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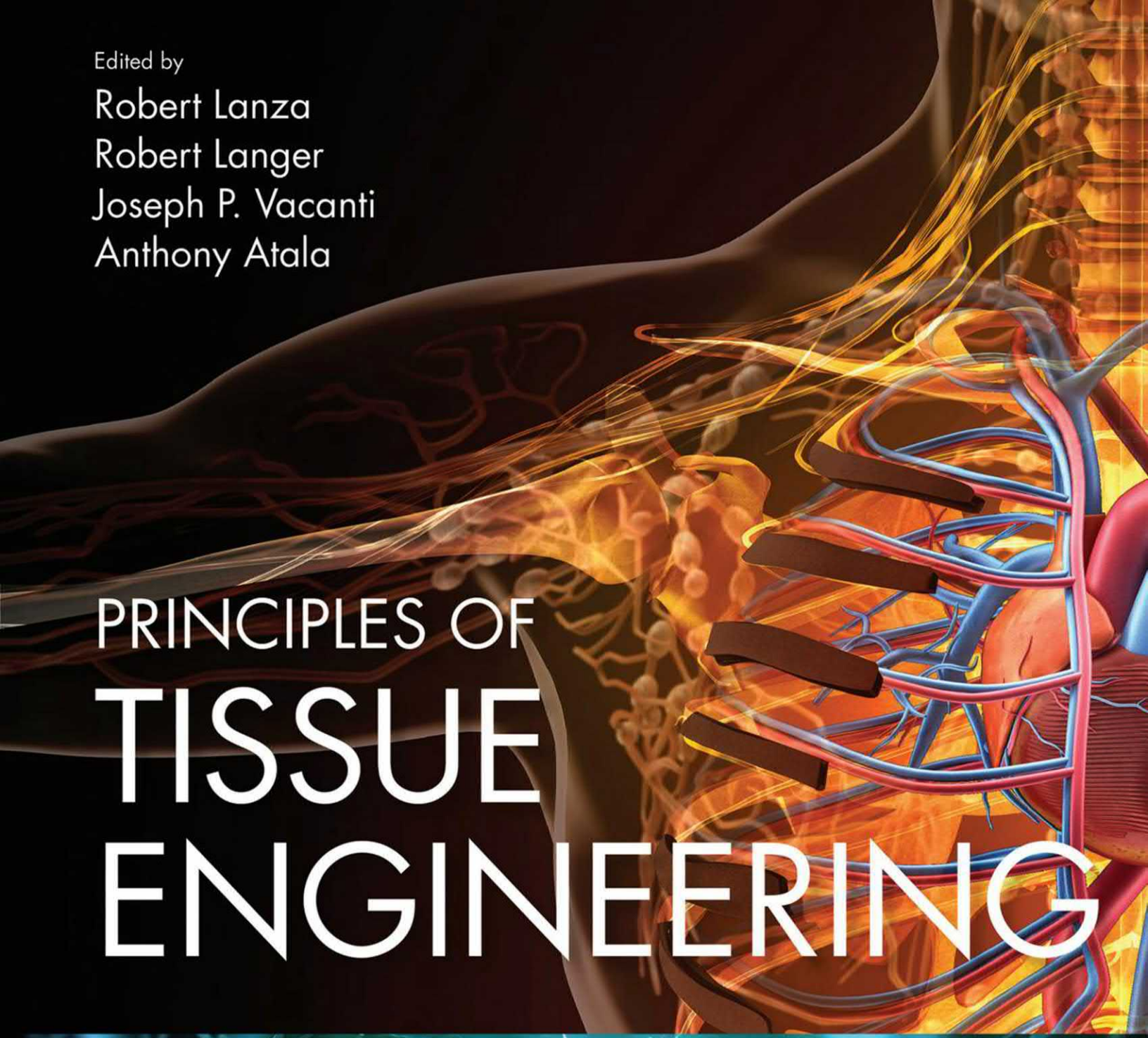

PRINCIPLES OF TISSUE ENGINEERING

FIFTH EDITION

Principles of Tissue Engineering

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Preface

The first edition of *Principles of Tissue Engineering* was published almost a quarter-of-a-century ago—back in the 1990s when the term "tissue engineering" was first coined—and quickly became the most widely relevant and cited textbook in the field. Since that time there have been powerful developments, including breakthroughs at all stages of development, ranging from two Nobel Prizes for pioneering work in the area of stem cells, which could be used as an unlimited source of cells for repair and engineering of tissues and organs, to actual clinical therapies, ranging from skin and bladder replacement to cartilage, bone, and cardiovascular repair.

The fifth edition of "Principles" covers all of this tremendous progress as well as the latest advances in the biology and design of functional tissues and organs for repair and replacement, from mathematical models to clinical reality. We have also added Anthony Atala, the W.H. Boyce Professor and Director of the Wake Forest Institute for Regenerative Medicine, as a new editor and have expanded the book to include a new section on emerging technologies, including 3D bioprinting and biomanufacturing for tissue-engineering products. As in the previous editions, the book attempts to simultaneously connect the basic sciences with the potential application of tissue engineering to diseases affecting specific organ systems. While the fifth edition furnishes a much needed update of the rapid progress that has been achieved in the field in the last 6 years, we have retained the fundamentals of tissue engineering, as well as those facts and sections which, while not new, will assist scientists, clinicians, and students in understanding this exciting area of biology and medicine.

The fifth edition of "Principles" is divided into an introductory section, followed by 23 parts starting with the basic science of the field and moving upward into applications and clinical experience. The organization remains largely unchanged, combining the prerequisites for a general understanding of cellular differentiation and tissue growth and development, the tools and theoretical information needed to design tissues and organs, as well as a presentation by the world's experts of what is currently known about each specific organ system, including breast, endocrine and metabolism, ophthalmic, oral/dental applications, skin, and the cardiovascular, gastrointestinal, hematopoietic, kidney and genitourinary, musculoskeletal, nervous, and respiratory systems. We have again striven to create a comprehensive book that, on one hand, strikes a balance among the diversity of subjects that are related to tissue engineering, including biology, chemistry, material science, medicine, and engineering, while emphasizing those research areas that are likely to be of clinical value in the future.

While we cannot describe all of the new and updated material of the fifth edition, we continue to provide expanded coverage of stem cells, including neonatal, postnatal, embryonic, and induced pluripotent stem cells and progenitor populations that may soon lead to new tissue-engineering therapies for cardiovascular disease, diabetes, and a wide variety of other diseases that afflict humanity. This up-to-date coverage of stem cell biology and other emerging technologies is complemented by updated chapters on gene therapy, the regulatory process, and the challenges of tissue engineering for food and in vitro meat production, which someday may end up a routine part of our food system, potentially reducing environmental pollution and land use. As with previous editions, we believe the result is a comprehensive textbook that will be useful to students and experts alike.

Robert Lanza, Robert Langer, Joseph Vacanti and Anthony Atala

Chapter 1

Tissue engineering: current status and future perspectives

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Clinical need

Tissue and organ failure due to disease, injury, and developmental defects has become a major economical and healthcare concerns [1]. At present, use of donated tissues and organs is the clinical practice to address this situation. However, due to the shortage of organ donors, the increasing number of people on the transplant waiting lists, and an ever-increasing aging population, dependence on donated tissues and organs is not a practical approach. In addition, due to severe logistical constraints, many organs from donors cannot be matched, transported, and successfully transplanted into a patient within the very limited time available. In the United States alone, more than 113,000 people are on the National Transplant Waiting list and around 17,000 people have been waiting for more than 5 years for an organ transplant (US Department of Health and Human Services, Organ Procurement and Transplantation network; https://optn.transplant.hrsa.gov; data as of February, 2019). To address this critical medical need, tissue engineering (TE) has become a promising option. TE and regenerative medicine (RM) are multidisciplinary fields that combine knowledge and technologies from different fields such as biology, chemistry, engineering, medicine, pharmaceutical, and material science to develop therapies and products for repair or replacement of damaged tissues and organs [2,3].

The process of TE is multistep and involves engineering of different components that will be combined to generate the desired neo-tissue or organ (Fig. 1.1). Today, this field has advanced so much that it is being used to develop therapies for patients that have severe chronic disease affecting major organs such as the kidney, heart, and liver. For example, in the United States alone, around 5.7 million people are suffering from congestive heart failure [5], and around 17.9 million people die or cardiovascular diseases globally (World Health Organization data on Cardiovascular disease; https://www.who.int/cardiovascular_diseases/en/). TE can help such patients by providing healthy engineered tissues (and possibly whole organ in future) to replace their diseased tissue for restoring function. For example, chronic kidney disease (CKD) is a worldwide health crisis that can be treated, but it also depends on organ donation. In the United States alone, around 30 million people are suffering from CKD (Center for Disease Control & Prevention; National Chronic Kidney Disease Fact Sheet 2017; https://www.cdc.gov/kidneydisease/pdf/kidney factsheet), while close to 10% of the population is affected worldwide. Liver disease is another healthcare problem, which is responsible for approximately 2 million deaths per year worldwide [6]. Other diseases or conditions that can benefit from TE technologies include skin burns, bone defects, nervous system repair, craniofacial reconstruction, cornea replacement, volumetric muscle loss, cartilage repair, vascular disease, pulmonary disease, gastrointestinal tissue repair, genitourinary tissue repair, and cosmetic procedures. The field of TE, with its goal and promise of providing bioengineered, functional tissues, and organs for repair or replacement could transform clinical medicine in the coming years.

Current state of the field

TE has seen continuous evolution since the past two decades. It has also seen assimilating of knowledge and technical advancements from related fields such as material science, rapid prototyping, nanotechnology, cell biology, and developmental biology. Specific advancements that have benefited TE as a field in recent years include novel

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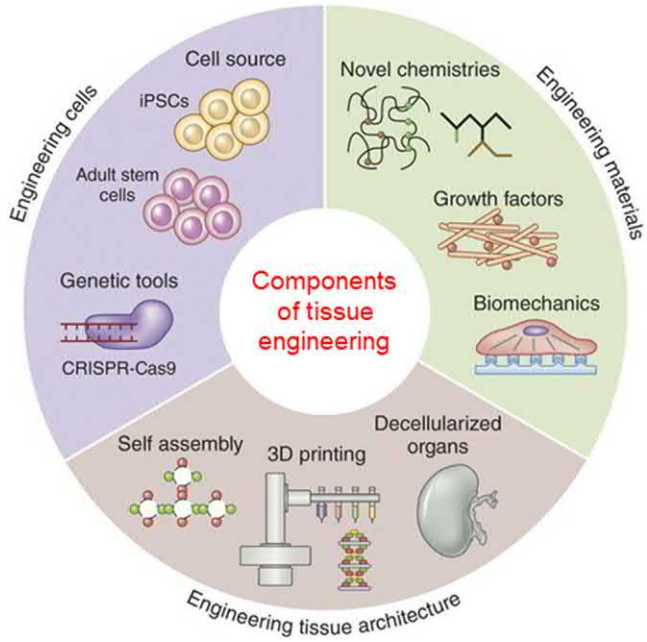

FIGURE 1.1 Schematic representation of different aspects of tissue engineering. Each component (materials, cells, and tissue architectures) can be engineered separately or in combination to achieve the therapeutic goals. *Reprinted with permission from Khademhosseini A., Langer R. A decade of progress in tissue engineering. Nat Protoc 2016;11 (10):1775–81. doi: 10.1038/nprot.2016.123 [4]. ©2016 Springer Nature Publishing AG.*

biomaterials [7], three-dimensional (3D) bioprinting technologies [8], integration of nanotechnology [9], stem-cell technologies such as induced pluripotent stem cells (iPSCs) [9,10], and gene editing technology such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) [11]. All these have led to promising developments in the field that include smart biomaterials, organoids, and 3D tissue for disease modeling and drug development, whole organ engineering, precise control and manipulation of cells and their environments, and personalized TE therapies.

Biomaterials are critical components of many current TE strategies. Recent developments in this field that are benefiting TE include synthesis of new biomaterials that can respond to their local environment and cues (smart biomaterials). Advancements in 3D bioprinting technologies are at the core of many developments in TE. It is now possible to print multiple biocompatible materials (both natural and synthetic), cells, and growth factors together into complex 3D tissues, many with functional vascular networks, which match their counterparts in vivo. We have also learned a great deal about cell sourcing, culture, expansion, and control of differentiation. This is also true for stem cells, where new sources such as placenta, amniotic fluid, and iPSCs have been explored and optimized for use. Vascularization and innervation in bioengineered tissue is a continuing challenge essential to warrant sustained efforts success of tissues implanted in vivo would be very low. Therefore there is a need for greater understanding of vascularization and innervation as applied to bioengineered tissues. This is an ongoing effort, and the results we are seeing from various studies are encouraging. Biofabrication technologies are playing a great role in this regards.

Several engineered tissues are moving toward clinical translation or are already being used in patients. These include cartilage, bone, skin, bladder, vascular grafts, cardiac tissues, etc. [12]. Although, complex tissues such as liver, lung, kidney, and heart have been recreated in the lab and are being tested in animals, their clinical translation still has many challenges to overcome. For in vitro use, miniature versions of tissues called organoids are being created and used for research in disease modeling, drug screening, and drug development. They are also being applied in a diagnostic format called organ-on-a-chip or body-on-a-chip, which can also be used for the above stated applications. Indeed, the development of 3D tissue models that closely resemble in vivo tissue structure and physiology are revolutionizing our understanding of diseases such as cancer and Alzheimer and can also accelerate development of new and improved therapies for multiple diseases and disorders. This approach is also expected to drastically reduce the number of animals that are currently being used for testing and research. In addition, 3D tissue models and organ-on-a-chip or body-on-a-chip platforms can support advancement of personalized medicine by offering patient-specific information on the effects of drugs, therapies, environmental factors, etc.

Development of advanced bioreactors represent another recent developments that are supporting clinical translation of TE technologies. Such bioreactors can better mimic in vivo environments by provide physical and biochemical control of regulatory signals to cells and tissue being cultured. Examples of such control include application of mechanical forces, control of electrical pacing, dynamic culture components, induction of cell differentiation. Incorporation of advanced sensors and imaging capabilities within these bioreactors are also allowing for real-time monitoring of culture parameters such as pH, oxygen consumption, cell proliferation, and factor secretion from a growing tissue. 3D modeling is also a new tool relevant to TE that provides great opportunities and better productivity for translational research, with wide clinical applicability [13]. Recent advancements in specific field that are helping advance TE are discussed next.

Smart biomaterials

Smart biomaterials are biomaterials that can be designed to modulate their physical, chemical, and mechanical

properties in response to changes in external stimuli or local physiological environment (Fig. 1.2) [14,15]. Advances in polymer synthesis, protein engineering, molecular self-assembly, and microfabrication technologies have made producing these next-generation biomaterials possible. These biomaterials can respond to a variety of physical, chemical, and biological cues such as temperature, sound, light, humidity, redox potential, pH, and enzyme activity [16,17]. Other unique characteristics displayed by some smart biomaterials are self-healing or shape-memory behavior [18]. The development of biomaterials with highly tunable properties has been driven by the desire to replicate the structure and function of extracellular matrix (ECM). Such materials can enable control of chemical and mechanical properties of the engineered tissue, including stiffness, porosity, cell attachment sites, and water uptake. For hydrogels, use of reversible cross-linking through physical methods, self-assembly, or thermally induced polymer chain entanglement is creating hydrogels that undergo structural changes in response to external stimuli [19,20]. Another class of hydrogels that are recent developments is called self-healing and shear thinning hydrogels. These materials are now being used to develop injectable biomaterials, which have low viscosity during application (injection) due to shear thinning and once at their target site, they self-crosslink (or heal) to fill the defect site [21]. Injectable biomaterials are also often loaded with drugs, biologics, and cells. For example, Montgomery et al. created an injectable shape-memory biomaterial for minimally invasive delivery of functional tissues [22]. In other applications, tissue glues are being developed using smart biomaterials, where they are used to bond and allow the tissue to self-heal. An example of this approach is a study by Bhagat and Becker

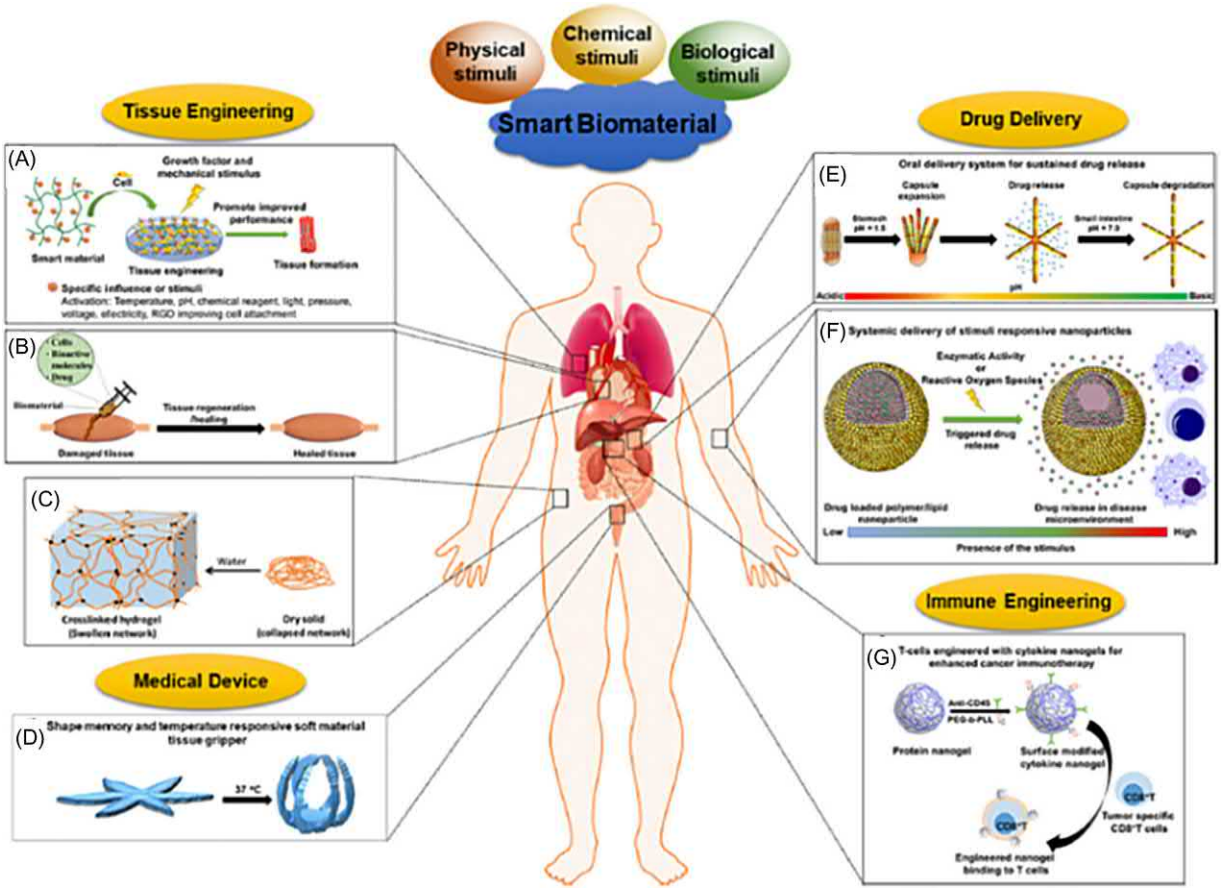

FIGURE 1.2 Different applications of smart biomaterials in the fields of tissue engineering and related fields. (A) Stimuli-responsive material that can promote cell differentiation and tissue growth; (B) injectable biomaterial loaded with cells, drugs, or bioactive molecules can be delivered less-invasively and can promote healing of tissue at the target damage site; (C) swelling polymer can be delivered as small scaffolds but can expand in vivo to achieve 3D structure of the target defect after exposure to water; (D) shape-memory and temperature-responsive soft material can be used as a tissue adhesive; (E) star-shaped delivery system for sustained drug release in the gastrointestinal tract; (F) nanoparticle-based stimuli-responsive drug delivery system for systemic application; (G) materials for enhanced cancer immunotherapy using targeted delivery of chimeric antigen receptor T cell. *3D*, Three-dimensional. *Reprinted with permission from Kowlaski PS, Bhattacharya C, Afewerki S, Langer R. Smart biomaterials: recent advances and future directions. ACS Biomater Sci Eng 2018;4(11):3809−17 [14].*

who created a chondroitin-based tissue glue that helps direct improved tissue repair [23].

The ECM is a complex and dynamic structural scaffold for cells within tissues and plays an important role in regulating cell function [1]. Given the role of the ECM in structural support of tissues, there has been significant effort in developing ECM-based scaffolds for TE and RM [24,25]. However, as with all materials implanted into the body, the immune response significantly influences the ability of scaffold-containing engineered tissues to integrate and functionally interact with the host [26]. Thus an emerging strategy in TE is to design materials that can directly control the host immune response [27]. For example, the Arg-Gly-Asp (RGD) of ECM proteins can exert immunomodulatory effects on both innate and adaptive immune cells while also having an inhibitory effect on phagocytosis and neutrophil chemotaxis [28]. In the context of TE, synthetic ECM-mimetic hydrogels containing the RGD sequence have been shown to cause increased cellular adhesion on polymer scaffolds and also have an antiinflammatory effects from macrophages [29,30]. Under certain conditions, the RGD peptides have also been found to effect cytokine secretion from T cells [31]. Therefore use of RGD as part of TE scaffolds or hydrogels can be used to enhance cells adhesion in addition to controlling the ability of macrophages to degrade and remodel the surrounding tissue environment.

Matrix metalloproteinases (MMPs) are a family of proteases that not only selective degrade a wide variety of ECM proteins but also interact with bioactive molecules, some of which have immunomodulatory effects [32,33]. So, another strategy to control the extent of matrix remodeling, integration of engineered tissues into native host tissues or invasion of immune cell into implanted materials could be by incorporating MMP-sensitive peptides into the TE constructs. Examples of this approach include studies by Patterson and Hubbell, who showed that the rate of scaffold material degradation depends on the MMP-sensitive peptide sequence, the type of MMP, and also the MMP concentrations [34]. In a separate study, West and Hubbell created biomimetic poly(ethylene glycol) (PEG) hydrogels that incorporated peptides that could be degraded by either a fibrinolytic protease (plasmin) or a fibroblast collagenase (MMP-1) [35,36]. One drawback of this using MMP-sensitive peptides in TE constructs is their immunogenicity and more work will be needed to get around this issue. Possibly, use of immunomodulatory domains along with MMP-sensitive peptides could support long-term viability and integration within native host tissues.

Another category of smart biomaterials is multidomain peptides (MDPs) hydrogels. These are injectable ECM mimetic materials that are engineered to form self-assembling meshes at the target site [37,38]. These MDPs can also control cellular behavior. For example, in a mouse study by Moore et al., MDPs alone were found to be biocompatible and had prohealing effects in vivo [39]. Hydrogel have also been prepared from multiple ECM mimetic peptides for the purpose of enhancing the viability of the biomaterial in vivo. Smart biomaterials are going to have a big impact on 3D printing of tissues and organs. By combining smart biomaterials with 3D bioprinting, a wide variety of architectures can be created which can further offer control over how these materials perform in a biological environments. Smart biomaterials can also be made from proteins. Some protein−protein interactions can be utilized to physically crosslink protein chains, while small coiled-coil domains within some proteins (called leucine zippers) can self-assemble into superhelical structures. Leucine zippers have been used to make hydrogels by physically crosslinking protein domains [40]. The stability of the leucine zipper self-assembly (and hence the hydrogel) can be controlled by changing the temperature. Another way to control the stability of some protein-based hydrogels is by arrangement of the interacting domains [41].

One drawback of hydrogels made of self-interacting protein domains is their low-to-moderate mechanical properties, which is not ideal for TE applications. However, these week interactions can be reinforced by introducing covalent bonds into the network (e.g., disulfide bonds between cysteine in the protein chains). This will not only improve the mechanical properties of the hydrogel but also its stability [42].

Cell sources

For TE, a variety of cell types are now being used. They include autologous, allogeneic, progenitors, adult unipotent or multipotent stem cells and iPSCs (Fig. 1.3). For some applications, the ability to expand a sufficient number of autologous cells from a small biopsy is well-established [44]. A good example is bladder augmentation, where smooth muscle and urothelium can be easily isolated from then native tissue, expanded in culture and used for engineering a new bladder tissue. However, in many cases, it is challenging to harvest and/or expand enough appropriate autologous cells for this purpose. Examples of such cell types include hepatocytes, kidney cells, insulin-producing pancreatic beta cells, cardiomyocytes, neurons. New sources or methods to obtain these cell types in quantities can advance engineering of these tissues/organs and significantly benefit treatment of associated diseases. Immature precursor cells present within tissue such as skin, cartilage, muscle, and bladder are essential for the expansion of corresponding cells from biopsies and enabling engineering of neo-tissues [45]. The extension of this approach to other tissue and organ

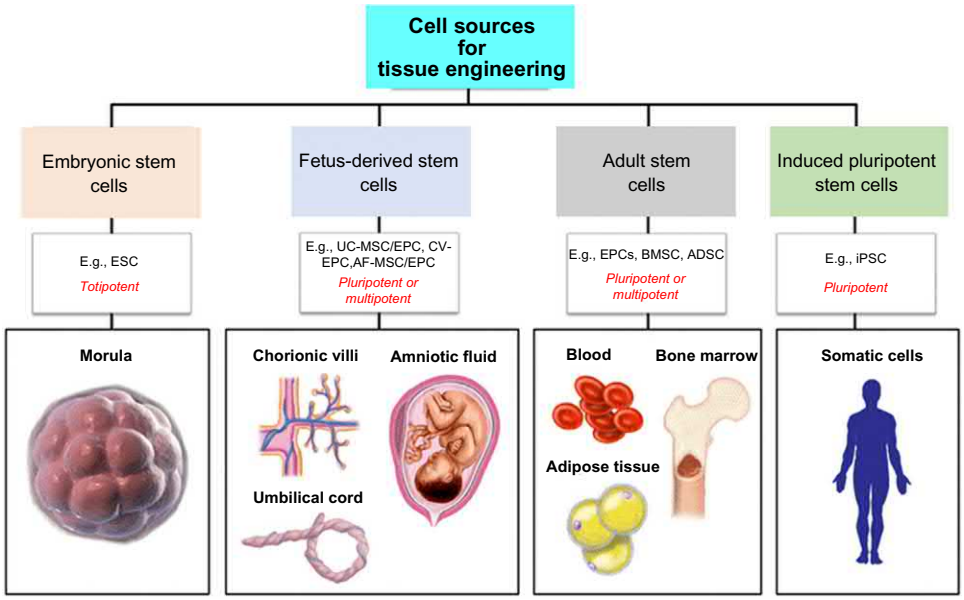

FIGURE 1.3 Different sources of cells for tissue engineering. Fetus-derived and induced pluripotent stem cells are gaining more attention for tissue engineering applications. *Reprinted from Al-Himdani S, Jessop ZM, Al-Sabah A, Combellack E, Ibrahim A, Doak SH, et al. Tissue-engineered solution in plastic and reconstructive surgery: principles and practice. Front Surg 2017;4:4. doi: 10.3389/fsurg.2017.00004. [43]. ©2017 Al-Himdani, Jessop, Al-Sabah, Combellack, Ibrahim, Doak, Hart, Archer, Thornton and Whitaker. Open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). Some portions of the original artwork have been modified.*

systems will depend greatly on finding sources of appropriate stem and progenitor cells.

Three major stem-cell sources are currently under intensive investigation:

1. embryonic stem (ES) cells, which are derived from discarded human embryos, and the equivalent embryonic germ (EG) cells;
2. iPSCs derived by genetic reprograming of somatic cells; and
3. Autologous or allogeneic adult tissue stem cells (sourced from fetal, neonatal, pediatric, or adult donor tissue).

Shared features of all stem cells include their capacity self-renewal and their ability to give rise to particular classes of differentiated cells. The ES, EG, and iPSCs can serve as precursors for many specialized cell type found during normal development and therefore are pluripotent. Adult stem cells are generally restricted to limited sets of cell lineages, hence called unipotent (constrained to a single fate) or multipotent (can give rise to multiple cell types). It appears likely that multiple tissue-engineered products based on each class of stem-cell source will be tested in the clinic in the coming years. Previous clinical and commercial experience sheds light on key differences between personalized products containing autologous cells and off-the-shelf products containing allogeneic cells. The vast majority of human studies till date have focused on using either adult stem or progenitor cells. More recently, clinical trials have begun with tissue-engineered products derived from pluripotent stem cells and their future looks promising.

The first clinical tissue-engineered products to achieve marketing approval from the US Food and Drug Administration (FDA) were skin substitutes that were used for wound healing. Examples of such products include Dermagraft (Shire Regenerative Medicine Inc., CT, United States) and Apligraf (Organogenesis, MA, United States), which were off-the-shelf products that used cells (fibroblasts for Dermagraft and fibroblasts plus keratinocytes for Apligraf) expanded from donated human foreskins. Whereas fibroblasts have been cultured in vitro since the early 20th century, the successful large-scale culture of human keratinocytes represented an important breakthrough for RM [46]. The success of off-the-shelf skin substitutes can be attributed to the lack of antigen-presenting cells, because of which they were not acutely rejected despite the inevitable histocompatibility mismatches between donors and recipients [47,48]. Eventually, the cells in the skin substitutes could be rejected, but the grafts has enough time for patients' own skin cells to regenerate. This stands in contrast to standard tissue/organ transplantation in which immune rejection is a major concern and immunosuppressive drug therapy is generally part of the application of allogeneic grafts [49]. Tissue-engineered products based on harvesting and expanding autologous cells containing stem and/or progenitor populations have also been developed successfully. Prominent examples include Epicel (Genzyme, MA, United States), a permanent skin replacement product based on expanded keratinocytes for patients with life-threatening burns, and Carticel (Genzyme, MA, United States), a chondrocyte-based treatment for large articular cartilage lesions [50,51].

Embryonic stem cells

ES cells and EG cells are indeed quite similar to early germ cells, with an apparently unlimited self-renewal capacity and pluripotency. Their great degree of plasticity represents both a strongest virtue and a significant potential limitation to their use in TE. A major ongoing challenge is in efficiently obtaining pure populations of specific desired specialized cell types from human ES cells [52,53]. Efforts during recent years have yielded more robust methods to isolate and grow ES cells under conditions consistent with Good Manufacturing Practice (GMP) and to generate differentiated cell products. While initial efforts have focused on cell therapies, these advances will positively impact production of tissue-engineered constructs using ES cells. Human ES cells are considerably more difficult to isolate and maintain stably in culture than the cell types that have previously been used in clinical testing. However, they can now be derived, grown, and cryopreserved without exposure to nonhuman cells or proteins, even under a GMP environment [54,55]. In the future, use of bioreactors, microcarriers, along with improved xeno-free and serum-free media and possibly small molecules that inhibit spontaneous differentiation of these cells would facilitate expansion of these stem cells to population sizes that are normally required for product development and clinical application [56,57].

Human tissues include more than 200 distinct cell types, and ES cells, in principle, can give rise to all of them. The historical approach of allowing ES cells to differentiate spontaneously has now been supplanted. Current strategies employ staged differentiation guided by knowledge of signaling events that regulate normal embryonic development [58]. For example, fine tuning of the exposure of early embryonic cells to the growth factor Nodal (a member of the transforming growth factor beta or TGF-β family) or its analog Activin A, in conjunction with other growth factors or small molecules, can now allow consistent generation of endoderm-specific cells from ES cells in vitro [59,60]. This is an early, but key milestone in a multistep process to generate differentiated cells that can eventually be used for TE of tissues/organs like the liver and pancreas. Conversely, inhibition of Nodal/Activin signaling favors the production of ectoderm specific cells, a precursor for neural lineage cells [61].

Despite substantial challenges, the first ES-cell-derived therapeutic product to enter clinical trials was the human ES-cell-derived oligodendrocyte progenitors (Geron Corporation; CA, United States) for stimulating nerve process growth in subjects with spinal cord injury [62]. Similarly, ES-cell-derived retinal pigment epithelium cells (Advanced Cell Technology, now Astellas Institute for Regenerative Medicine; CA, United States) were used in clinical trials in patients to treat Stargardt's macular dystrophy and dry age-related macular degeneration. Encouraging results from such clinical studies using ES cell-derived product will have a positive impact to develop tissue-engineered products from pluripotent stem cells in the near future. Areas of clear unmet medical need that might benefit from stem-cell-derived products include type 1 diabetes and Parkinson's disease. For type 1 diabetes, research at a biotech company called Viacyte Inc. (CA, United States) similarly pursued the produced progenitors of pancreatic endocrine cells from human ES cells using growth factors and hormones [63]. The progenitor cells from the final-stage differentiation in vitro were able to mature further in vivo to yield glucose-responsive β-like cells [64]. As a potential therapy for Parkinson's disease, significant advances have been made in the production of functional midbrain dopaminergic neurons by staged differentiation from ES cells [65,66]. Studies in the past few years have demonstrated that efficient grafting of these cells can lead to physiological correction of symptoms in several animal models, including nonhuman primates [67]. A particular safety concern is that undifferentiated pluripotent ES and iPS cells form teratomas in vivo. The risk of tumorigenicity makes it essential to rigorously determine the residual level of undifferentiated stem-cell population in any therapeutic product derived from ES or iPS cells [68]. It will also be valuable to determine whether a small number of undifferentiated pluripotent stem cells can be introduced into human patients without significant risk of tumor growth and if this threshold is influenced by use of immune suppressive drugs during treatment.

Induced pluripotent stem cells

Theoretically, the development of iPSCs represent the most direct way to ensure immune compatibility of tissue-engineered products when the recipient themselves serve as the donor. Generation of iPSCs through reprograming of mature somatic cells to a pluripotent state was first accomplished by ectopic expression of four transcription factors: OCT4 and SOX2, both with KLF4 and c-MYC [69] or NANOG and LIN28 [70]. The resulting iPSCs closely resembled ES cells in key properties such as the capacity for extensive self-renewal, ability to differentiate to multiple cell lineages, and generation of teratomas in vivo. Initial studies on reprograming of fibroblasts soon were extended to a variety of other cell types such as peripheral blood cells [71], cord blood cells [72], keratinocytes from hair shafts [73], and urine-derived cells [74]. Many recent developments have advanced this reprograming technology toward a safer, efficient translation toward therapeutic products. Also,