

# TISSUE ENGINEERING: CURRENT STATUS, CHALLENGES AND APPLICATIONS

## Abstract

Artificial organs or organ transplantation are the first options when tissues or organs have been so severely damaged or lost due to cancer, congenital anomaly, or trauma that conventional pharmaceutical treatments are no longer effective. "Tissue Engineering is an interdisciplinary field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ". Tissue engineering is a promising topic that has arisen as a method to encourage, direct, and stimulate tissues' innate potential for regeneration and to help tissues regain function and structure in situations where spontaneous healing is unlikely to occur. Tissue engineering often involves the use of cells placed on tissue scaffolds in the formation of new viable tissue for a medical purpose, but is not limited to applications involving cells and tissue scaffolds. When it was once categorized as sub field of biomaterials, having grown in scope and importance, it can be considered as a field of its own. For tissue engineering, cells, a scaffold, and growth agents are essential. While cells create new tissue matrix, a scaffold offers the right conditions for cells to successfully carry out their tasks. Growth factors have the ability to assist and encourage cells to renew new tissue. There are still many important problems in regenerative medicine that need to be resolved, despite the extensive research that has been done to regenerate different tissues. including the cell source, the way the scaffold was built, how the cells were seeded, the culture environment, the caliber of the matrix produced, the mechanical characteristics of the cell-scaffold construct, and the appropriate animal models.

**Keywords:** Tissue Engineering, Cells, Scaffold, Growth agent, Regenerative medicine

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## I. INTRODUCTION

Artificial organs (including tissues) or organ transplantation are the first options when tissues or organs have been so severely damaged or lost due to cancer, congenital anomaly, or trauma that conventional pharmaceutical treatments are no longer effective. However, there are now a number of difficulties with these surgical procedures. The biomedical engineering field has made incredible strides in the last few years, yet artificial organs still require improvement in biocompatibility and biofunctionality. Even though immunosuppressive medicine has lately made significant advancements, there is still a lack of donated organs and immunological rejection in the existing organ donation system [1]. In order to restore or establish normal function, regenerative medicine tries to replace, engineer, or regenerate human cells, tissues, or organs. "Tissue Engineering is an interdisciplinary field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ" [2].

Regenerative medicine combines tissue engineering with other techniques, such as cell-based therapy, gene therapy, and immune modulation, to induce in vivo tissue/organ regeneration. Tissue engineering uses cells, scaffolds, and growth factors to regenerate tissues or replace damaged or diseased tissues. Researching cutting-edge solutions to enhance the healthcare of the aging and ill population continues to be a challenge on a worldwide scale. Tissue engineering and regenerative medicine (TERM), one of several approaches to achieving this objective, has steadily developed into a potential strategy to address patients' future needs [3]. In the tissue engineering (TE) paradigm, tools from engineering and the life sciences are combined to create bioartificial organ and tissue substitutes. These substitutes can then be used in regenerative medicine, pharmaceutical, diagnostic, and basic research to elucidate fundamental facets of cell functions in vivo or to pinpoint mechanisms underlying aging processes and the onset and progression of disease[4].

## II. HISTORY OF TISSUE ENGINEERING

In the early 1970s, W. T. Green, M.D., a pediatric orthopedic surgeon at Children's Hospital, conducted a number of studies to create new cartilage using chondrocytes sown onto bone spicules and implanted in nude mice. Despite his failure, he came to the accurate conclusion that the development of novel biocompatible materials would make it possible to create new tissue by seeding viable cells onto suitably shaped scaffolds. Years later, Drs. Burke and Yannas of Massachusetts General Hospital and M.I.T. worked together in research in the lab and on humans to create a tissue-engineered skin substitute utilizing a collagen matrix to support the development of dermal fibroblasts. Dr. Eugene Bell seeded collagen gels with fibroblasts, referring to them as contracted collagen gels, while Dr. Howard Green later applied sheets of keratinocytes to burn patients. These examples are the beginnings of the brand-new field of tissue engineering. The idea to prospectively design suitable scaffoldings for cell delivery rather than seeding cells onto readily available naturally occurring scaffolds having physical and chemical properties that could not be manipulated, resulting in unpredictable outcomes, was presented to Dr. Robert Langer of MIT by Dr. Joseph Vacanti of the Children's Hospital in the middle of the 1980s.

Using a branching network of synthetic biocompatible/biodegradable polymers set up as scaffolds seeded with live cells, Dr. Vacanti devised and carried out comprehensive

experiments to produce functioning tissue analogues. A number of centers have been established in the United States and Europe in an effort to investigate and identify the potential of this new subject. While most of these initiatives are extensions of those headquartered in the Boston region, a few of them emerged on their own. The creation of the Pittsburgh Tissue Engineering Initiative (PTEI) by Peter Johnson in the early 1990s, the Cardiovascular Tissue Engineering initiative at Georgia Tech under the leadership of Dr. Robert Nerem, the labs run by Drs. Antonios Mikos and Larry McIntire at Rice University in Houston, and an initiative started at UMass Medical School by Dr. Charles A. Vacanti are just a few of the first notable initiatives outside of Boston.

Dr. Julia Polak, a pathologist and stem cell biologist in London, organized a British-based society that formed a loose association with the Tissue Engineering Society (TES), which had previously been incorporated in Boston, and led an effort in tissue engineering at the Imperial College outside of the United States. Dr. Una Chen started doing stem cell and tissue engineering research in Giessen, Germany, in the middle to late 1990s. The National Institute for Rehabilitative Medicine in Mexico City's tissue engineering facilities were established by Dr. Clemente Ibarra, who also formed the Mexican Tissue Engineering Society. Innsbruck's Leopold Institute now has a tissue engineering lab founded by Dr. Wolfgang Pulacher. Drs. Raymund E. Horch and G.B. Stark at the University of Freiburg led the construction of laboratories and a tri-state initiative in Southern France, Switzerland, and Germany at this time. As a result of their efforts, a Tissue Engineering Society was eventually established in Germany and throughout Western Europe. By the late 1990s, Dr. R. Hetzer, a cardiovascular surgeon at the University of Berlin, Dr. Christof Brelsch, a liver transplant surgeon in Hamburg, and a team at Kyoto University led by Dr. Koichi Tanaka had all formed partnerships with the Children's Hospital in Boston.

Dr. Minora Ueda of Nagoya University launched a significant tissue engineering initiative in Japan and hosted the inaugural conference of the Japanese Tissue Engineering Society in Nagoya (1997). Dr. Yi Lin Cao established the first Chinese tissue engineering project in Shanghai, which was supported by the Chinese government. Another was conducted by Dr. Steven Kim in Seattle, at the University of Washington under Dr. Buddy Rattner's guidance, and in Toronto under Dr. Michael Sefton's direction. Tissue engineering initiatives, such as the one started at Yale University by Drs. Chris Brewer and Mark Saltzman, were sprouting up in almost every developed nation by the mid to late 1990s, and some privately sponsored tissue engineering ventures started to emerge [5].

### **III.SCOPE OF TISSUE ENGINEERING**

1. Tissue engineering currently has a negligible impact on patient care. Some examples of created tissues that have actually received FDA approval include artificial skin, valves, additional bladders, tiny arteries, trachea, and cartilage.
2. Complex bodily organs, including heart, lung, and liver cells, have been successfully replicated in lab settings.
3. However, these tissues can be somewhat useful in research, notably in the discovery of new drugs. It may be possible to speed up development and provide essential tools for assistance in tailored therapy while saving money and reducing the use of animal models for the study by using functioning human tissue to help screen drug candidates.

4. The primary drivers of research advancement in the emerging field, which seeks to endow critical tissues with the capacity to function, grow, repair, and remodel[6], are organ deficiency and inadequate biological or prosthetic materials for repair or replacement of diseased or destroyed human organs and tissues.
5. Tissue engineering is a promising topic that has arisen as a method to encourage, direct, and stimulate tissues' innate potential for regeneration and to help tissues regain function and structure in situations where spontaneous healing is unlikely to occur [7, 8].

#### IV. COMPONENTS OF TISSUE ENGINEERING

For tissue engineering, cells, a scaffold, and growth agents are essential. While cells create new tissue matrix, a scaffold offers the right conditions for cells to successfully carry out their tasks. Growth factors have the ability to assist and encourage cells to renew new tissue[9, 10]. There are still many important problems in regenerative medicine that need to be resolved, despite the extensive research that has been done to regenerate different tissues[10, 11]. including the cell source, the way the scaffold was built, how the cells were seeded, the culture environment, the caliber of the matrix produced, the mechanical characteristics of the cell-scaffold construct, and the appropriate animal models.

1. **Cell Source:** The success of tissue engineering is greatly influenced by the cell source. The three types of cells that can be used in tissue engineering are autologous (from the patient), allogenic (from a human other than the patient), and xenogenic (from an animal)[10, 12]. Allogenic and xenogenic cells are immunogenic and will require an immunosuppressive medication when a new tissue is made, but autologous cells are the most suitable for tissue engineering. Harvesting enough healthy cells with high regeneration potential, especially when a patient is old or ill, is a possible drawback of using autologous cells[10, 13]. However, advances in regenerative medicine now make it possible to quickly and effectively grow a variety of progenitor cells that are subsequently employed to create tissue-engineered promedical constructs[10, 14]. Mesenchymal stem cells (MSCs) have been found in a variety of tissues, such as bone marrow, adipose tissue, fetal tissue, placenta, and umbilical cord. Although BM and adipose tissue contain an astonishingly high percentage of MSCs, the harvesting technique is intrusive, traumatizing, and only a small amount of material may be retrieved without the use of anesthesia[10, 15]. Although they contain large amounts of MSCs and can be harvested without the use of intrusive techniques, fetal tissues, placentas, and umbilical cords are not always readily available when needed[10, 16]. It is therefore of significant importance to investigate new cell isolation methods and sources. It is important to mobilize hematopoietic stem/progenitor cells from bone marrow to peripheral circulation since they circulate in that fluid at a very low level under steady-state settings.

Neovascularization is crucial for supplying nutrients to the wound bed that is healing and for eliminating waste. It has been demonstrated that MSCs secrete and release a variety of angiogenesis-promoting substances, including tissue-type plasminogen activator, bFGF, platelet-derived growth factor, TGF- $\beta$ , VEGF, hepatocyte growth factor, and insulin-like growth factor-1[10, 17]. Nitric oxide and VEGF, which encourage endothelial cell proliferation and vascular permeability, are both expressed by human MSCs[10, 18]. Despite having similar multipotency and morphologies, MSCs from various tissues have unique ways of promoting angiogenesis. While BMSC only use

membrane-type MMPs to drive capillary formation, ASCs primarily use the plasmin system to facilitate vascular morphogenesis[10, 19]. Endothelial cells cocultured with mural cell precursors or fibroblasts are examples of cells that can produce angiocrine factors and drive de novo blood vessel growth, leading to the formation of capillary networks and a prevascularized construct[10, 20].

- 2. Scaffolds:** Cells can communicate with one another and the surrounding ECM thanks to the intricate structure of in vivo tissue organization. In order to allow cells to adhere, disseminate, proliferate, differentiate, mature, and make ECM similarly to what they do in vivo, the scaffold in an engineered in vitro model must be built to precisely reproduce in vitro the architecture of the native tissue, i.e., its ECM framework. The complicated relationship between cells and materials has been better understood thanks to the convergence of expertise in materials science, biomedical engineering, and molecular biology [4, 21]. A crucial component of the model design is the selection of the best biomaterial for the production of the scaffold since it has a significant impact on cellular processes. Depending on the modeled tissue or organ, biomaterials should be carefully chosen. They serve as a synthetic ECM that interacts with cells at the molecular level, impacting cell activities and driving the intricate cellular processes that result in the creation of a reliable in vitro manufactured tissue model. The mechanical characteristics of the tissue must match those of the scaffold in both healthy and pathological states, hence tissue mechanical properties are a key factor in material selection.

In actuality, a pathologic tissue exhibits altered ECM characteristics, such as the different architecture and mechanical characteristics of osteoporotic bone in comparison to its healthy counterpart [4, 22] and tissues stiffening under inflammatory conditions and aging processes, as discussed in more detail for pancreas and cardiac tissue in the following paragraphs [4, 23, 24, 25, 26]. Therefore, the scaffold should be created to replicate these changed ECM properties in order to represent a pathologic system. The use of scaffolds with time-varying features could be a simple strategy for simulating the dynamics of disease progression. For instance, by controlling their crosslinking reaction, hydrogels can be effectively constructed to provide time-dependent stiffening [4, 27, 28].

Studies on mechanobiology have emphasized the significance of the mechanical characteristics of the scaffold in correctly guiding cell activity [4, 29]. Ceramics and their composites are frequently used in the TE of hard tissues due to their high stiffness and load-bearing capabilities, whereas polymers are primarily used in the engineering of soft tissues [4, 30]. Being the main point of contact for cell interaction, the material surface also plays a significant role in determining cell behavior and fate. The biomaterial surface can be altered with bioactive molecules, such as particular proteins or peptide sequences (for example, the fibronectin-derived arginylglycylaspartic acid peptide sequence -RGD), that cells recognize as integrin-binding domains in order to elicit the desired cell response. Usually, scaffold construction is followed by surface modification, which has little impact on the scaffold's mechanical capabilities [4, 31]. The final model's properties are greatly influenced by the fabrication method that is chosen and by the possibility of adjusting the processing parameters to meet the needs of the intended application. So, modeling applications can make use of TE scaffolding techniques created for regenerative medicine. Tissue-engineered in vitro models have been created using both top-down and bottom-up strategies. In top-down approaches, cells are cultivated on scaffolds that have

been created to structurally, chemically, and mechanically match the tissue being modeled.

The bottom-up strategy, on the other hand, tries to imitate and duplicate the functional unit of a tissue and to provide a more biologically realistic scaffold. Both microencapsulation and microfabrication methods, as well as the use of conventional cell culture procedures, can be used to create these modular scaffolds [4, 32]. The scaffold needs to be highly porous, with linked pores and pore sizes that are appropriate for the intended use. This porous construction promotes waste elimination, nutrient/oxygen diffusion, and cell migration even in the interior of the 3D build [4, 21]. Numerous studies have shown that cells cultivated on 3D scaffolds exhibit markedly different morphologies from cells cultured on 2D surfaces [4, 33, 34]. Only when cultured in a 3D environment will the majority of cells be able to specialize and produce a medically meaningful tissue in vitro [4, 35, 36, 37]. Furthermore, studies have demonstrated that compared to 2D substrates, 3D patterned scaffolds encourage increased cell aggregation, proliferation, and differentiation [4, 33, 38, 39, 40]. Cell morphology, proliferation, and migration are affected by pattern size [4, 41, 42, 43]. Additionally, it was shown that the cell type has a significant impact on how a cell responds to the substrate's shape [4, 44]. Topography can also help progenitor cells differentiate along their predetermined course [4, 45]. All of these findings highlight the significance of developing suitable microstructures that can imitate the underlying tissue. Scaffolds with functionally dispersed spatial gradients have been created in order to mimic the spatial gradient of characteristics, composition, and functions that is typical of many biological tissues (such as bone and cartilage) [4, 46]. To ensure a biomimetic environment for in vitro tissue development, these scaffolds' intricate design calls for the use of computer-aided tools and computational modeling [4, 47, 48].

- 3. Growth Factors:** A variety of proteins are essential for the proliferation and differentiation of cells. These proteins are endogenously released in the body either as a result of communication between neighboring cells (paracrine) or by the cells themselves (autocrine). Cell growth factor, or simply growth factor, is the name of these proteins. Even though the designed tissue is allogenic, one benefit of engineered skin tissue over non-biological wound coverings is its ability to deliver growth factors to the wound site when it is applied. Bone morphogenetic proteins (BMPs), basic fibroblast growth factor (bFGF or FGF-2), vascular epithelial growth factor, and transforming growth factor- $\beta$  (TGF- $\beta$ ) are among the growth factors that have commonly been used in tissue engineering. BMP and bFGF alone can cause bone and vascular tissue regeneration, respectively, without the need of a scaffold or seeded cells, demonstrating the extraordinary potential of growth factors. Evidently, compared to not using growth factors, the inclusion of the appropriate growth factors to a cell-scaffold construct must further boost tissue regeneration.

How to transport growth factors to the site of action is what is most important in the application of growth factors to tissue engineering. Bolus injections of growth factors in solution are, as in common knowledge, ineffective because the injected protein molecules soon diffuse away from the injection site. Delivery of the growth factor has been explored using three different approaches. Using DNA plasmids that contain the gene encoding the desired growth factor is one option. As long as the plasmid is active

after being injected into the body, it will biosynthesize the growth factor and secrete it from the cells it lives in. The second approach makes use of gene technology as well. A vector is used to deliver a gene encoding the growth factor to a particular type of cells, and the processed cells are then transplanted into the body where the desired tissue is to be engineered. As long as the transferred gene is active in the cells, the growth factor it encodes will be released into the body. The third technique involves the direct application of growth factor protein and a carrier. The most common application of this strategy in research is the delivery of growth factors in tissue engineering. The growth factor's release kinetics are significantly influenced by the carrier chosen.

It is necessary for a carrier to denaturize growth factor molecules as little as possible during their integration or entrapment, to permit the best growth factor release kinetics, and to be absorbed by the body. The detailed in vivo release profile of growth factors has only been attempted in a few number of studies. It appears likely that the majority of commonly used carriers have shown a burst profile rather than a continuous, continual release. In the US, BMP and a collagen carrier have been combined in therapeutic settings. In 1965, Urist used the BMPs' powerful bioactivity for the first time to cause ectopic bone development in the muscle pouches of rabbits, rats, mice, and guinea pigs [1, 49]. Since then, other BMPs have been discovered, studied, and cloned [1, 50]. The US Food and Drug Administration has approved recombinant human BMP-2 for use in spinal fusion surgeries after a number of animal studies and human clinical trials showed osteoinductive qualities on par with or better than bone autograft. Gelatin, a collagen derivative, has been used by us to transport growth factors. Acidic and basic gelatin are the two varieties that are commercially marketed. With basic proteins, acidic gelatin can create an ionic compound.

Therefore, it is anticipated that after being implanted in the body and being broken down by enzymes, bFGF will be liberated from the ionic complex produced when mixing acidic gelatin with ionically basic bFGF. When the ionic complex was implanted in mice, an excellent release kinetics was indeed seen, but a mixture of basic gelatin and bFGF did not show any sustained release in vivo [1, 51]. It's interesting to note that mice implanted subcutaneously with a mixture of BMP and basic gelatin showed persistent release profiles [1, 52]. Probability suggests that gelatin and BMP molecules interact in ways other than electrostatic force. The majority of tissue engineering for one tissue has utilized a single growth factor. Evidently, using many growth factors would be preferable to promoting tissue regeneration. Many efforts are being done right now to stimulate neovascularization utilizing different growth factors in order to provide the cells involved in tissue regeneration with enough nutrition. Growth factors will be used in tissue engineering more frequently once they become more widely available and less expensive [1].

- 4. Physicochemical Stimuli:** The in vivo environment ensures the existence of essential chemical cues that control cell function, and vascularization facilitates the provision of nutrients and the elimination of waste. To effectively mimic morphogenetic events, molecular variables affecting cellular division, shape, spreading, proliferation, death, and secretion of ECM components must be present [4, 53].

A 3D model's design should take into account the possibility that, depending on the gradient in nutrition content, cells developing in the middle of the construct may behave differently from those growing on the surface. A restricted diffusive movement of nutrients via its thickness may obstruct the successful development of a 3D manufactured tissue. Chemical and mechanical signals should be combined in order to avoid local concentrations and overcome the diffusion constraints that affect cell function [4, 54]. Additionally, extracellular and intracellular mechanical forces that affect cells *in vivo* alter their fate. Particularly, cells alter the extracellular matrix around them in response to dynamic stimuli such as electric fields, osmotic and hydrostatic pressure, stress, strain, fluid flow, and streaming potential [4, 55]. Bioreactors created particularly to mimic *in vivo* conditions are typically used to apply mechanical stimulation to tissue-engineered constructions. Bioreactors in particular offer mechanical or electrical stimulation and enable fine-grained control of culture conditions to achieve tissue maturation [4, 56, 57]. Innovative systems based on microfabrication and microfluidics, which enable real-time monitoring and high throughput results with the ability to test a single parameter independently, have emerged as key microscale technologies [4, 58]. These technological tools might be a reliable aid in the creation of 3D models with pertinent functional properties, guaranteeing good reproducibility.

## V. CHALLENGES IN TISSUE ENGINEERING

This multidisciplinary engineering method has received a lot of interest as a potential new therapeutic approach that could overcome the limitations of existing artificial organs and organ transplantation, both of which aim to replace lost or severely damaged tissues or organs. However, because there is relatively little tissue regeneration with the TE approach, it cannot be used on a large number of patients.

- The clinical applications of TE have advanced extremely slowly and subtly within the current paradigm [1, 8].
- A small number of clinical trials have also been reported [8, 59], despite the fact that a huge number of fundamental research investigations have been conducted in this area. Cells, a scaffold, and growth factors are three essential components for the TE approach [2, 8, 60].
- Tissue engineering also depends on a number of other aspects, including cell source, scaffold design, cell seeding and culture environment, matrix preparation, cell mechanical properties, scaffold architecture, and animal models [8, 61].
- The different cell sources have a huge impact on TE. The three main cell types taken into account in TE are autologous (patient's cells), allogenic (other than patient's cells), and xenogeneic (produced from animal cells). In this group, xenogeneic cells are regarded as the least secure due to findings of porcine endogenous retrovirus in pigs [8, 59].
- Although safe for TE, individuals who were elderly or very unwell had trouble extracting autologous cells adequately [8, 61]. Another issue with cardiac cells is that they are only harvested in insufficient quantities from myocardial infarction patients [8, 62]. The culture procedure mediates the expansion of cells in circumstances of inadequate cell collection (8, 62).
- To eliminate any potential of contamination, only clean cell processing facilities are advised for this operation [8, 62]. The procedure is very drawn-out and time-



consuming. Fetal calf serum, which is often used for cell culture, has been reported to be infected [8, 61].

- Because to their strong growth factor production, allogenic cells are the ideal candidates for skin tissue engineering; nevertheless, xenogeneic feeder cells, which were employed to create epidermal tissues from keratinocytes (because to their high growth activity), had a high risk of viral infection [8, 63].
- Support in the form of a scaffold, template, or artificial extracellular matrix (ECM) is required in situations involving the regeneration and growth of large-sized tissues and organs in a three-dimensional way [1, 8].
- 'Cell therapy' and 'tissue engineering' are two crucial words connected to the formation and proliferation of cells and tissues via regenerative medicine [2, 8].
- For tissue engineering objectives, the scaffold should adhere to certain standards. For appropriate nutrition delivery and neovasculature production, a scaffold needs to be suitably porous [8, 61].
- These micropores, which are crucial for cell viability, can also convey waste. Neovascularization, which is crucial for the provision of oxygen and nutrients to the cells in the construct, is a serious difficulty with the scaffold, though [1, 8].
- Vascularization of the construct is not achieved with *in vitro* tissue engineering [8, 61]. In contrast, if the right stimuli and circumstances are available, neovascularization is achievable *in vivo* tissue engineering [8, 61].
- The development, differentiation, and proliferation of cells are significantly influenced by a wide variety of growth factor proteins [1, 8]. These may be endogenously released in an autocrine or paracrine manner.
- Bone morphogenic proteins (BMP) [8, 64], basic fibroblast growth factors (bFGF, bFGF-2), vascular epithelial growth factor (VEGF), and transforming growth factor-beta (TGF-) [8, 66] are the growth factors that are currently most commonly used.
- Growth factors (GFs), which have a remarkable capacity to regenerate tissues, must be added to the cell scaffold build in order for tissue to regenerate [1, 8].
- The transport of GFs to the site of action is the most important concern, however bulking injection to the site of regeneration is not a practical solution [8, 61]. The use of DNA plasmids encoded with the gene of the desired GF, introducing a gene encoding a particular GF into a specific cell type using a vector, and implanting GF proteins directly into the cell via certain carriers are the three main methods of delivering GFs that have been developed so far [1, 8].
- A carrier that delivers GF to the site makes a decision regarding the GFs-release kinetics as well. Typically, only one GF is required to construct a single tissue. According to research, GFs can cause neovascularization, which gives growing tissues a sufficient supply of nutrients [8, 67]. However, using GFs is not very cost-effective, which limits their usefulness in TE.
- The availability of animal models [8, 61], which cannot be regularly exploited mostly due to ethical considerations, is another barrier to TE. In fact, nude mouse models are frequently small to prevent immunological rejection of implanted cell scaffold constructs [8, 61], but big animal models are required to replicate clinical conditions in humans. The examination of the biochemical characteristics of typical bone and cartilage, as well as their functional assessment, is crucial in order to determine the scope of tissue engineering of bones and articular cartilages [8, 68].
- The fundamental method for assessing the aforementioned traits of healthy, sick, and bioengineered bone *in vivo* is still being developed [8, 68]. Similar to this, even

though numerous *in vitro* and *in vivo* studies on cardiovascular diseases—which are the leading cause of death—have been conducted (8, 69), longer-term studies in larger animals are still required before bioengineered blood vessel valves and heart tissues are commercially available[8].

## VI. APPLICATIONS OF TISSUE ENGINEERING

1. Bone tissue engineering, cartilage tissue engineering, heart tissue engineering, pancreatic tissue engineering, and vascular tissue engineering are all examples of tissue engineering for the regeneration of injured cells.
2. Drug Discovery with Tissue Engineering for Human Physiology Modeling.
3. In cases of serious burns or injuries, tissue engineering is used in surgery to transplant skin.
4. By using tissue engineering, it is possible to study the impact of various chemicals or medications (which are still in research) on living cells without endangering humans or lab animals.
5. Dentistry uses tissue engineering.
6. It is utilized to heal skeletal muscles, the nervous system, and the heart, among other things.
7. *In vitro* meat is imitation meat produced in a lab setting.
8. Several examples of tissue engineering include the bioartificial liver device, the artificial pancreas, the artificial bladders, the cartilage, the artificial bone marrow, the artificial airways, the artificial veins and Tissue engineered oral mucosa etc [6].

## VII. CONCLUSION

The topic of tissue engineering shows great promise for successfully addressing a variety of difficulties with fresh, novel discoveries and may soon bring about many advancements [8]. Because of the gaps between experimental research and clinical practice, tissue engineering has been extended to all fields of reconstructive surgery but still faces some limitations for widespread clinical application [10]. Since cell-scaffold structures must be physically placed in patients' bodies, medical professionals who use tissue engineering for medical therapies are essentially surgeons. Using large animal models, surgeons also assess the effectiveness of cell-scaffold structures [1]. While tissue bioengineering's quick and inventive advancements show great promise for the future of regenerative medicine, realistic consideration and promotion of potential clinical applications demand a balanced and critical evaluation of these new technologies, including robust ethical discussion

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