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Tissue engineering: Advancements, challenges and future perspectives

Ingeniería de tejidos: Avances, desafíos y perspectivas futuras

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Abstract

Tissue engineering integrates biology, medicine, engineering, and materials science principles to design and develop functional substitutes for damaged or diseased tissues and organs. Research explores tissue's history, function, challenges, and applications in biomedical engineering. It is explained with fact-based examples demonstrating how tissue engineering influences decision-making, research practices, and the development of medical technologies to improve patient care and outcomes. Additionally, it explores the latest advancements in biomaterials, cell biology, and tissue fabrication techniques, highlighting their potential to revolutionize medical treatments. This multidisciplinary approach aims to conceptualize and identify the paradigm, processes, and design of tissue engineering, focusing on restoring, maintaining, or enhancing tissue function and ultimately improving patients' quality of life and longevity.

Keywords: Biomaterials, Tissue Engineering, Biocompatibility, Scaffolds, Biomedical Applications.

Resumen

La ingeniería de tejidos integra principios de biología, medicina, ingeniería y ciencia de materiales para diseñar y desarrollar sustitutos funcionales para tejidos y órganos dañados o enfermos. La investigación explora la historia, función, desafíos y la aplicación del tejido en la ingeniería biomédica. Siendo explicado con ejemplos basado en hechos, que demuestran cómo la ingeniería de tejidos influye en la toma de decisiones, las prácticas de investigación y el desarrollo de tecnologías médicas para mejorar la atención y los resultados del paciente. A su vez, explora las últimas mejoras en biomateriales, biología celular y técnicas de fabricación de tejidos, destacando su potencial para revolucionar los tratamientos médicos. Este enfoque multidisciplinario parte del objetivo de conceptualizar, identificar el paradigma, los procesos y el diseño de la ingeniería de tejidos focalizado en restaurar, mantener o mejorar la función de los tejidos y, en última instancia, mejorar la calidad de vida y la longevidad de los pacientes.

Palabras clave: Biomateriales, Ingeniería de Tejidos, Biocompatibilidad, Andamios, Aplicaciones Biomédicas.

1 Introduction

Tissue engineering stands at the vanguard of modern biomedical research, offering promising solutions to address the critical challenges in regenerative medicine and healthcare (Anyanwu *et al.*, 2024). At its core, tissue engineering integrates engineering, biology, and materials science principles to design and develop functional substitutes for damaged or diseased tissues and organs. This multidisciplinary approach aims to restore, maintain, or improve tissue function, ultimately enhancing patients' quality of life and longevity (De Chiara *et al.*, 2024). However, it is essential to clarify that tissue engineering involves fabricating

artificial tissues and organs utilizing biological elements, which sets it apart from creating artificial organs solely through mechanical methods. The latter domain, which concentrates on mechanical hearts and left ventricular assist devices, has matured and has been in clinical practice for many years (Kubrusly, 2019).

In contrast, tissue engineering endeavors to produce biological organs that closely emulate mammalian organs structurally and functionally. This is accomplished by employing cells and biomaterials that mimic the extracellular matrix, facilitating tissue regeneration and integration. Consequently, the ultimate long-term goal of tissue engineering is to develop fully functional artificial biological organs, marking a significant advancement within this scientific field (Huang *et al.,* 2024). It is enough to note that their development will potentially allow transplants in patients with organ problems or with damaged organs, replacing them with biological artificial organs, which are so necessary given the chronic deficiencies of donor organs and the long waiting lists of people to undergo transplantation, far outnumber available donor organs. This could be minimized by manufacturing biological artificial organs for clinical use (Reddy *et al.,* 2023).

It should also be mentioned that research in tissue engineering has been expanding during the last decade with active research in the United States and the rest of the world, including a wide variety of organ and tissue systems. It's currently focusing on the development of cardiovascular tissue engineering, with studies directed at the production of artificial heart muscle, blood vessels, valves, cell-based heart pumps, ventricles, and complete bio-artificial hearts (Birla & Williams, 2020; Brimmer *et al.,* 2023; Ronan *et al*., 2023).

Likewise, the musculoskeletal system has been actively investigated, encompassing the manufacture of bone, cartilage, skeletal muscle, and tendons (Li Z *et al*., 2021; Park *et al*., 2024; Zhang *et al.*; 2009; Zhou *et al*., 2024). Another study area is the airway system, specifically the production of artificial tracheas and artificial lung tissue (Shakir *et al*., 2022; Derman *et al*., 2023; Mammana *et al*., 2024; Xu *et al*., 2023). Besides, work is underway on developing artificial organs and tissues of the urinary system, such as kidneys, urinary bladder, ureters, and urethra (Hester & Atala., 2016; Chan *et al*., 2017). The digestive system also develops artificial liver, pancreas, intestinal, and esophageal tissue (Elia *et al*., 2022; Collier *et al*., 2022). Remember that there is a relevant interest in developing artificial skin and tissue engineering strategies for the central nervous system (Cai *et al*., 2023; Metcalfe & Ferguson, 2007; Li Y *et al*., 2021).

2 Methodology

The methodology used in developing this research will be to conduct a comprehensive review of relevant scientific literature, including research articles, review papers, and textbooks, to gather information on tissue engineering principles, methodologies, recent advancements, and challenges.

a. Search and data compilation: databases will be used, such as Pubmed, Frontiers, UPComing, Wiley Online Library, Royal Society of Chemistry, MDPI, ACS Publications, ScienceDirect, SCOPUS, IEEE, SciELO, RedALyC and GoogleScholar were utilized; key search terms included “Tissue engineering,” and “Biomedical engineering.”
b. Information selection and refinement: With a search period from 1993 to 2024, a comprehensive exploration was conducted. Utilizing Mendeley (Elsevier, 2021) as a bibliography management tool, the data was organized based on their relevance to this study.
c. Selection of subtopics: the refined information facilitated the organization of the research structure and clarified the chosen subtopics related to the study.
d. Analysis of results: a critical analysis of the data was conducted, resulting in comprehensive conclusions found in this study (Rondón *et al*.,2024)

3 Results and Discussion

3.1 Definition of tissue engineering

Tissue engineering has been evolving rapidly because of scientific and technological advances, generating its field of action to be optimized in any new discipline**.** The diverse participation of researchers from various scientific backgrounds has contributed to its evolution and adaptation to new scientific paradigms (Rondón *et al*.,2023). Therefore, when defining tissue engineering, it is necessary to analyze the concepts put forth by key researchers and scientific institutions in this domain (Figure 1).

According to the National Science Foundation, in 1997, tissue engineering was described as producing large amounts of functional tissues for research and applications by elucidating basic mechanisms of tissue development combined with fundamental engineering production processes (Viola *et al*., 2003). This definition helps underscore the integration of engineering principles to address problems at a basic level. For Eugene Bell this discipline is responsible for several reasons: First, providing cellular prosthesis or replacement parts for the human body; Second, providing formed acellular replacement parts capable of inducing regeneration; Third,

providing tissue or organ-like model systems populated with cells for basic research and many applied uses such as the study of disease states using aberrant cells; Fourth, providing vehicles for delivering engineered cells to the organism, and fifth, surfacing nonbiological devices (Bell, 1993).

As for Langer and Vacanti, tissue engineering is defined as an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue formation (Langer & Vacanti, 1993). This conceptualization highlights interdisciplinary research and the goal of developing products that enhance tissue function, making it one of the most cited definitions in the field.

The National Institute of Health (NIH) 2001 unified the terms reparative medicine, regenerative medicine, and tissue engineering, emphasizing their role in repairing, replacing, or enhancing organ function by engineering and implanting functional tissue substitutes (Sipe *et al.*, 2002).

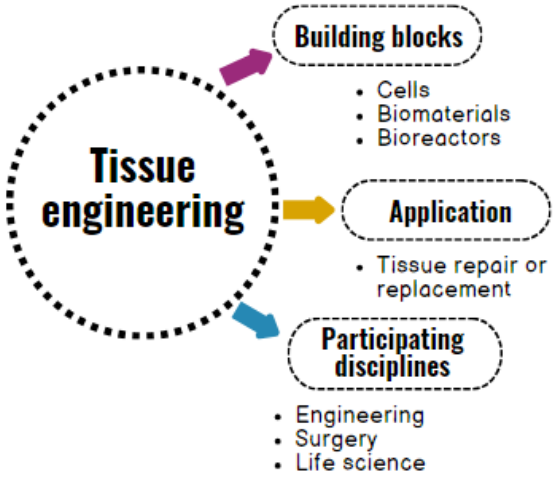

Fig 1. Definition of tissue engineering.

They unify the terms reparative medicine, regenerative medicine, and tissue engineering, highlighting that it is a unique scientific discipline. However, the NIH's unification of terms is not strictly so since, in practice, there are slight differences between these three fields. Also, with this definition, the NIH's approach is transparent to help in health care and improve medical treatments, for which they use the in vivo implantation of artificial tissues and biological organs to replace those found damaged or diseased in the human body. Analogously, Atala described tissue engineering as a significant component of regenerative medicine, emphasizing its role in developing biological substitutes to restore normal function (Atala, 2004).

As for Sefton, tissue engineering relates to encapsulation technology, outlining requirements for tissue engineering constructs (Sefton, 2002). Nerem saw tissue engineering and regenerative medicine as similar disciplines focused on tissue and organ replacement, repair, and regeneration (Nerem, 2006). However, Mason and Dunnill focused on regenerative medicine, highlighting its interdisciplinary nature and goal of repairing, replacing, or regenerating impaired cells, tissues, or organs (Mason & Dunnill, 2007).

Yet Birla emphasized the multidisciplinary nature of tissue engineering and its focus on developing artificial tissues and organs using cells, biomaterials, and bioreactors (Birla, 2014). In this definition, tissue engineering is highlighted as a scientific discipline whose principle is multidisciplinary, whose objective is to provide information on the essential components of the field of study and offer everything concerning the potential use of artificial tissues and organs. Overall, while various terms like tissue engineering, regenerative medicine, and reparative medicine have been used interchangeably or considered as part of a broader discipline, tissue engineering stands out as the predominant term in the literature using methodologies by which cells act autonomously (after stimulating them) as therapeutic agents (Palsson & Bhatia, 2004).

3.2 The tissue engineering historical perspective

Looking back on human history, the scope of tissue engineering is before the development of its definition. The Etruscan and Roman peoples made dental prostheses from biomaterials (ivory and seashell) to replace damaged dental pieces in 800 B.C. In India, injuries began to be medically treated with skin grafts for reconstructive work. However, it was not until the second half of the 20th century that modern surgical procedures were developed that allowed organ transplants. These have increased since the late 1980s due to cyclosporine, an immunosuppressant approved in 1983 by the Food and Drug Administration (FDA) to reduce organ rejection (Dennis, 1992).

Today, twenty-five different organs and tissues (bone and cartilage, bone marrow, cornea, hearts, heart-lung, kidney, liver, lung, and pancreas, among others) can be transplanted with high success. However, it is not so easy to carry out, mainly due to a chronic shortage of donor organs and tissues, which has increased interest in scientific research aimed at the development of new therapies that include the manufacture of artificial biological organs and tissues for replacement or repair of the damaged or diseased. This interest formally kicked off in the spring of 1987 when the National

Science Foundation (NSF) held a roundtable on bioengineering, asking Bioengineering and Research investigators to Help the Disabled (BRAH) and Biotechnology (BIOTECH) research areas. At the time, it was reported that BRAH researchers were inclined to develop comprehensive organ replacement procedures. On the other hand, BIOTECH intended the study of new homologous cell culture methods (Edgington, 1992). Observing these ideas, the NSF table established the term "tissue engineering" to unify the efforts. With this goal set in October of that same year, a new panel was held. Still, this time, not only representatives of the NSF participated but also the National Institutes of Health (NIH), the Department of Energy (DoE), the National Aeronautical Administration and from Space (NASA), the Office of Naval Research (ONR), the Red Cross and representatives of universities in the areas of bioengineering, cell and molecular biology and medicine (Heineken & Skalak, 1991).

NSF also held a forum on emerging technology expectations and prospects hosted by the Division of Emerging Engineering Technologies. This forum was held from October 29 to 30, 1987. From this, a recommendation was made to use tissue engineering and micromechanical technology as active research areas for emerging technologies with great potential for industrial expansion. Another point made by this forum was the recommendation of a workshop to identify research areas in tissue engineering. It was held between February 26 and 29, 1988, near Lake Tahoe, CA. Obtaining recommendations for the NSF on technological objectives. These served to help the NSF create funding for tissue engineering (1988). Since then, many projects have been carried out to understand and develop the underlying mechanisms in tissues and organs made with these tissues. This impulse has borne fruit; it is enough to observe the high number of academic and applied research events currently carried out nationally and internationally. Also, biotechnology companies are already focused on commercially producing tissue engineering products (Patrick *et al*., 1998). It should be noted within this drive that the chief editor of BIO / TECHNOLOGY has designated tissue engineering as "a new force in biotechnology" (Edgington, 1994).

3.2 The tissue engineering paradigm

The tissue engineering paradigm can be analyzed using the cardiovascular system. As we know, some of the diseases that can compromise the proper functioning of the heart are acute myocardial failure, atherosclerosis, valve stenosis, or hyperplastic left heart syndrome. There are medical treatments and procedures such as medications, mechanical pumps, or transplants for this. Heart to relieve patients. However, these strategies have saved numerous lives, although many have limitations, such as the chronic shortage of donor hearts that reduces heart transplants. Bioengineering of the heart and the artificial components of the cardiovascular system sometimes provide alternative treatments for several patients, improving their quality of life and saving many patients. On the other hand, the scope of cardiovascular tissue engineering is based on the manufacture of artificial heart muscle, blood vessels, three-leaf heart valves, cell-based heart pumps, tissue-designed ventricles, and bio-artificial hearts (Khait *et al*., 2008).

These artificial tissues and organs can be used differently to help patients with cardiovascular disorders. An example of this would be using the heart muscle to provide adequate support to the left ventricle of damaged hearts, thereby improving the proper functioning of the heart. Likewise, another example would be that with the production of bio-artificial hearts, they could be used for transplants in patients with end-stage heart failure, thereby facilitating and providing an option to save the lives of many patients worldwide. This analysis provides a general illustration of the tissue engineering paradigm using the cardiovascular system as an example. With it, the tissue engineering strategies applied to the production of bio-artificial hearts and components of the cardiovascular system were proposed to be used to repair, replace, or increase the functional performance of composite hearts (Birla & Williams, 2020; Augustine *et al*., 2021). In conclusion, it was observed that the primary goal of tissue engineering is to manufacture biological artificial organs and tissues that can be used clinically to assist patients by providing functional recovery of diseased or damaged tissues and organs.

3.3 The tissue engineering challenge

The great challenge of tissue engineering is to perfect various factors such as cell isolation, proliferation, and differentiation in addition to designing scaffolds or delivery systems suitable to prop up and coordinate the growth of three-dimensional tissues in the laboratory. The ideal for them will be to collect the patient's stem cells, multiply them by cell culture, and implant them in support. With this, they would obtain any specific mature cells required through the process of differentiation of the stem cells to diversify into any type of cell when specific biological stimuli are applied to it. The support would have to be the template or framework and a stimulant for the multiplication and differentiation of stem cells into specific cells that replicate and form new tissue.

For the tissue to grow in a support that will be reabsorbed, the new tissue must replicate and grow. So, it can implant new tissue or provide biocomposite support. Subsequently, this implanted tissue must survive, restore the host's normal function (patient), and integrate with the surrounding tissues. With the use of the patient's cells, the immune rejection that can occur with tissue and/or donor organ transplants is eliminated (Buttery & Bishop, 2005).

3.3 Process and design in tissue engineering

3.3.1 Process of bioengineering 3D artificial tissue

The study of the tissue manufacturing process has been extensively analyzed in the last decade, highlighting that researchers have different ways of manufacturing artificial tissues and organs. However, there are common points of these procedures that let us outline the process necessary for producing 3D artificial tissue. These steps have been developed and optimized based on many studies in universities and national research centers. They are general, and for a specific type of tissue or organ to be manufactured, adding or removing this process flow diagram may be necessary.

The description of the bioengineering process of 3D artificial tissue has eight steps, and they will be briefly explained in this subtheme. Furthermore, depending on the type of fabric and the specific technology required, these steps can change the order of the sequence. Below are the steps (Figure 2):

1. Source of cells: they are the raw material of artificial tissue. In this supply step, the identification, isolation, purification, expansion, and characterization of a suitable cellular source are relevant. Cells of animal origin or continuous cell lines can be used during the initial stages of development and technological feasibility. Furthermore, the origin of the cells (autologous or allogenic sources) must be established throughout the investigation. The field of stem cells is opening more options for cell provisioning, including embryonic stem cells, induced pluripotent stem cells, and stem cells derived from adults (hematopoietic stem cells and mesenchymal stem cells derived from bone marrow).

2. Synthesis of biomaterials: These materials aim to serve as structural support for the manufacture of three-dimensional tissues and to play the role provided by the mammalian extracellular matrix. It is essential to know the variables for optimizing the synthesis and characterization of materials during the fabric manufacturing process. The biomaterial to be synthesized is adopted depending on the specific application of the tissue. There are a variety of biomaterials, such as polymers, ceramics, and metals.

3. Genetic manipulation: before the cellularization of the structural support, the genetic profile of the cells can be varied to maximize the possibility of cell survival or functional integration with the receptor, manipulating genes that allow to minimize apoptosis or increase integrins. Specifically to optimize the interactions of the matrix cell. Also, the myosin-heavy chain can be regulated for the cardiac muscle, thereby increasing the functional performance of three-dimensional tissue.

4. Cellularization of the scaffold: this step describes the process in which the isolated cells are seeded inside the three-dimensional scaffold. Coupling isolated cells to the structural support to promote functional integration at the cell-cell and material-cell interface is a fundamental variable in the scaffold cellularization process. Furthermore, the success of this process is critical to promote 3D tissues, so it must be optimized so that there is cell uniformity throughout the entire support (Scarritt, *et al*., 2015).

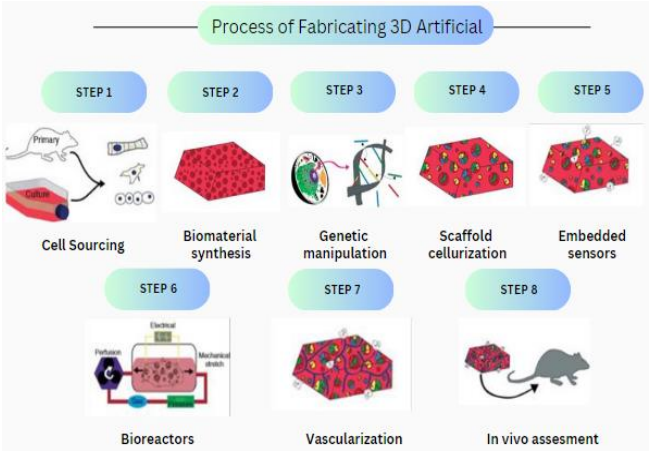

Fig 2. Process of fabricating 3D artificial.

5. Sensor technology: Control of the general state of health of artificial tissue during the tissue manufacturing process (formation, development, and maturation) is carried out using integrated sensors, which are essential for monitoring the functional performance of the manufactured tissue. Also, the data they collect provides valuable information for feedback and regulation of manufacturing variables. These sensors monitor cellular behavior, tissue formation and function, cell-cell interaction, and cell-matrix interaction.

6. Bioreactors for orientation: the normal physiological function of mammalian tissues is immersed in a diverse series of stimuli, such as electromechanical impulses, fluid stress, and variation in the chemical environment because of changes in the concentrations of the factors of growth, cytosines, and hormones. These stimuli or signals are relevant for properly maintaining tissues, so it is essential to develop a strategy that guarantees that these signals are emulated and delivered to artificially manufactured tissues. For this, bioreactors are used to deliver physiological signals to the 3D artificial tissue, encouraging the synthetic tissue's development and maturation (Helmrich & Barnes, 1998).

7. Vascularization: This stage involves the integration of the capillary vessels into the artificial tissue, a critical requirement necessary to support the metabolic function of the synthetic tissue.

8. In vivo evaluation: this is the final step and consists of testing in vivo the effectiveness of the tissue graft to repair, replace, and/or increase the function of the damaged or diseased tissue once its manufacture has been completed.

Analysis of the fabric manufacturing process:

It is essential to think about the proper origin of the cell since it is a considerable challenge, especially for heart applications where adult-derived cardiomyocytes are difficult to obtain and are non-proliferative in vitro, which restricts their field of action. However, there are other sources for obtaining cells, such as human embryonic stem cells, those derived from adults, and the affected individual's cells (autologous). Also, this selection of the cellular source will depend on the application you want to give it; for example, autologous-derived musculoskeletal cells can be used for cardiac regeneration, but it is not advisable to use autologous-derived cardiac cells. The selection of the biomaterial for adequate support depends on the material's ability to emulate the properties of the extracellular matrix (ECM), generate cell viability and propagation, have degradation kinetics that can be controlled, and possess high immunotolerance when implanted alive.

Several biomaterials possess these characteristics today, and new and more effective biomaterials are also being developed. Subsequently, the cells are subjected to genetic manipulation, increasing their function and minimizing programmed cell death (apoptosis). Next, successful cell colonization on the structural support is required, the viability of the cells on the scaffold, the ability of the cells to conserve a differentiated phenotype, and the ability of the cells to functionally interact with the biomaterial to become essential variables. Integrated non-invasive sensors provide real-time data on tissue function and development and feedback on the manufacturing process. Upon completion of scaffold cellularization, bioreactors direct the growth and maturation of artificial tissue. Mechanical, electrical, and chemical/hormonal signals are provided to support the functional development of three-dimensional artificial tissue.

Genetic expression of tissue in vivo is emulated. Bioreactors employ microperfusion systems to replicate the physiological flow conditions observed in vivo. Subsequently, vascularization is introduced during the growth and maturation of the bioengineered tissue. Finally, it is necessary to test the ability of the new tissue to integrate with the receptor, staying alive and without immunological rejection occurring (Birla, 2014; Papaioannou *et al*., 2019; Saini *et al*., 2021).

3.3.2 Design principles for tissue engineering

As in any other engineering, this discipline is governed by design principles for the manufacture of artificial fabric, and, as such, critical decisions must be made at each step of the manufacturing process. In principle, an input to the process feeds the raw material necessary to manufacture the fabric and a final product at its output (3D artificial fabric, Figure 3). To make it easier to understand this process, we will only take two variables: the supply of cells and the synthesis of biomaterials. In the first variable, specific design considerations should be considered, such as the number and density of cells, the percentage of viable cells, the relative proportion of different cell types, and the expression of specific cell surface markers. These variables can be optimized before feeding the 3D fabric manufacturing process (process input).

Similarly, it occurs for the synthesis of biomaterials, considering the relevant considerations of the process, such as the composition and alignment of the fiber, the tensile properties of the materials, and the porosity of the material, which, as in cells, can be regulated by the researcher or manufacturer before the process occurs. These input variables (cells and biomaterials) are entered to start the manufacturing process, leading to a final product at the output (3D artificial tissue). The success of the process is measured by the user who establishes the numbers he wants to reach according to a predefined scale for each specific application that he wants to achieve, so the criteria vary depending on this (Birla, 2014).

Although we only take two variables as an example (cell

agglomeration and biomaterial synthesis) in tissue manufacturing, each of the eight steps is valid for the process explained with only the two variables. Thus, researchers must define the specific design considerations and requirements for each 3D fabric manufacturing step. Knowing the integral process of fabric manufacturing and the input and output variables (Hasirci & Hasirci, 2024).

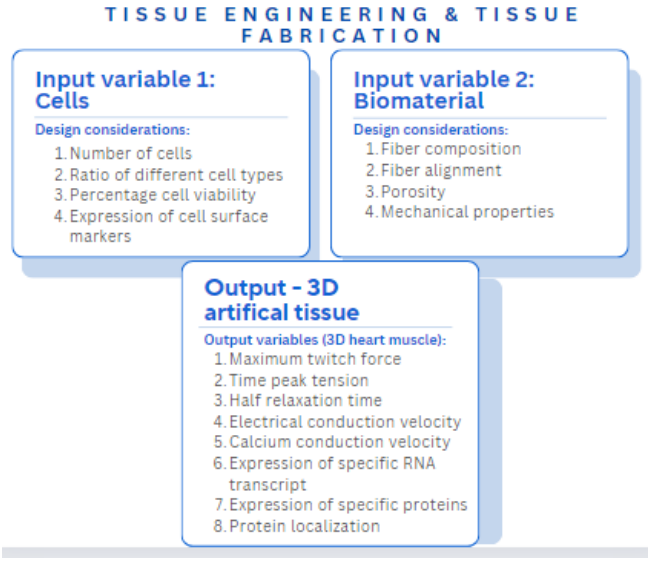

Fig 3: Tissue engineering and tissue fabrication.

3.3.3 Building blocks of tissue engineering

Knowing that the eight steps of the 3D artificial tissue manufacturing process are critical and the absence of any of them would ensure the process is completed on time. However, three steps are considered the essential components of the manufacturing process: cells are the functional elements of artificial tissue, biomaterials represent the structural support of artificial tissue, and bioreactors guide the development and maturation of the tissue (Figure 4).

These three primary elements are necessary for tissue engineering to avoid being paralyzed, as these components are limiting. To create tissue engineering blocks, the researcher must, in principle, identify the source of the cells, the supporting biomaterial, and the orientation stimuli that it will use since, with these three components, he/she will have the platform to initiate any research in the engineering of tissues. Using these three components, a prototype can be built for artificial tissue, laying the foundation for the tissue manufacturing process (Birla, 2014).

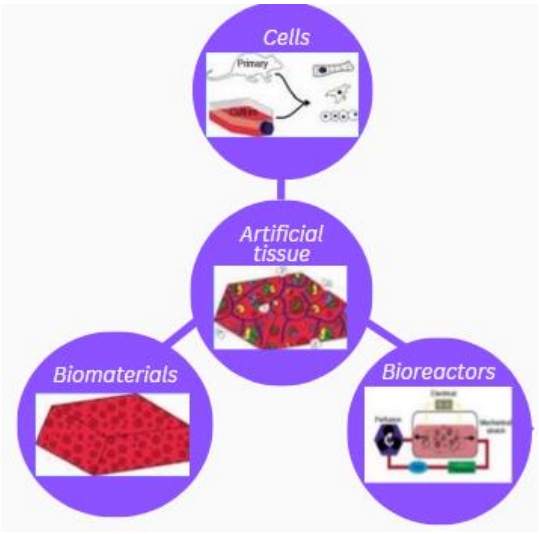

Fig 4. Building blocks of tissue engineering.

4 Conclusion

In conclusion, while the vision of tissue engineering reaching its full potential remains aspirational, it is a journey worth pursuing with determination and innovation. As we refine our understanding and capabilities in optimizing biomaterials, cell sources, and signaling factors, we move closer to a future where artificial tissues and organs are both a possibility and a reality. The road ahead is challenging, requiring interdisciplinary collaboration, rigorous research, and technological advancements. Yet, with each breakthrough, we inch closer to overcoming the hurdles that stand between us and the transformative potential of tissue engineering. Together, let us remain steadfast in our commitment to turning this vision into tangible solutions that improve lives and revolutionize healthcare.

The vast potential of tissue engineering poses significant challenges that, once surmounted, could facilitate the repair, maintenance, and replacement of deficient or damaged tissues. To achieve this, it is crucial to standardize criteria for optimizing the development of the most effective biomaterials and processes that enhance our understanding of tissue engineering, aiming to identify the ideal combination of its three fundamental components: cells, scaffolds, and signaling factors.

Once this is accomplished, artificial tissues and organs could be fabricated with sufficient angiogenesis and biomaterials exhibiting optimal kinetic degradation, possessing physicochemical properties that minimize or eliminate immune rejection, establishing secure cell sources, and implementing novel methods for manufacturing three-dimensional

structural supports with controlled spatial distribution of biomaterials and cells, as well as comprehending the required growth factors. However, this remains a mere aspiration, urging us to strive to transform it into reality diligently.

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