

An introduction of tissue engineering and regenerative medicine

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2.1 Introduction

Regenerative medicine is a branch of medicine that focuses on developing methods to repair, replace, or regenerate damaged or diseased cells, tissues, and organs. Unlike traditional medicine, which often focuses on treating symptoms or halting disease progression, regenerative medicine aims to restore normal function by using the body's healing mechanisms or by introducing new, functional tissues created in the laboratory (Bahari Golamkaboudi et al., 2024). Tissue engineering is a rapidly advancing

field focused on developing and modifying laboratory-grown cells and molecules to create functional tissues or organs to replace or repair damaged body parts. While scientists have been able to grow cells outside the body for many years, the ability to construct complex, three-dimensional (3D) cell networks that can effectively replace damaged tissues has only recently been achieved (Aseer et al., 2024). The foundational concept of tissue engineering requires the design of a scaffold with an appropriate physical structure that facilitates cell adhesion, migration, proliferation, and

differentiation. This scaffold ultimately supports the growth and integration of new tissue within the body (Nazeri et al., 2019).

Tissue engineering, a field first introduced by Alexis Carrel and Charles Lindbergh in the early 1900s, originally aimed to sustain tissues in lab conditions for replacement in living organisms. Significant advances occurred in the 1980s with the creation of artificial skin, marking the field's emergence as a distinct scientific discipline (Kretlow & Mikos, 2010). Tissue engineering addresses major challenges in organ transplantation such as high costs, contamination risks, immune reactions, and rejection by offering innovative solutions for repairing tissue defects. This approach involves harvesting or differentiating cells, exposing them to growth factors, and growing them within a scaffold. Once implanted, the scaffold supports tissue regeneration, with soft tissues gradually replacing it, and hard tissues using durable materials for long-term support (Arabpour et al., 2019). This process involves harvesting or differentiating cells, exposing them to growth factors, and growing them on scaffolds that mimic the extracellular matrix (ECM) of the target tissue. These highly porous and biodegradable scaffolds are crucial for directing cell growth and organization, supporting nutrient exchange, and ensuring mechanical stability. As cells proliferate and mature, the scaffold is degraded, allowing new tissue to form and integrate. Effective scaffolds must balance porosity for nutrient flow with structural support necessary for tissue development and function (Arabpour et al., 2020). These engineered modules can serve as living materials to repair scar tissue at injury sites or as building blocks to create larger tissue grafts or organ implants. In the future, the availability of engineered "living" tissues or organ substitutes could significantly reduce the need for organ transplantation and accelerate the development of new treatments for patients with reparable organ failure and potentially the need for organ transplantation (Chen & Liu, 2016).

Although the biotechnology to produce fully functional complex organs is not yet available, there is growing evidence that the body's natural regenerative capabilities can be enhanced by replacing tissue segments and enhancing the regenerative cascade (Soto-Gutierrez et al., 2012). Current tissue engineering strategies often involve the ex vivo expansion of multipotent cell populations such as mesenchymal stem cells (MSCs) followed by their transplantation into damaged areas. MSCs are particularly promising in tissue engineering and regenerative medicine due to their unique regenerative potential and immunomodulatory properties (Soleimani et al., 2023). These cells not only directly contribute to wound healing and tissue regeneration, but also modulate the host's immune response to the transplant. Typically, MSCs are grafted onto a biomaterial scaffold consisting of a biodegradable 3D matrix that provides the necessary extracellular environment with physical and chemical cues to guide tissue growth and development (Banani et al., 2021).

2.2 Scaffolds in tissue engineering

The main goal of tissue engineering is to repair and regenerate damaged tissues using various approaches. A crucial element in this process is the use of biomaterials, which can be sourced from natural materials or created synthetically. These biomaterials are used to replace tissue either partially or completely (Arabpour et al., 2024a). To be effective, they must meet certain key requirements: they need to be biocompatible to prevent immune responses, sterilizable to ensure safety, biodegradable so that they break down after serving their purpose, and bioactive to promote tissue response (Fig. 2.1) (Suhag et al., 2024).

At the core of tissue engineering techniques is the scaffold, a 3D porous matrix that provides a suitable surface for cell attachment and interaction with specific biomolecules. The

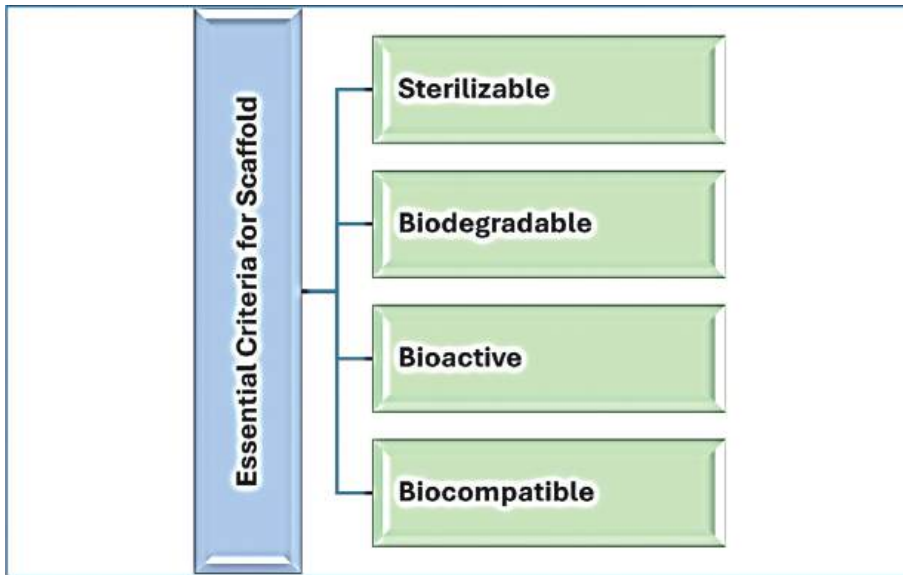


FIGURE 2.1 Essential criteria for scaffold design.

scaffold's internal structure and composition significantly influence cell behavior and tissue formation (Okamoto, 2019). Scaffolds serve as supportive structures *in vivo* or as substrates for cell attachment *in vitro*, shaping the overall structure of organs and tissues without replicating the fine nanoscale details of natural organs. However, the ECM nanoarchitecture plays a crucial role, featuring a complex network of fibrillar systems where molecular interactions occur among elastins, collagens, proteoglycans, and adhesive proteins like laminins and fibronectins (Frantz et al., 2010). This intricate environment sends signals that guide cell behavior, facilitating the development of complex tissues such as bone, liver, heart, and kidney (Noro et al., 2024).

Scaffolds in tissue engineering must possess certain characteristics to function effectively as ECM substitutes. These include:

- **Biocompatibility:** The materials used must support cell attachment and growth without causing adverse tissue reactions or inflammation from degradation byproducts.

- **Porous structure:** Scaffolds should feature an interconnected porous structure with controlled pore geometry and size. This design is crucial for maintaining mechanical stability, allowing adequate tissue regeneration, cell penetration, nutrient transport, and waste removal. The optimal pore size and shape can vary by cell type but must be sufficient to support 3D tissue formation and maximize tissue growth while minimizing material use.
- **Mechanical properties:** The scaffold must possess mechanical properties similar to the target tissue. This similarity helps promote proper vascularization and reduces the risk of creating unwanted tissue types due to differences in mechanical properties between the scaffold and the newly formed tissue (Williams, 2018).

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Natural polymers (NPs) like chitosan, gelatin, collagen, cellulose, and alginates are often favored over synthetic options such as Poly Lactic-co-glycolic Acid (PLGA), poly (ϵ -caprolactone) (PCL), poly(lactic acid) (PLA), fibronectin, and polyurethane due to their superior biocompatibility, excellent biodegradability, and low toxicity (Guo et al., 2021). However, plant-derived biomaterials are becoming more popular than animal-derived ones because of concerns related to diversity, ethical and environmental issues, higher costs, and more complex extraction and purification processes. In addition to providing mechanical support, an ideal tissue engineering biomaterial should mimic the native tissue's ECM, facilitate vascularization and integration with the host tissue, and degrade as new tissue forms and remodels the area initially occupied by the scaffold (Emami et al., 2023). Scaffolds can be used without cells (acellular), where they are expected to be populated by host cells after implantation, or they can be preseeded with cells

in vitro before being implanted. Proper scaffold design is critical, as cell adhesion is key to tissue growth and maintenance. It triggers signals that regulate the cell cycle, migration, differentiation, and survival. Therefore, designing scaffold matrices that enhance cell affinity is essential for creating an optimal environment for cell attachment and tissue development (Fani et al., 2024).

Polymer-based scaffolds offer a valuable solution in tissue repair by supporting tissue regeneration and creating an environment that promotes faster healing. Polymers are long-chain macromolecules composed of repeating units called monomers linked by covalent bonds. Understanding the synthesis and construction of polymers is very important in the field of biomedicine. Among the various biomaterials available for medical use, NPs and synthetic polymers (SPs) are the most widely used for making scaffolds (Ozdil & Aydin, 2014).

2.3 Natural polymers

Nanoparticles derived from biological sources have been used in various human applications such as pharmaceuticals, drug delivery, cosmetics, prostheses, and scaffolds. As components of the ECM, nanoparticles are bioactive, allowing them to be recognized and degraded by the body and enhance cellular interactions with materials (Simorgh et al., 2021). Also, compared to SPs, NPs cause less chronic inflammation or immune reactions and can be chemically modified, biodegradable, and biocompatible. These advantages, along with affordability and availability, make NPs attractive for biomedical applications. However, they have disadvantages, such as sensitivity to temperature, which can lead to degradation before reaching the melting point, and the risk of disease transmission from their biological sources. Examples of nanoparticles used in clinical applications include proteins such as silk fibroin, collagen, and gelatin, as well as polysaccharides such as chitosan, chitin, and alginate (Arabpour et al., 2024b; Maharjan et al., 2021).

2.4 Synthetic polymers

Synthetic polymers, which were introduced later than NPs, have become increasingly important in recent years. They offer greater versatility for biomedical applications with the ability to create custom designs and control chemical changes (Arabpour et al., 2020). SPs have several advantages, including favorable mechanical properties, controlled degradation rates, mass production, and long shelf life. Many Food and Drug Administration (FDA)-approved SPs, such as PLA, poly(glycolic acid) (PGA), and their copolymer PLGA, degrade to nontoxic byproducts through hydrolysis. Other SPs such as PCL and poly(hydroxybutyrate) (PHB) are also used in tissue engineering, with PCL especially for long-term implants and controlled material release due to its slower degradation rate. SPs such as poly(propylene fumarate) (PPF) and poly(glycerol subcategory) (PGS) are ideal for bone tissue engineering and offer biocompatibility, biodegradability, and osteoconductive (Jeong & Atala, 2015). Polymers are usually degraded by hydrolysis to produce natural metabolites, and their degradation rates can be adjusted to match specific tissue needs. This is particularly useful for the controlled release of molecules such as hormones and growth factors. However, some metabolites can induce immunological or toxic responses when combined with certain polymers that the host tissue cannot integrate. A promising solution is to combine natural and SPs to balance their strengths and weaknesses, creating scaffolds that take advantage of the best qualities of both types (Guo & Ma, 2014).

2.5 Stem cells in tissue engineering

Stem cells possess the unique ability to self-renew while also having the potential to differentiate into any cell type within the body (Hao et al., 2020). As cells undergo various stages of specialization, their developmental potency gradually decreases (Fig. 2.2). Totipotent cells

have the highest differentiation potential, capable of forming both embryos and extraembryonic tissues. In contrast, pluripotent cells, such as embryonic stem cells (ESCs) (derived from the inner cell mass of a preimplantation embryo) and induced pluripotent stem cells (iPSCs) (somatic cells reprogrammed artificially), can form nearly all cell types but not extraembryonic structures. As the spectrum of differentiation narrows further, it reaches unipotent cells, which, despite having the most limited differentiation capacity, retain the ability to divide repeatedly (Zakrzewski et al., 2019).

ESCs are highly versatile, pluripotent cells that originate from the inner cell mass of blastocysts. Through precise manipulation of their culture conditions, these cells can be directed to differentiate into a wide variety of specific cell types (Vazin & Freed, 2010). While ESCs offer significant advantages due to their inherent pluripotency and capacity for self-renewal, several obstacles have hindered their widespread clinical use (Rong et al., 2014). One of the main challenges is that ESCs, being derived from embryos, are allogeneic when transplanted into a patient. This mismatch can trigger an immune response, leading to the potential rejection of the cells (Boyd et al., 2012). Furthermore, the process of inducing differentiation into the desired cell type is complex and not always efficient, which increases the risk of leaving behind undifferentiated cells. These residual cells may form teratomas, a type of tumor, thus posing a significant safety concern. Additionally, the ethical debate surrounding the use of human embryos to obtain ESCs has further delayed the progression of ESC-based therapies into clinical practice (Kwon et al., 2018).

In contrast, the groundbreaking work of Yamanaka and his colleagues (2006) introduced a revolutionary approach by reprogramming mature somatic cells into iPSCs. This process involves the introduction of four key transcription factors that restore pluripotency to the cells, thereby allowing them to function similarly to ESCs. One of the major advantages of iPSCs

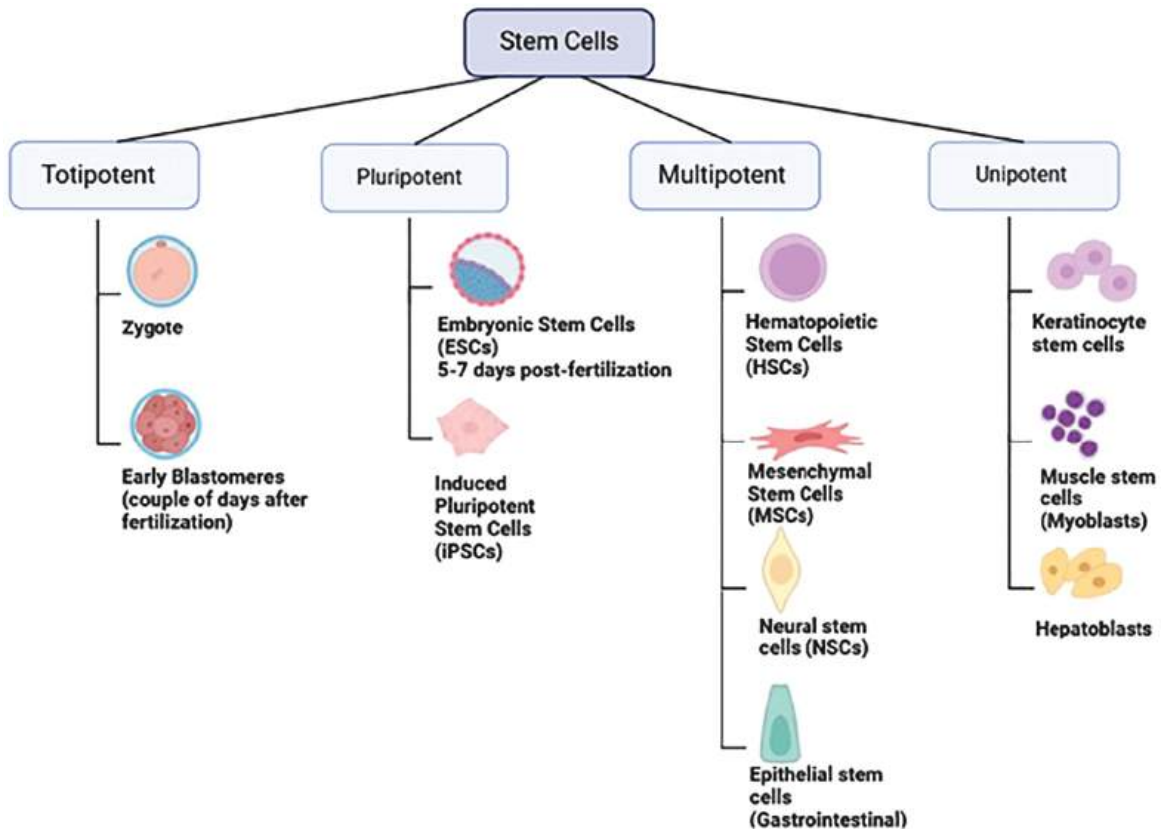


FIGURE 2.2 Classification of stem cells based on potency.

is that they bypass the ethical issues associated with the use of embryonic cells (Hu et al., 2015). Despite this, iPSCs are not without their risks, particularly the potential for tumorigenesis. However, using autologous iPSC-derived cells from the patient's own body can mitigate some of the safety concerns, particularly those related to immune rejection (Mandai et al., 2017). A pioneering example of this approach is seen in the work of Japan's RIKEN Institute, where iPSC-derived cells were successfully transplanted into patients with age-related macular degeneration, marking a significant milestone in regenerative medicine (Mandai et al., 2017). Nonetheless, the risk of tumor formation remains a critical issue, as the factors used in

reprogramming are also implicated in cancer development (Medvedev et al., 2010).

MSCs on the other hand, offer a different therapeutic potential. These cells can be harvested from various tissues, including adipose tissue and bone marrow, and are characterized by their fibroblast-like shape and the expression of specific surface markers such as CD73, CD90, and CD105. MSCs are not only capable of self-renewal, but they can also differentiate into multiple mesodermal cell lineages, including adipocytes (fat cells), myocytes (muscle cells), chondrocytes (cartilage cells), and osteoblasts (bone cells) (Tong et al., 2015). Beyond their differentiation potential, MSCs exhibit immunomodulatory properties and promote

angiogenesis, making them particularly valuable in the context of tissue repair and regeneration (Murphy et al., 2013). As a result, several MSC-based therapies have already been developed and are commercially available, highlighting their practical application in clinical settings (Jossen et al., 2018).

2.6 Advanced in tissue engineering

Recent advancements in tissue engineering have significantly sped up progress, especially in areas like tissue culture, scaffold creation, 3D printing, and testing with animal models. These developments are helping overcome challenges related to the clinical use of tissue engineering techniques (O'Donnell et al., 2019).

Due to the limited availability of a patient's own stem cells for tissue culture, there has been increasing interest in the flexibility of stem cells. Scientists have isolated multi- and pluripotent stem cells from different parts of the body, such as MSCs, which have been particularly useful in repairing cartilage. Techniques like microencapsulation have made MSCs last longer and work more effectively (Li et al., 2017). Additionally, human embryonic stem cells (hESCs) and iPSCs have shown great potential in creating various cell types in the lab (Kobold et al., 2015).

Improvements in the conditions for cell growth have further boosted the efficiency of cell regeneration. For instance, some stem cells grow better in low-oxygen environments, similar to those inside the body, rather than in the standard high-oxygen lab settings. By optimizing factors like oxygen levels, growth signals, and the ECM (environment surrounding cells), researchers have significantly enhanced cell responses in tissue engineering processes (Yoshioka & Yoshiko, 2017). Moreover, non-coding RNAs (ncRNAs) have been identified as important regulators of cell behavior and tissue growth, making them new targets for

developing tissues in the lab and in living organisms (Chaturvedi et al., 2017).

There have also been major improvements in creating scaffolds, which support tissue growth. Natural extracellular matrices (ECMs), which help guide tissue formation, can be obtained by carefully removing cells from tissues while preserving the ECM. Although human acellular scaffolds have been successfully used in transplants, concerns about infection and immune reactions from animal-derived ECMs have led to a focus on synthetic materials for 3D scaffolds. These artificial scaffolds, made from materials like collagen, silk, alginate, and apple cellulose, are often combined with stem cells, such as MSCs or hiPSCs (Sharma et al., 2019). Researchers are also working on improving blood supply to thick, implantable tissues, using combinations like endothelial cells and muscle precursors to create vascularized heart muscles (Perry et al., 2017). The development of 3D scaffold printing has revolutionized tissue engineering by enabling the creation of lifelike tissues, bringing us closer to producing vascularized 3D organs to address the shortage of organs for transplantation (Kim et al., 2017).

Key technologies used in fabricating multimaterials in advanced tissue engineering include 3D bioprinting, micro-nano processing, and electrostatic spinning (Zhao et al., 2023b). Three critical strategies for designing these materials are bio-inspired design, performance-based design, and data-driven design. Bio-inspired designs replicate natural structures to enhance biocompatibility, while performance-based design focuses on aligning material properties with specific application requirements and optimizing material combinations through experiments and simulations. The data-driven design leverages extensive data analysis to refine material choices and improve performance (Chen et al., 2023).

The applications of multimaterial fabrication in tissue engineering are varied, such as hydrogel composites that merge flexibility and biocompatibility with other functional materials,

and fiber-reinforced composites that enhance strength. The goal is to integrate biocompatible materials into advanced systems with gradient properties and smart response capabilities. These materials can adapt to various environments and react to external stimuli like temperature and pH, making them valuable in biomedicine, drug delivery, and other fields. By carefully controlling the composition and interactions of materials, innovative and safe systems can be designed to perform complex tasks efficiently (Reveté et al., 2022).

2.7 Clinical translation and functional restoration

Tissue engineering has made significant strides, particularly in the development of engineered flat organs like skin and cartilage, showing promising clinical feasibility. For instance, skin, which normally protects the body from external threats, has been innovatively engineered using dermal fibroblasts and epidermal cells from the NIKS cell line. This antimicrobial skin tissue was successfully tested on patients, showing similar immune responses to traditional cadaveric allografts without triggering antibody production against the NIKS cells (Shafiee & Atala, 2017).

In the field of cartilage repair, autologous chondrocyte implantation has been effectively used to reduce pain and improve mobility in patients with cartilage defects. A study demonstrated the successful creation of cartilage using chondrocyte-derived progenitor cells, which offer greater chondrogenic potential than MSCs, particularly for repairing substantial knee injuries (Macmull et al., 2011).

Tissue-engineered tubular organs, such as tracheas and blood vessels, have also been successfully fabricated and implanted in patients. Notably, a trachea was transplanted into a pediatric patient using a decellularized donor trachea

seeded with the recipient's cells, which showed positive outcomes over 4 years of follow-up. Additionally, 3D bioprinting has been used to create tracheal splints for newborns, further advancing this field (Wang et al., 2021).

For patients with end-stage renal disease requiring hemodialysis, both autologous and allogeneic tissue-engineered vascular grafts have been developed. Autologous grafts, made from the patient's own fibroblasts, have proven effective but have long production times, making allogeneic grafts, which can be stored and maintain their strength, a more practical option. These grafts have been used successfully without signs of degradation or immune rejection (Wystrychowski et al., 2014).

In 2011, autologous urethras were engineered and transplanted into five boys with urethral defects. The engineered urethras, created using the patient's own muscle and epithelial cells on biodegradable scaffolds, were successfully implanted, with follow-up showing that they function similarly to native urethras (Raya-Rivera et al., 2011).

Efforts to engineer hollow nontubular organs have also shown positive results. For example, autologous bladders were created for seven patients with poorly compliant bladders due to myelomeningocele. These bladders were fabricated using biodegradable scaffolds seeded with the patient's own cells, resulting in functional engineered bladders. Solid organs are the most complex to engineer and despite advances in fabricating flat, tubular, and hollow nontubular organs, creating functional solid organs remains beyond current technological capabilities (Atala et al., 2006).

However, progress in engineering small tissues and organoids is encouraging, particularly in the treatment of heart disorders like myocardial infarction. Various tissue engineering approaches have been employed to combine cardiomyocytes with both biodegradable and non-degradable biomaterials to repair damaged heart

muscle. For example, scaffold-free cell sheets, cultured on temperature-sensitive dishes, have been used to partially repair myocardial injuries (Chen et al., 2008). In one study, scaffold-free induced adipocyte cell sheets were implanted into rats with experimental autoimmune myocarditis, resulting in increased levels of adiponectin and hepatocyte growth factor in the heart, indicating potential clinical applications for treating myocarditis (Kamata et al., 2014).

Cardiac patches have shown significant promise in restoring heart function after myocardial infarction in animal models. For instance, a fibrin-based heart patch containing neonatal rat heart cells significantly reduced infarct size. Additionally, cells encapsulated in hydrogels have been used to improve the engraftment and survival of cardiac stem cells after myocardial injection, enhancing heart function *in vivo*. Decellularized ECMs are also being utilized in cardiovascular tissue engineering, with cell-laden constructs of heart tissue being created using 3D printing and decellularized ECMs (Wendel et al., 2014).

The engineering of human kidneys is a critical need, particularly to replicate functions like perfusion, filtration, secretion, and drainage of urine. In one study, researchers decellularized rat kidneys to create scaffolds, which were then seeded with epithelial and endothelial cells and perfused in a bioreactor. After transplantation, the bioengineered kidneys produced urine and cleared metabolites, demonstrating *in vivo* functionality (Ibi & Nishinakamura, 2023).

Liver tissue engineering also faces challenges due to the liver's complex cellular composition, including hepatocytes, which are crucial for functions like metabolism, protein synthesis, and detoxification. To address this, researchers have decellularized livers to obtain vascular tree scaffolds, which were then seeded with human fetal liver and endothelial cells. This approach successfully reproduced liver-like tissue behavior *in vitro*, though most liver tissue engineering

efforts are currently focused on drug development rather than clinical transplantation (Zhao et al., 2023a).

2.8 Tissue engineering polymers in the market

Organ replacement costs account for approximately 8% of global healthcare spending, and projections show that by 2040, 25% of the US gross domestic product (GDP) will be dependent on healthcare. Advances in the design and engineering of biomaterials have led to a new generation of promising materials for regenerative medicine. However, the key question is: which of these materials will successfully establish themselves in the market? Success depends on a combination of clinical effectiveness, performance, marketability, and profitability (Socci et al., 2023).

Materials used in tissue engineering must be designed with complex physical and chemical structures that can influence cell behavior. However, this complexity must be balanced with affordability to ensure financial viability. Product development should proceed through several steps, starting with the identification of the simplest functional requirements needed to address a specific clinical problem. Early ambitious goals, such as regenerating whole organs, have shifted toward more achievable goals instead of replacing the entire heart, for example, current clinical advances in heart repair are focused on building specific components such as coronary arteries, valves, and the myocardium (Place et al., 2009).

Several companies have successfully developed tissue engineering scaffolds in various materials and configurations that have reached commercialization (Table 2.1). These products are currently available off the shelf and have undergone rigorous testing and quality control. The Nanotechnology Products Database (NPD)

TABLE 2.1 Various polymer-based medical devices have been authorized for use in clinical trials.

Products	Polymers	Applications	References
SERI Surgical Scaffold	Silk	Breast renovation	Jewell et al. (2015)
Bioactive Glass Scaffold	SiO ₂ /CaO	Bone loss, vertical alveolar bone loss, horizontal alveolar bone loss	El Shazley et al. (2016)
Chitosan Scaffold	Chitosan	Repair of the sellar floor during endoscopic endonasal transsphenoidal surgery	Zhao et al. (2017)
Firesorb	PLA	Coronary artery disease	Song et al. (2021)
ABSORB Scaffold	poly-L-lactic acid (PLLA)	Cardiac allograft vasculopathy	Pighi et al. (2016)
Bioresorbable Vascular Scaffold (BVS)	poly-L-lactic acid (PLLA)	Bone loss, vertical alveolar bone loss, horizontal alveolar bone loss	Du & Zhou (2018)
3D-Printed Scaffold	PLA, PCL, polyethylene glycol (PEG)	Ridge preservation after tooth extraction	Goh et al. (2015)
Bio ACL	PLA, PCL, polyglycolic acid (PGA)	Ligament rupture	DiDomenico et al. (2016)
Absorb GT1 BVS	PLLA	Heart and coronary artery disease, coronary artery occlusion, angina pectoris, myocardial ischemia	Suzuki et al. (2019)
BMAC Nerve Allograft	PLA, PCL, PEG	Peripheral nerve injury	Cho et al. (2012)
Neuro-spinal Scaffold	PLA, PCL, PEG	Traumatic spinal cord injury at the nerve level T2-T12 injury	Kim et al. (2022)

serves as a reliable source of information on nanotechnology products currently used in various industrial applications ([Socci et al., 2023](#)).

2.9 The future of regenerative medicine

According to recent studies and technological advances, regenerative medicine faces a significant transformation in the future of treatment. As stem cell technology, gene editing, and 3D bioprinting continue to evolve, these techniques not only treat but potentially cure, previously untreatable conditions. The goal of this technology, beyond symptomatic treatments, is to offer hope for complete tissue and organ repair, reversing the effects of aging and significantly increasing

quality of life. The paradigm shift heralded by regenerative medicine has the potential to fundamentally transform healthcare, focusing on healing from within and restoring health and vitality ([Altyar et al., 2023](#)).

Stem cell innovations and the development of iPSCs have opened new avenues for regenerative therapies. iPSCs are adult cells that are reprogrammed to an embryonic state, allowing them to differentiate into different cell types. Recent advances have increased the efficiency and safety of iPSC generation, enabling the creation of patient-specific cells for personalized therapies. For example, researchers have made advances in using iPSCs to model complex diseases and test new drugs in a patient-specific context, potentially accelerating the development of targeted therapies ([Lee & Son, 2021](#)).

Advances in gene editing, especially the CRISPR-Cas9 system, have revolutionized gene editing with its accuracy and efficiency. Newer iterations of CRISPR technology, such as CRISPR/Cas12 and CRISPR/Cas13, offer greater specificity and reduced off-target effects. These advances are crucial for correcting the genetic mutations responsible for various inherited disorders. For example, recent studies have shown the successful use of CRISPR to correct mutations in genes associated with conditions such as muscular dystrophy and cystic fibrosis, potentially paving the way for therapeutic treatments (Mani, 2021).

Advances in 3D bioprinting and 3D bioprinting have made significant advances in the creation of complex tissue structures and organ models. Researchers can now print tissues with multiple cell types and vascular networks, mimicking natural organs. Recent advances include bioprinting functional liver tissues that can perform essential metabolic functions, which can be useful in drug testing and disease modeling. Additionally, efforts are underway to develop bioprinted organ scaffolds that can integrate with the body's own tissues, offering the potential for organ regeneration and transplantation (Jammalamadaka & Tappa, 2018).

Research on cell aging and rejuvenation is one of the most important goals of regenerative medicine. Scientists are investigating ways to counter the aging process at the cellular level, such as using senolytics to remove old cells or using gene therapy to restore the function of young cells. Recent studies have shown promising results in reversing age-related decline in tissue function and improving overall lifespan (Klok et al., 2019).

Tissue engineering is moving toward the creation and regeneration of fully functional organs. Recent studies have demonstrated the successful growth of complex tissues such as the heart and kidney in the laboratory, which, although still in the early stages, highlight the potential for organ

regeneration in the future. Integration of bio-engineered tissues with native tissues is a major area of focus to overcome challenges related to safety and long-term performance (Lanza et al., 2020).

2.10 Conclusion

Tissue engineering represents significant progress in accelerating tissue repair and increasing the quality of life of patients with organ defects. It offers a promising alternative to organ transplantation using various biomaterials. These materials can be obtained from natural sources (such as gelatin, collagen, cellulose, and zein) or synthetic sources (such as PLGA, PCL, and polyurethanes). NPs, especially those from plant sources, are often preferred over SPs due to their ethical advantages, ease of extraction, and lower cost.

This chapter reviews the recent advances in tissue engineering and highlights the use of various biopolymers and their composites for various tissue regeneration applications. The choice of biomaterial usually depends on the specific needs of the target tissue. Composite materials offer the flexibility to fine-tune scaffold properties, while bioactive mineral fillers (such as silica, titanium, and niobium pentoxide) increase mechanical strength and regenerative capabilities.

Modern advances in tissue engineering include the use of stem cells that can differentiate into a variety of tissues and innovative techniques such as 3D and 4D printing to create scaffolds. Despite considerable research, the clinical applications of tissue engineering are limited and require further investigation.

References

- Altayar, A. E., El-Sayed, A., Abdeen, A., Piscopo, M., Mousa, S. A., Najda, A., & Abdel-Daim, M. M. (2023). Future regenerative medicine developments and their therapeutic applications. *Biomedicine & Pharmacotherapy*, 158, 114131.

- Arabpour, Z., Abedi, F., Salehi, M., Baharnoori, S. M., Soleimani, M., & Djalilian, A. R. (2024a). Hydrogel-based skin regeneration. *International Journal of Molecular Sciences*, 25(4), 1982.
- Arabpour, Z., Baradaran-Rafii, A., Bakhshaiesh, N. L., Al, J., Ebrahimi-Barough, S., Esmaeili Malekabadi, H., Nazari, N., Vaez, A., Salehi, M., & Sefat, F. (2019). Design and characterization of biodegradable multi layered electrospun nanofibers for corneal tissue engineering applications. *Journal of Biomedical Materials Research Part A*, 107(10), 2340–2349.
- Arabpour, Z., Salehi, M., AN, S., Moghtader, A., Anwar, K. N., Baharnoori, S. M., Shah, R. J., Abedi, F., & Djalilian, A. R. (2024). Exploring hydrogel nanoparticle systems for enhanced ocular drug delivery. *Gels*, 10(9), 589.
- Arabpour, Z., Youseffi, M., Soon, C. F., Sultana, N., Bazgeir, M. R., Masoud, M., & Sefat, F. (2020). Designing biomaterials for regenerative medicine: State-of-the-art and future perspectives. In N. Sultana, S. Bandyopadhyay-Ghosh, & C. F. Soon (Eds.), *Tissue engineering strategies for organ regeneration* (pp. 1–9). CRC Press.
- Aseer, M., Taleb, M., Arabpour, Z., Bhatti, Q. A., & Ghanbari, H. (2024). Potential of collagen/PLA-based nanofibrous scaffold to support PC12 cells and neural repair. *Journal of Contemporary Medical Sciences*, 10(1), 13–18.
- Atala, A., Bauer, S. B., Soker, S., Yoo, J. J., & Retik, A. B. (2006). Tissue-engineered autologous bladders for patients needing cystoplasty. *The Lancet*, 367(9518), 1241–1246.
- Bahari Golamkaboudi, A., Vojoudi, E., Babaeian Roshani, K., Porouhan, P., Houshang, D., & Barabadi, Z. (2024). Current non-surgical curative regenerative therapies for knee osteoarthritis. *Stem Cell Reviews and Reports*, 20(8), 2104–2123.
- Banani, M. A., Rahmatullah, M., Farhan, N., Hancox, Z., Yousaf, S., Arabpour, Z., Moghaddam, Z. S., Mozafari, M., & Sefat, F. (2021). Adipose tissue-derived mesenchymal stem cells for breast tissue regeneration. *Regenerative Medicine*, 16(1), 47–70.
- Boyd, A. S., Rodrigues, N. P., Lui, K. O., Fu, X., & Xu, Y. (2012). Concise review: Immune recognition of induced pluripotent stem cells. *Stem Cells*, 30(5), 797–803.
- Chaturvedi, V., Naskar, D., Kinneer, B. F., Grenik, E., Dye, D. E., Grounds, M. D., Kundu, S. C., & Coombe, D. R. (2017). Silk fibroin scaffolds with muscle-like elasticity support in vitro differentiation of human skeletal muscle cells. *Journal of Tissue Engineering and Regenerative Medicine*, 11(11), 3178–3192.
- Chen, F.-M., & Liu, X. (2016). Advancing biomaterials of human origin for tissue engineering. *Progress in Polymer Science*, 53, 86–168.
- Chen, Q.-Z., Harding, S. E., Ali, N. N., Lyon, A. R., & Boccacini, A. R. (2008). Biomaterials in cardiac tissue engineering: Ten years of research survey. *Materials Science and Engineering: Reports*, 59(1-6), 1–37.
- Chen, Z., Guan, M., Bian, Y., & Yin, X. (2023). Multifunctional electrospun nanofibers for biosensing and biomedical engineering applications. *Biosensors*, 14(1), 13.
- Cho, M. S., Rinker, B. D., Weber, R. V., Chao, J. D., Ingari, J. V., Brooks, D., & Buncke, G. M. (2012). Functional outcome following nerve repair in the upper extremity using processed nerve allograft. *The Journal of Hand Surgery*, 37(11), 2340–2349.
- Didomenico, L. A., Orgill, D. P., Galiano, R. D., Serena, T. E., Carter, M. J., Kaufman, J. P., Young, N. J., & Zelen, C. M. (2016). Aseptically processed placental membrane improves healing of diabetic foot ulcerations: Prospective, randomized clinical trial. *Plastic and Reconstructive Surgery—Global Open*, 4(10), e1095.
- Du, F., & Zhou, J. (2018). Vascular intervention: From angioplasty to bioresorbable vascular scaffold. In B. M. Fu, & N. T. Wright (Eds.), *Molecular, Cellular, and Tissue Engineering of the Vascular System* (pp. 181–189). Springer.
- EL Shazley, N., Hamdy, A., El-Eneen, H., EL Backly, R., Saad, M., Essam, W., Moussa, H., EL Tantawi, M., Jain, H., & Marei, M. (2016). Bioglass in alveolar bone regeneration in orthodontic patients: Randomized controlled clinical trial. *JDR Clinical & Translational Research*, 1(3), 244–255.
- Emami, A., Namdari, H., Parvizpour, F., & Arabpour, Z. (2023). Challenges in osteoarthritis treatment. *Tissue and Cell*, 80, 101992.
- Fani, N., Moradi, M., Zavari, R., Parvizpour, F., Soltani, A., Arabpour, Z., & Jafarian, A. (2024). Current advances in wound healing and regenerative medicine. *Current Stem Cell Research & Therapy*, 19(3), 277–291.
- Frantz, C., Stewart, K. M., & Weaver, V. M. (2010). The extracellular matrix at a glance. *Journal of Cell Science*, 123(24), 4195–4200.
- Goh, B. T., Teh, L. Y., Tan, D. B. P., Zhang, Z., & Teoh, S. H. (2015). Novel 3 D polycaprolactone scaffold for ridge preservation: A pilot randomised controlled clinical trial. *Clinical Oral Implants Research*, 26(3), 271–277.
- Guo, B., & Ma, P. X. (2014). Synthetic biodegradable functional polymers for tissue engineering: A brief review. *Science China Chemistry*, 57, 490–500.
- Guo, L., Liang, Z., Yang, L., Du, W., Yu, T., Tang, H., Li, C., & Qiu, H. (2021). The role of natural polymers in bone tissue engineering. *Journal of Controlled Release*, 338, 571–582.
- Hao, J., Ma, A., Wang, L., Cao, J., Chen, S., Wang, L., Fu, B., Zhou, J., Pei, X., & Zhang, Y. (2020). General requirements for stem cells. *Cell Proliferation*, 53(12), e12926.

- Hu, M. S., Leavitt, T., Malhotra, S., Duscher, D., Pollhammer, M. S., Walmsley, G. G., MAAN, Z. N., Cheung, A. T., Schmidt, M., & Huemer, G. M. (2015). Stem cell-based therapeutics to improve wound healing. *Plastic Surgery International*, 2015(1), 383581.
- Ibi, Y., & Nishinakamura, R. (2023). Kidney bioengineering for transplantation. *Transplantation*, 107(9), 1883–1894.
- Jammalamadaka, U., & Tappa, K. (2018). Recent advances in biomaterials for 3D printing and tissue engineering. *Journal of Functional Biomaterials*, 9(1), 22.
- Jeong, C. G., & Atala, A. (2015). 3D printing and biofabrication for load bearing tissue engineering. In L. E. Bertasconi, & P. G. Coelho (Eds.), *Engineering Mineralized And Load Bearing Tissues*: 881. Springer.
- Jewell, M., Daunch, W., Bengtson, B., & Mortarino, E. (2015). The development of SERI® surgical scaffold, an engineered biological scaffold. *Annals of the New York Academy of Sciences*, 1358(1), 44–55.
- Jossen, V., Van Den Bos, C., Eibl, R., & Eibl, D. (2018). Manufacturing human mesenchymal stem cells at clinical scale: Process and regulatory challenges. *Applied Microbiology and Biotechnology*, 102, 3981–3994.
- Kamata, S., Miyagawa, S., Fukushima, S., Imanishi, Y., Saito, A., Maeda, N., Shimomura, I., & SAWA, Y. (2014). Targeted delivery of adipocytokines into the heart by induced adipocyte cell-sheet transplantation yields immune tolerance and functional recovery in autoimmune-associated myocarditis in rats. *Circulation Journal*, 79(1), 169–179.
- Kim, K. D., Lee, K. S., Coric, D., Harrop, J. S., Theodore, N., & Toselli, R. M. (2022). Acute implantation of a bioresorbable polymer scaffold in patients with complete thoracic spinal cord injury: 24-month follow-up from the INSPIRE study. *Neurosurgery*, 90(6), 668–675.
- Kim, M. S., Lee, B., Kim, H. N., Bang, S., Yang, H. S., Kang, S. M., Suh, K.-Y., Park, S.-H., & JEON, N. L. (2017). 3D tissue formation by stacking detachable cell sheets formed on nanofiber mesh. *Biofabrication*, 9(1), 015029.
- Klokol, D., Nallenthiran, L., Chan, M. K., Wong, M. B., Chernykh, V., Yefimov, S., ... Pan, P. (2019). Cell therapy as the main stratagem of anti-aging and regenerative medicine. *European Journal of Pharmaceutical and Medical Research*, 6(6), 295–299.
- Kobold, S., Guhr, A., Kurtz, A., & Löser, P. (2015). Human embryonic and induced pluripotent stem cell research trends: Complementation and diversification of the field. *Stem Cell Reports*, 4(5), 914–925.
- Kretlow, J. D., & Mikos, A. G. (2010). Tissue engineering: A historical perspective. In J. Chang, & G. Gupta (Eds.), *Tissue Engineering for the Hand: Research Advances and Clinical Applications*: 1. World Scientific Publishing.
- Kwon, S. G., Kwon, Y. W., Lee, T. W., Park, G. T., & Kim, J. H. (2018). Recent advances in stem cell therapeutics and tissue engineering strategies. *Biomaterials Research*, 22, 1–8.
- Lanza, R., Langer, R., Vacanti, J. P., & Atala, A. (2020). *Principles of tissue engineering*. Academic Press.
- Lee, H., & SON, M.-Y. (2021). Current challenges associated with the use of human induced pluripotent stem cell-derived organoids in regenerative medicine. *International Journal of Stem Cells*, 14(1), 9–20.
- Li, F., Truong, V. X., Thissen, H., Frith, J. E., & Forsythe, J. S. (2017). Microfluidic encapsulation of human mesenchymal stem cells for articular cartilage tissue regeneration. *ACS Applied Materials & Interfaces*, 9(10), 8589–8601.
- Macmull, S., Parratt, M. T., Bentley, G., Skinner, J. A., Carrington, R. W., Morris, T., & Briggs, T. W. (2011). Autologous chondrocyte implantation in the adolescent knee. *The American Journal of Sports Medicine*, 39(8), 1723–1731.
- Maharjan, C. K., Mo, J., Wang, L., Kim, M.-C., Wang, S., Borchering, N., Vikas, P., & ZHANG, W. (2021). Natural and synthetic estrogens in chronic inflammation and breast cancer. *Cancers*, 14(1), 206.
- Mandai, M., Watanabe, A., Kurimoto, Y., Hirami, Y., Morinaga, C., Daimon, T., Fujihara, M., Akimaru, H., Sakai, N., & Shibata, Y. (2017). Autologous induced stem-cell-derived retinal cells for macular degeneration. *New England Journal of Medicine*, 376(11), 1038–1046.
- Mani, I. (2021). CRISPR-Cas9 for treating hereditary diseases. *Progress in Molecular Biology and Translational Science*, 181, 165–183.
- Medvedev, S., Shevchenko, A., & Zakian, S. (2010). Induced pluripotent stem cells: Problems and advantages when applying them in regenerative medicine. *Acta Naturae*, 2(2), 18–27.
- Murphy, M. B., Moncivais, K., & Caplan, A. I. (2013). Mesenchymal stem cells: Environmentally responsive therapeutics for regenerative medicine. *Experimental & Molecular Medicine*, 45(11), e54 e54.
- Nazeri, N., Tajerian, R., Arabpour, Z., Hadjighassem, M. R., Gheibi, N., Manouchehrabadi, M., & Ghanbari, H. (2019). Bioinspired immobilization of carbon nanotubes on scaffolds for nerve regeneration. *Bioinspired, Biomimetic and Nanobiomaterials*, 8, 198–205.
- Noro, J., Vilaça-Faria, H., Reis, R. L., & Pirraco, R. P. (2024). Extracellular matrix-derived materials for tissue engineering and regenerative medicine: A journey from isolation to characterization and application. *Bioactive Materials*, 34, 494–519.
- O'donnell, B. T., IVES, C. J., Mohiuddin, O. A., & Bunnell, B. A. (2019). Beyond the present constraints that

- prevent a wide spread of tissue engineering and regenerative medicine approaches. *Frontiers in Bioengineering and Biotechnology*, 7, 95.
- Okamoto, M. (2019). The role of scaffolds in tissue engineering. In M. Mozafari, F. Sefat, & A. Atala (Eds.), *Handbook of Tissue Engineering Scaffolds* (1, pp. 23–49). Elsevier.
- Ozdil, D., & Aydin, H. M. (2014). Polymers for medical and tissue engineering applications. *Journal of Chemical Technology & Biotechnology*, 89(12), 1793–1810.
- Perry, L., Flugelman, M. Y., & Levenberg, S. (2017). Elderly patient-derived endothelial cells for vascularization of engineered muscle. *Molecular Therapy*, 25(4), 935–948.
- Pighi, M., Tomai, F., Petrolini, A., De Luca, L., Tarantini, G., Barioli, A., Colombo, P., Klugmann, S., Ferlini, M., & Ormezzano, M. F. (2016). Everolimus-eluting bioresorbable vascular scaffold system in the treatment of cardiac allograft vasculopathy: The CART (cardiac allograft reparative therapy) prospective multicenter pilot study. *Journal of Cardiovascular Translational Research*, 9, 40–48.
- Place, E. S., Evans, N. D., & Stevens, M. M. (2009). Complexity in biomaterials for tissue engineering. *Nature Materials*, 8(6), 457–470.
- Raya-Rivera, A., Esquiliano, D. R., Yoo, J. J., Lopez-Bayghen, E., Soker, S., & Atala, A. (2011). Tissue-engineered autologous urethras for patients who need reconstruction: An observational study. *The Lancet*, 377(9772), 1175–1182.
- Revete, A., Aparicio, A., Cisterna, B. A., Revete, J., Luis, L., Ibarra, E., Segura González, E. A., MOLINO, J., & REGINENSI, D. (2022). Advancements in the use of hydrogels for regenerative medicine: Properties and biomedical applications. *International Journal of Biomaterials*, 2022(1), 3606765.
- Rong, Z., Wang, M., Hu, Z., Stradner, M., Zhu, S., Kong, H., Yi, H., Goldrath, A., Yang, Y.-G., & Xu, Y. (2014). An effective approach to prevent immune rejection of human ESC-derived allografts. *Cell Stem Cell*, 14(1), 121–130.
- Shafiee, A., & Atala, A. (2017). Tissue engineering: Toward a new era of medicine. *Annual Review of Medicine*, 68(1), 29–40.
- Sharma, P., Kumar, P., Sharma, R., Bhatt, V. D., & Dhot, P. (2019). Tissue engineering; current status & futuristic scope. *Journal of Medicine and Life*, 12(3), 225.
- Simorgh, S., Milan, P. B., Saadatmand, M., Bagher, Z., Gholipourmalekabadi, M., Alizadeh, R., Hivechi, A., Arabpour, Z., Hamidi, M., & Delattre, C. (2021). Human olfactory mucosa stem cells delivery using a collagen hydrogel: As a potential candidate for bone tissue engineering. *Materials*, 14(14), 3909.
- Socci, M. C., Rodríguez, G., Oliva, E., Fushimi, S., Takabatake, K., Nagatsuka, H., FELICE, C. J., & Rodríguez, A. P. (2023). Polymeric materials, advances and applications in tissue engineering: A review. *Bioengineering*, 10(2), 218.
- Soleimani, M., Mirzaei, A., Cheraqpour, K., Baharnoori, S. M., Arabpour, Z., Ashraf, M. J., Ghassemi, M., & Djalilian, A. R. (2023). The potential of mesenchymal stem/stromal cell therapy in mustard keratopathy: Discovering new roads to combat cellular senescence. *Cells*, 12(23), 2744.
- Song, L., Xu, B., Chen, Y., Zhou, Y., Jia, S., Zhong, Z., Su, X., Ma, Y., Zhang, Q., & Liu, J. (2021). Thinner strut sirolimus-eluting BRS versus EES in patients with coronary artery disease: FUTURE-II trial. *Cardiovascular Interventions*, 14(13), 1450–1462.
- Soto-Gutierrez, A., Wertheim, J. A., Ott, H. C., & Gilbert, T. W. (2012). Perspectives on whole-organ assembly: Moving toward transplantation on demand. *The Journal of Clinical Investigation*, 122(11), 3817–3823.
- Suhag, D., Kaushik, S., & Taxak, V. B. (2024). Scaffold design in tissue engineering. In D. Suhag, S. Kaushik, & V. B. Taxak (Eds.), *Handbook of Biomaterials for Medical Applications*: 1. Springer.
- Suzuki, N., Kozuma, K., Nakamura, S., Aramaki, K., Saito, S., Shibata, Y., Nanasato, M., FUJII, K., Kusano, H., & Ediebah, D. (2019). Absorb GT1 bioresorbable vascular Scaffold system: 1-year post-marketing surveillance in Japan. *Circulation Journal*, 83(12), 2460–2465.
- Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*, 126(4), 663–676.
- Tong, Z., Solanki, A., Hamilos, A., Levy, O., Wen, K., Yin, X., & Karp, J. M. (2015). Application of biomaterials to advance induced pluripotent stem cell research and therapy. *The EMBO Journal*, 34(8), 987–1008.
- Vazin, T., & Freed, W. J. (2010). Human embryonic stem cells: Derivation, culture, and differentiation: A review. *Restorative Neurology and Neuroscience*, 28(4), 589–603.
- Wang, P., Sun, Y., Shi, X., Shen, H., Ning, H., & Liu, H. (2021). 3D printing of tissue engineering scaffolds: A focus on vascular regeneration. *Bio-Design and Manufacturing*, 4(2), 344–378.
- Wendel, J. S., Ye, L., Zhang, P., Tranquillo, R. T., & Zhang, J. J. (2014). Functional consequences of a tissue-engineered myocardial patch for cardiac repair in a rat infarct model. *Tissue Engineering Part A*, 20(7-8), 1325–1335.
- Williams, D. F. (2018). Biocompatibility pathways in tissue-engineering templates. *Engineering*, 4(2), 286–290.
- Wystrychowski, W., Mcallister, T. N., Zagalski, K., Dusserre, N., Cierpka, L., & L'heureux, N. (2014). First human use of an allogeneic tissue-engineered vascular graft for hemodialysis access. *Journal of Vascular Surgery*, 60(5), 1353–1357.
- Yoshioka, H., & Yoshiko, Y. (2017). The roles of long non-protein-coding RNAs in osteo-adipogenic lineage commitment. *International Journal of Molecular Sciences*, 18(6), 1236.

- Zakrzewski, W., Dobrzyński, M., Szymonowicz, M., & Rybak, Z. (2019). Stem cells: Past, present, and future. *Stem Cell Research & Therapy*, 10(1), 1–22.
- Zhao, S., Zhang, Q., Liu, M., Du, J., Wang, T., LI, Y., & Zeng, W. (2023). Application of stem cells in engineered vascular graft and vascularized organs. *Seminars in Cell & Developmental Biology*, 144, 31–40.
- Zhao, T., Liu, Y., Wu, Y., Zhao, M., & Zhao, Y. (2023b). Controllable and biocompatible 3D bioprinting technology for microorganisms: Fundamental, environmental applications and challenges. *Biotechnology Advances*, 69, 108243.
- Zhao, Y., Wang, Y., Gong, J., Yang, L., Niu, C., NI, X., Wang, Y., Peng, S., Gu, X., & Sun, C. (2017). Chitosan degradation products facilitate peripheral nerve regeneration by improving macrophage-constructed microenvironments. *Biomaterials*, 134, 64–77.

