Features and Biomechanical Properties. Adv Healthc Mater. 2017;6(5).
Sloff M, De Vries R, Geutjes P, IntHout J, Ritskes-Hoitinga M, Oosterwijk E, et al. Tissue engineering in animal models for urinary diversion: A systematic review. PLoS One. 2014;9(6):e98734.
Sokolis DP. In vitro study of age-related changes in human ureteral failure properties according to region, direction, and layer. Proc Inst Mech Eng H. 2019;233(5):570–83.
Sokolis DP, Petsepe DC, Papadodima SA, Kourkoulis SK. Age- and region-related changes in the biomechanical properties and composition of the human ureter. J Biomech. 2017;51:57–64.
Soliman S, Laurent J, Kalenjian L, Burnette K, Hedberg B, La Francesca S. A multilayer scaffold design with spatial arrangement of cells to modulate esophageal tissue growth. J Biomed Mater Res B Appl Biomater. 2019;107(2):324–31.
Song HG, Rumma RT, Ozaki CK, Edelman ER, Chen CS. Vascular Tissue Engineering: Progress, Challenges, and Clinical Promise. Cell Stem Cell. 2018;22(3):340–54.
Spirka T, Kenton K, Brubaker L, Damaser MS. Effect of material properties on predicted vesical pressure during a cough in a simplified computational model of the bladder and urethra. Ann Biomed Eng. 2013;41(1):185–94.
Stock UA, Vacanti JP. Tissue engineering : Current State and Prospects. Annu Rev Med. 2001;52(1):443–51.
Subbiah T, Bhat GS, Tock RW, Parameswaran S, Ramkumar SS. Electrospinning of nanofibers. J Appl Polym Sci. 2005;96(2):557–69.
Takeda T, Kassab G, Liu J, Puckett JL, Mittal RR, Mittal RK. A novel ultrasound technique to study the biomechanics of the human esophagus in vivo. Am J Physiol Gastrointest Liver Physiol. 2002;282(5):G785–93.
Takeoka Y, Matsumoto K, Taniguchi D, Tsuchiya T, Machino R, Moriyama M, et al. Regeneration of esophagus using a scaffold-free biomimetic structure created with bio-three-dimensional printing. PLoS One. 2019;14(3):e0211339.
Tan Z, Gao X, Liu T, Yang Y, Zhong J, Tong C, et al. Electrospun vein grafts with high cell infiltration for vascular tissue engineering. Mater Sci Eng C Mater Biol Appl. 2017;81:407–15.
Taniguchi D, Matsumoto K, Tsuchiya T, Machino R, Takeoka Y, Elgalad A, et al. Scaffold-free trachea regeneration by tissue engineering with bio-3D printing. Interact Cardiovasc Thorac Surg. 2018;26(5):745–52.
Townsend JM, Ott LM, Salash JR, Fung KM, Easley JT, Seim HB, et al. Reinforced Electrospun Polycaprolactone Nanofibers for Tracheal Repair in an In Vivo Ovine Model. Tissue Eng Part A. 2018;24(17–18):1301–8.
Townsend JM, Hukill ME, Fung KM, Ohst DG, Johnson JK, Weatherly RA, et al. Biodegradable electrospun patch containing cell adhesion or antimicrobial compounds for trachea repair in vivo. Biomed Mater. 2020;15(2):025003.
Trabelsi O, del Palomar AP, López-Villalobos JL, Ginel A, Doblaré M. Experimental characterization and constitutive modeling of the mechanical behavior of the human trachea. Med Eng Phys. 2010;32(1):76–82.
Tuan-Mu HY, Lu PC, Lee PY, Lin CC, Chen CJ, Huang LLH, et al. Rapid Fabrication of a Cell-Seeded Collagen Gel-Based Tubular Construct that Withstands Arterial Pressure: Rapid Fabrication of a Gel-Based Media Equivalent. Ann Biomed Eng. 2016;44(11):3384–97.
Udelsman B, Mathisen DJ, Ott HC. A reassessment of tracheal substitutes-A systematic review. Ann Cardiothorac Surg. 2018;7(2):175–82.
Urbanska AM, Sefat F, Yousaf S, Kargozar S, Milan PB, Mozafari M. Nanoengineered biomaterials for intestine regeneration [Internet]. Elsevier Inc. 2018. p. 363–78.
Vacanti JP, Vacanti CA. Chapter 1: The History and Scope of Tissue .Engineering. Princ. Tissue Eng. 4th ed. Boston: Academic Press; 2014. p. 3–8.
Vanags I, Petersons A, Ose V, Ozolanta I, Kasyanov V, Laizans J, et al. Biomechanical properties of oesophagus wall under loading. J Biomech. 2003;36(9):1387–90.
Van Hoorick J, Tytgat L, Dobos A, Ottevaere H, Van Erps J, Thienpont H, et al. (Photo-)crosslinkable Gelatin Derivatives for Biofabrication applications. Acta Biomater. 2019;97:46–73.
Versteegden LRM, de Jonge PKJD, IntHout J, van Kuppevelt TH, Oosterwijk E, Feitz WFJ, et al. Tissue Engineering of the Urethra: A Systematic Review and Meta-analysis of Preclinical and Clinical Studies. Eur Urol. 2017;72(4):594–606.
Wagenseil JE, Mecham RP. Vascular Extracellular Matrix and Arterial Mechanics. Physiol Rev. 2009;89(3):957–89.
Wang F, Hu S, Jia Q, Zhang L. Advances in Electrospinning of Natural Biomaterials for Wound Dressing. J Nanomaterials. 2020;2020:1.
Wang K, Zhang Q, Zhao L, Pan Y, Wang T, Zhi D, et al. Functional Modification of Electrospun Poly(ε-caprolactone) Vascular Grafts with the Fusion Protein VEGF-HGFI Enhanced Vascular Regeneration. ACS Appl Mater Interfaces. 2017;9(13):11415–27.
Wei G, Li C, Fu Q, Xu Y, Li H. Preparation of PCL/silk fibroin/collagen electrospun fiber for urethral reconstruction. Int Urol Nephrol. 2015;47(1):95–9.
Wen M, Zhi D, Wang L, Cui C, Huang Z, Zhao Y, et al. Local Delivery of Dual MicroRNAs in Trilayered Electrospun Grafts for Vascular Regeneration. ACS Appl Mater Interfaces. 2020;12(6):6863–75.
Willerth SM. Melt electrospinning in tissue engineering. Electrospun Mater. Tissue Eng Biomed Appl Res Des Commer. Elsevier Ltd. 2017. p. 87–100.
Wissing TB, Bonito V, Bouten CVC, Smits AIPM. Biomaterial-driven in situ cardiovascular tissue engineering-a multi-disciplinary perspective. NPJ Regen Med. 2017;2(1):18.
Wu Y, Qin Y, Wang Z, Wang J, Zhang C, Li C, et al. The regeneration of macro-porous electrospun poly(ε-caprolactone) vascular graft during long-term in situ implantation. J Biomed Mater Res B Appl Biomater. 2018;106(4):1618–27.
Wu Y, Kang YG, Kim IG, Kim JE, Lee EJ, Chung EJ, et al. Mechanical stimuli enhance simultaneous differentiation into oesophageal cell lineages in a double-layered tubular scaffold. J Tissue Eng Regen Med. 2019;13(8):1394–405.
Wu T, Zhang J, Wang Y, Li D, Sun B, El-Hamshary H, et al. Fabrication and preliminary study of a biomimetic tri-layer tubular graft based on fibers and fiber yarns for vascular tissue engineering. Mater Sci Eng C Mater Biol Appl. 2018b;82:121–9.

Wu T, Zhang J, Wang Y, Sun B, Yin M, Bowlin G, et al. Design and Fabrication of a Biomimetic Vascular Scaffold Promoting in Situ Endothelialization and Tunica Media Regeneration. Appl Bio Mater. 2018a;1:833–44.
Wu T, Zheng H, Chen J, Wang Y, Sun B, Morsi Y, et al. Application of a bilayer tubular scaffold based on electrospun poly(l-lactide-co-caprolactone)/collagen fibers and yarns for tracheal tissue engineering. J Mater Chem B. 2017;5(1):139–50.
Xu Y, Hu Y, Liu C, Yao H, Liu B, Mi S. A Novel Strategy for Creating Tissue-Engineered Biomimetic Blood Vessels Using 3D Bioprinting Technology. Materials (Basel). 2018;11(9):1581.
Xu J, Shi GP. Vascular wall extracellular matrix proteins and vascular diseases. Biochim Biophys Acta. 2014;1842(11):2106–19.
Yang J, Liao D, Zhao J, Gregersen H. Shear modulus of elasticity of the esophagus. Ann Biomed Eng. 2004;32(9):1223–30.
Yang W, Li H, Chen X. Melt electrospinning, in Electrospinning Nanofabrication Appl. Elsevier Inc.; 2018. p. 339–61.
Yao F, Laudano MA, Seklehner S, Chughtai B, Lee RK. Image-based simulation of urethral distensibility and flow resistance as a function of pelvic floor anatomy. Neurourol Urodyn. 2015;34(7):664–8.
Yekrang J, Semnani D and Karbasi S. Optimizing the mechanical properties of a bi-layered knitted/nanofibrous esophageal prosthesis using artificial intelligence. e-polymers. 2016; 16(5):359–71.
Yin FC, Fung YC. Mechanical properties of isolated mammalian ureteral segments. Am J Physiol. 1971;221(5):1484–93.
Zhang K, Fu Q, Yoo J, Chen X, Chandra P, Mo X, et al. 3D bioprinting of urethra with PCL/PLCL blend and dual autologous cells in fibrin hydrogel: An in vitro evaluation of biomimetic mechanical property and cell growth environment. Acta Biomater. 2017;50:154–64.
Zhang WJ, Liu W, Cui L, Cao Y. Tissue engineering of blood vessel: Tissue Engineering Review Series. J Cell Mol Med. 2007;11(5):945–57.
Zhou P, Zhou F, Liu B, Zhao Y, Yuan X. Functional electrospun fibrous scaffolds with dextran- g -poly(l-lysine)-VAPG/microRNA-145 to specially modulate vascular SMCs. J Mater Chem B. 2017;5(47):9312–25.
Zou Q, Fu Q. Tissue engineering for urinary tract reconstruction and repair: Progress and prospect in China. Asian J Urol. 2018;5(2):57–68.