CHAPTER-6

Advanced Biodegradable system for Regenerative Therapeutics

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Abstract

The concept of regenerative therapeutics involves restoration, replacement, and regeneration of damaged tissues and organs in order to regain its proper functionality. Advanced biodegradable technologies play a significant role in regenerative therapeutics as they not only assist in treating damaged tissues temporarily but also allow them to degrade within the body without any side effects. Advanced biodegradable systems allow for the delivery of drugs, growth factors, or live cells right into the affected areas in the body. In this chapter, the use of advanced biodegradable systems in regenerative therapeutics is discussed. It covers the different areas where biodegradable systems play a vital role including tissue engineering, wound healing, bone tissue engineering, cartilage engineering, nerve tissue engineering, and cardiovascular disease therapy. Different types of biodegradable materials include natural polymers, synthetic polymers, hydrogels, nanofibers, and microspheres. This chapter also provides information on the latest technological advances in the field, such as 3D bio printing, electro spinning, and nanotechnology that enhance the performance of the current biodegradable materials. Particular emphasis is placed on the possibility of combining biodegradable materials with such elements as stem cells, growth factors, and genes to promote better healing and tissue regeneration. This chapter also discusses some of the most pressing issues related to biodegradable materials including the degradation rate control, preservation of mechanical integrity, prevention of immune response, and development and implementation of the technology. This chapter is informative concerning future trends in smart biodegradable materials and personalized regenerative therapies.

Keywords: Regenerative Therapeutics, Biodegradable Systems, Tissue Engineering, Drug Delivery, Stem Cell Therapy, Biomaterials

1. Introduction

1.1 Regenerative Therapeutics

Regenerative therapeutics can be defined as an advanced approach in contemporary healthcare concerned with recovering lost biological functionality through replacement and/or regeneration of damaged tissues and organs. While traditional treatments tend to focus on alleviation of disease symptoms and slowing down its progression, the aim of regenerative approaches is to restore normal functioning by addressing the root causes of tissue dysfunction (1). Regenerative medicine incorporates a wide variety of disciplines including cell biology, tissue engineering, biomaterial science, stem cell technology, gene therapy, and Nano medicine for the development of cutting-edge treatment approaches for both acute and chronic conditions (2). The idea behind regeneration has been transformed immensely in the course of several decades. Traditional regenerative treatments were based on either tissue grafting or organ transplantations; however, challenges related to donor availability, immune responses, and high cost triggered a shift towards finding new solutions. Stem cell biology research conducted throughout the latter part of the twentieth century became one more step towards the development of tissue regeneration. It allowed scientists to use the self-renewal and differentiation ability of stem cells for tissue repair (3). Later on, the introduction of tissue engineering made it possible to combine live cells and synthetic materials to develop functional substitutes. Though there have been significant advancements in the field, several healthcare concerns still necessitate advancements in regenerative medicine. The growing prevalence of chronic conditions, trauma, degeneration due to aging, and organ failure worldwide has resulted in a significant burden. Health problems like osteoarthritis, cardiovascular disorders, neurological disorders, diabetes, and skin damage, among others, generally lack self-regenerative properties leading to disabilities and decreased quality of life (4). Additionally, existing approaches to addressing these problems rarely provide comprehensive repair of the tissue affected. Hence, regenerative therapies represent an exciting approach towards promoting regeneration and decreasing the need for organ transplantation and prosthetic implants.

1.2 Role of Biomaterials in Regeneration

A key aspect of biomaterials is that they provide an integral part of regenerative medicine because they have biological properties needed for supporting regeneration of tissues. Biomaterials are tailored to facilitate interactions with biological environments and support cellular attachment, proliferation, differentiation, as well as extracellular matrix formation (5). It is the biological and physicochemical properties of biomaterials that allow creation of a microenvironment resembling natural tissues that will help the tissue regeneration process. Biomaterials act as scaffolds in tissue repair and replacement approaches, where they will support regeneration of the tissue while maintaining mechanical stability during the healing process (6). Depending on the type of regenerative therapy, biomaterials can be developed in various forms such as porous scaffolds, hydrogels, nanofibers, films, microspheres, or even injected systems (7). As a result, there are various fields of application of biomaterials for regeneration ranging from bone, cartilage, skin regeneration to cardiovascular and neural tissue engineering. One of the most important issues in regenerative medicine is cell–material interactions since they play a crucial role in achieving positive outcomes in therapy. Cell–material interactions depend on several properties of biomaterials including their surface chemistry, topography, porosity, and mechanical properties (8). On the contrary, improper material composition can lead to inflammation, fibrosis, and failure of implants. One of the many properties of regenerative biomaterials, which are of great significance, includes biodegradability. The main quality of biodegradable materials is that they can undergo gradual degradation in the body and be subsequently removed via metabolism. This ensures that there will be no need for further surgical procedures and that regenerative tissue will gradually substitute implanted materials. Properly controlled rates of degradation also ensure proper coordination between scaffold degradation and new tissue development (9).

1.3 Evolution of Biodegradable Systems

Biodegradable systems have seen a dramatic transformation over time due to developments in the field of materials science and regenerative medicine. The earliest generation of biomaterials mainly focused on biological inertness and mechanical compatibility. The materials used were metals, ceramics, and non-degradable polymers due to their stability and durability. The problem was that these materials were permanently embedded in the body leading to complications such as chronic inflammation, implant loosening, and need for repeated surgery (10).

This problem led to the development of second-generation biomaterials where the focus was shifted from biological inertness to bioactivity and biodegradability. Scientists came up with biodegradable polymers and bioactive ceramics that would interact with the host and cause some form of biological response. Polymers such as PLA, PGA, PLGA, collagen, chitosan, and ceramics like hydroxyapatite became very popular due to their regenerative capability and biodegradability. These types of materials were considered an improvement since they were involved in the regeneration process, rather than being simply structural substitutes (11). The current research is focused on third-generation biomaterials that would induce certain cellular and molecular reactions. Modern regenerative systems use bioactive substances, growth factors, stem cells, nanoparticles, and intelligent responsive structures to form highly efficient platforms for therapy. The latest innovations in nanomaterials, 3D bioprinting, self-assembled structures, and smart hydrogels can be used for improving the accuracy of regenerative processes. Third-generation biodegradable materials can be considered as the next step toward creating a system similar to natural tissue for personalized therapy (12).

1.4 Fundamentals of Biodegradable Biomaterials

Degradable bioceramics have turned out to be critical elements for regenerative medicine because of the capacity to offer transient mechanical assistance, which will later degrade and be replaced with new tissue. Differing from traditional implants, biodegradable materials are developed to have interactions with the living organism that facilitate tissue remodeling and functional reconstruction (13). This type of material is highly useful when applied to regenerative medicine because its degradation rate may be adjusted based on the needs of certain patients and their problems. A detailed understanding of the characteristics of these materials and their operational principle needs to be known for developing an efficient regenerative therapy technique. Biodegradable biomaterials can be described as any substance that may be organic or synthetic in nature, which is capable of breaking down under physiological conditions into harmless components that the body can excrete (14).

1.4.1 Biocompatibility

Another significant feature of biodegradable biomaterials is their biocompatibility. A material should be biocompatible when it fulfils its role without causing any negative effects on the body. A material should be able to support the cell adhesion, proliferation, migration, and differentiation process while causing minimal inflammation, toxicity, and immune response. Many factors determine how well the material is biocompatible, including its chemical nature, degradation rate, and interaction with the host tissues. Biocompatible materials create an environment favourable for healing and integration (15).

1.4.2 Bioactivity

More advanced than mere compatibility, many modern biodegradable biomaterials are expected to have bioactivity features. Bioactivity can be defined as the ability of the material to interact with biological processes, influencing particular cellular activity. Bioactive materials can facilitate various processes, such as angiogenesis, osteogenesis, chondrogenesis, and deposition of the extracellular matrix due to cellular and signalling molecule interaction. Growth factors, peptides, nanoparticles, and biologically active sequences can be incorporated into the biomaterial to enhance its regenerative properties (16).

1.4.3 Controlled Degradation

Another characteristic of degradable biomaterials is controlled degradation. This means that the rate of material degradation needs to match the rate of tissue formation and remodelling. If the degradation process occurs prematurely, then the structural integrity would be jeopardized; however, if it happens too late, then there could be problems in forming tissues because of the constant inflammation that arises due to the presence of degraded biomaterial. Control over degradation kinetics is important in order to ensure successful regenerative results (17).

1.4.4 Mechanisms of Biodegradation

The mechanism of biodegradation refers to the processes that take place in the physiological system in order for biomaterials to degrade.

1.4.4.1 Hydrolytic Degradation

Another common method of degradation of biodegradable polymers is called hydrolytic degradation. Water enters the material and degrades hydrolysable bonds like esters, anhydrides, and carbonates. Synthetic polymers poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and poly (lactic-co-glycolic acid) (PLGA) mostly degrade via hydrolysis. Hydrolytic degradation rate depends on the nature of the polymer, water penetration, molecular weight, and environmental factors (18).

1.4.4.2 Degradation by Enzymes

Degradation by enzymes is another degradation method, where biological enzymes degrade the polymer chains in a controlled way. Biomaterials such as collagen, gelatine, fibrin, chitosan, and hyaluronic acid easily undergo enzymatic degradation. This method of degradation is highly regulated, and tissue-specific enzymes control degradation depending on the biological environment. This makes the process resemble tissue remodelling (19).

1.4.4.3 Oxidative Degradation

Oxidative degradation occurs due to chemical reactions between biomaterials and oxidative species produced during inflammation processes such as reactions between biomaterials and ROS, produced by macrophages and neutrophils. Oxidative species cause degradation by inducing chain cleavage and changes in structures of polymer matrices. Therefore, oxidative degradation is important when applied to inflammatory sites, influencing the durability of implanted biomaterials (20).

1.4.5 Factors Affecting Biomaterials' Degradation Process

There are several intrinsic and extrinsic factors affecting the degradation of biodegradable biomaterials.

1.4.5.1 Molecular Weight

Intrinsically, the molecular weight of a polymer affects its degradation rate since high-molecular-weight polymers tend to have relatively longer and denser molecular structures, whereas low-molecular-weight polymers tend to have lower molecular densities. Low-molecular-weight polymers tend to degrade relatively faster (21).

1.4.5.2 Crystallinity

Crystallinity refers to the degree of molecular ordering within the structure of polymers. Highly crystalline polymers contain denser molecular structures compared to less crystalline and amorphous polymers, making water molecules hard to penetrate the structures (22).

1.4.5.3 Surface Properties

Surfaces, surface chemistry, roughness, hydrophobicity, and porosity play a major role in the degradation process. Hydrophilic surfaces make the material easier to absorb in aqueous solutions and hence promote hydrolytic degradation; hydrophobic surfaces on the other hand tend to repel water molecules. Moreover, a larger surface area arising from the porosity and roughness increases biological interaction and hence higher degradation rate (23).

1.4.5.4 Physiological Environment

Exogenous physiological variables can significantly impact biodegradation characteristics. Variables like pH level, temperature, enzymatic concentration, oxygen presence, and tissue environment can change degradation patterns. An acidic medium for example enhances hydrolytic degradation while an increased enzymatic concentration promotes enzymatic degradation. Thus, performance can be quite variable in different body tissues (24).

1.4.5.5 Design Considerations

For the design of an efficient biodegradable biomaterial, several characteristics should be fine-tuned to create an appropriate balance between mechanical, biological, and degradative properties (25).

1.4.5.5.1 Mechanical Properties

Mechanical properties must ideally match those of the target tissues to achieve proper support of tissue regeneration. Biomaterials used in bone regeneration must have high compressive strength, unlike materials employed in soft tissue engineering (26).

1.4.5.5.2 Porosity

It is important for certain features to be optimized in designing a successful degradable biomaterial for balancing the properties in mechanical, biological, and degrading aspects (27).

1.4.5.5.1 Mechanical Properties

The mechanical properties should resemble those of the target tissue in order to give good assistance to tissue regeneration. In cases where there is bone regeneration, high compressive properties are required (28).

1.4.5.5.4 Classification of Advanced Biodegradable Systems

There are three main classes of advanced biodegradable systems used for regenerative medicine purposes: natural biomaterials, synthetic biodegradable polymers, and composites/hybrid systems. All of these materials differ in terms of their physicochemical, biological, and mechanical properties. The choice of the right system depends on several features, including biocompatibility, degradation rate, mechanical properties, bioactivity, and tissue characteristics. Due to recent advances, it is now possible to create more complex systems that would utilize benefits of several material classes (29).

1.5 Natural Biodegradable Biomaterials

Natural biodegradable biomaterials are materials extracted from biological sources and thus are similar to the composition of ECM. Their high levels of biocompatibility and bioactivity make them attractive for tissue regeneration purposes.

1.5.1 Collagen

The structural protein collagen is highly abundant in human beings and constitutes an important part of the body’s connective tissues. Owing to good biocompatibility, biodegradation, cell adhesion and proliferation properties, collagen finds wide applications in wound healing, bone regeneration, and tissue engineering among others. Unfortunately, its poor mechanical properties and quick degradation rates require cross-linking or combining with other biomaterials (30).

1.5.2 Gelatine

Gelatine is another biologically active derivative of collagen with similar biological activities but better processing and lower immune reactivity levels. It also encourages cell attachment and tissue incorporation processes as well as forming hydrogels, scaffolds, and micro-spheres. Its downside is that it is not very mechanically stable and may degrade quickly under physiological conditions (31).

1.5.3 Chitosan

Chitosan is a natural polymer derived from chitin after being subjected to acetylation. Its superior biocompatibility, biodegradation, antimicrobial action and haemostasis properties have ensured extensive applications in wound dressings, delivery devices, and tissue engineering. Poor solubility in physiologic solutions and low mechanical performance prevent the use of chitosan in certain biomedical uses (32).

1.5.4 Alginate

Alginate is a naturally occurring polysaccharide isolated from brown algae. Alginate is extensively employed due to its capability to form hydrogels under gentle conditions. Alginate hydrogels display excellent biocompatibility and high water holding capacity. Poor cell adherence and undesirable degradation behaviour are often encountered, thus necessitating modifications for enhanced biological performance (33).

1.5.5 Hyaluronic Acid

Hydrophilic, highly elastic, and biologically active glycosaminoglycan found naturally in connective tissues, cartilages, and synovial fluid. Due to these characteristics, hyaluronic acid-based matrices are attractive candidates in cartilage repair, wound healing, and stem cell delivery therapies. However, its rapid degradation rate and lack of mechanical strength are significant limitations (34).

1.5.6 Natural Biodegradable Biomaterials

Some advantages of naturally occurring biodegradable biomaterials include excellent biocompatibility, biological properties, low toxicity, and native-like extracellular matrix resemblance. This allows for improved cell-material interactions and tissue regeneration processes. On the other hand, disadvantages associated with natural biomaterials include inconsistent material properties, poor mechanical properties, rapid degradation rates, immunogenicity, and scale-up problems (35).

1.5.7 Synthetic Biodegradable Polymers

Synthetic biodegradable polymers provide improved compositional, mechanical property, degradation rate, and reproducibility control. They have thus found widespread application as scaffold materials, drug delivery systems, and implantable devices (36).

1.5.7.1 Poly (lactic acid) (PLA)

Poly (lactic acid) is a biodegradable aliphatic polyester material known to have high mechanical strength and process ability. Degradation occurs via hydrolysis to form lactic acid, which is then metabolized by the body. The use of poly (lactic acid) is very widespread in orthopaedic implants, sutures, and tissue engineering scaffolds (37).

1.5.7.2 Poly (glycolic acid) (PGA)

One of the early biodegradable polymers used in biomaterials, poly (glycolic acid) is notable for its high tensile strength and fast degradation rates. Thus, it is an ideal material for use as resorbable sutures and temporary tissue supports (38).

1.5.7.3 Poly (lactic-co-glycolic acid) (PLGA)

PLGA is the copolymer of poly (lactic acid) and poly (glycolic acid). Through manipulation of the monomer ratio, one can obtain highly tunable degradation rates and mechanical properties. PLGA has emerged as the most extensively researched biomaterial for drug delivery and regeneration medicine (39).

1.5.7.4 Polycaprolactone (PCL)

Polycaprolactone is a semi-crystalline polyester characterized by excellent flexibility, process ability, and prolonged degradation profiles. Its slow degradation rate makes it particularly suitable for long-term tissue regeneration, including bone, cartilage, and vascular tissue engineering (40).

1.5.7.5 Polyurethane-Based Systems

Systems based on biodegradable polyurethanes have been shown to be flexible biomaterials because of the possibility of adjusting mechanical properties, elastic character, and degradation rate of these materials. They can be especially useful when applied in cardiovascular medicine, musculoskeletal disorders, or soft tissue engineering (41).

1.6 Composite and Hybrid Systems

Despite significant possibilities that arise from using either natural or synthetic biomaterials, their weaknesses were the key factors behind creating composite or hybrid materials that could provide better regenerative effects through combining different qualities of materials.

1.6.1 Polymer-Polymer Composites

The idea of mixing two or several biodegradable polymers can result in the increased ability to manipulate mechanical, degradation, and biological characteristics of composites. The following examples of such systems are collagen-chitosan or gelatine-PLGA composites (42).

1.6.2 Polymer-Ceramic Composites

Combining ceramics in the form of hydroxyapatite, tricalcium phosphate, or bioactive glass with biodegradable polymers results in creating composites whose composition and structure resemble that of native bone tissue very closely (43).

1.6.3 Nano composite Biomaterials

Nano composites biomaterials represent the latest generation of advanced regenerative materials. The use of nano scale fillers, such as nanoparticles, nanofibers, carbon-based nanomaterials, or nanoclays in biodegradable matrixes increases physical properties as well as stimulates cell attachment and regeneration, enables a controlled release of drugs and gives the material a response to stimuli. Due to ability to mimic natural architecture of ECM, nano-composites have become an indispensable tool in the modern advanced regenerative therapeutics (44).

1.7 Advanced Biodegradable Platforms for Regenerative Therapeutics

Regenerative therapeutic treatments require advanced biodegradable platforms that would not only help regenerate damaged tissues but would also be capable to deliver bioactive agents and stimulate cells proliferation, differentiation, and regeneration. Biomaterials scientists managed to produce sophisticated biodegradable platforms that simulate natural extracellular matrix (ECM), enable controlled delivery and stimulate tissue-specific regeneration. Such biodegradable platforms as scaffolds, injectable biomaterials, hydrogels, and nanomaterial-based systems became highly popular due to effectiveness of regenerative treatments and reduced complications compared to permanent devices (45).

1.7.1 Biodegradable Scaffolds

Biodegradable scaffolds are temporary three dimensional frameworks used to help cells attach, proliferate, differentiate and form tissue. Scaffold slowly decomposes and its volume is substituted by newly regenerated tissue (46).

1.7.1.1 Conventional Scaffolds

The conventional biodegradable scaffolds consist either of natural polymers like collagen and chitosan or of synthetic polymers like PLA, PGA, and PLGA. Such types of scaffolds serve as mechanical support and guides to tissue formation since they retain integrity throughout the tissue repair process. Conventional scaffold systems have been successfully applied in bone, cartilage, skin, and vascular tissue engineering (47).

1.7.1.2 Porous Scaffolds

The porous scaffolds have the interconnected pores structure that facilitates cell migration, nutrient exchange, delivery of oxygen and waste removal. Moreover, porous design stimulates tissue formation and angiogenesis that is essential for regenerative processes. Modern methods like freeze-drying, solvent casting, gas foaming, and even additive manufacturing allow regulating pores' structure and size (48).

1.7.1.3 Nano fibrous Scaffolds

The nano fibrous scaffold systems have been successfully used in numerous fields of tissue engineering as their structure resembles the extracellular matrix. It should be noted that the nano-fibrous scaffolds may be created by electro spinning and demonstrate high specific surface areas. Nano-fibrous scaffolds are highly useful in such types of tissue engineering as neural, cardiovascular, musculoskeletal, and skin tissue engineering (49).

1.7.2 Injectable Biomaterials

Injectable biomaterials are new technologies that have become minimally invasive solutions to implants and pre-fabricated scaffolds. Injectable biomaterials are injected using syringes or catheters and can then adapt to complex defect sites for local treatment (50).

1.7.3 Injectable Hydrogels

Injectable hydrogels are made up of polymeric materials that have an affinity to absorb large quantities of water. These are used to carry cells, growth factors, proteins, drugs, etc., to make an optimal environment for tissue regeneration. This property also allows easy application and reduces surgery-related injuries (51).

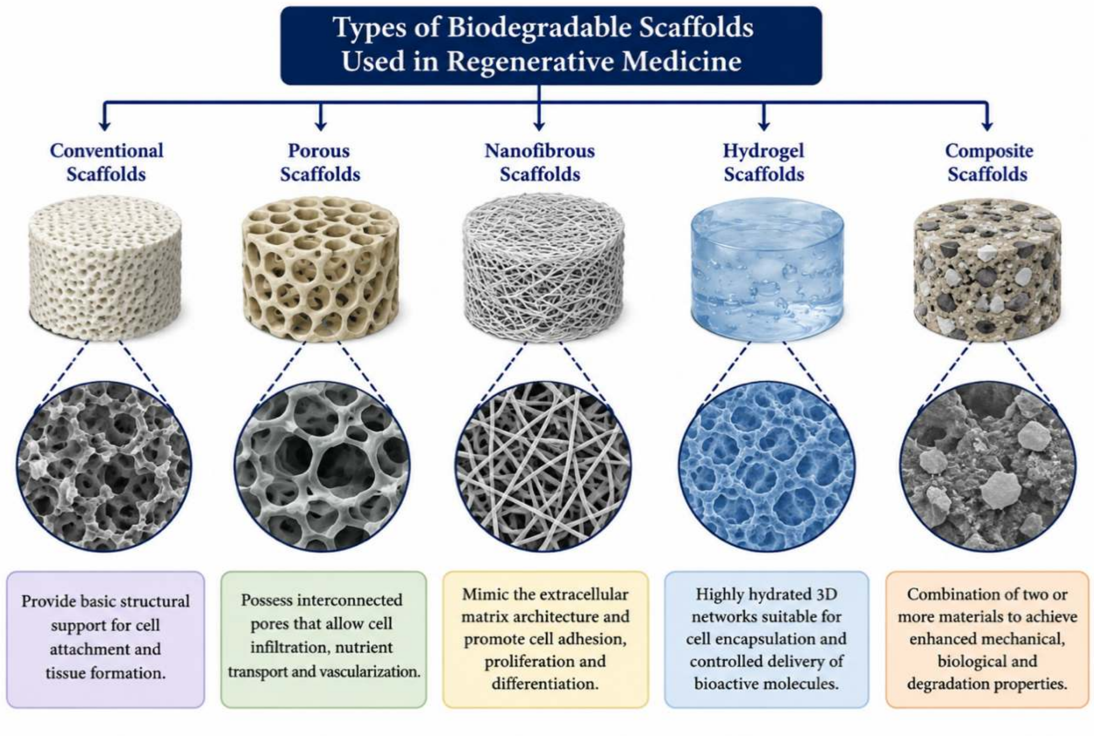

Figure 1. Illustration showing conventional scaffolds, porous scaffolds, nano-fibrous scaffolds, hydrogel scaffolds, and composite scaffolds utilized in tissue engineering applications

1.7.4 In Situ Forming Systems

In situ forming systems involve the process of transformation after being administered and then developing a gel matrix or semi-solid structure. This can be done through changes in temperature, pH levels, ionic strength, or enzyme catalysis, among others. This technology offers precise localisation and a sustained effect within the tissues (52).

1.7.5 Clinical Applications

There are several advantages of employing these biomaterials including their minimally invasive nature, minimal pain and risks of infection, reduced healing time, and better adaptability to deficiencies (53).

1.7.6 Biodegradable Hydrogels

Hydrogels represent one of the most extensively studied classes of biodegradable biomaterials because of their high moisture content and structural resemblance to extracellular matrices (54).

1.7.7 Natural Hydrogels

The biological hydrogels are made up of biological polymers, namely, collagen, gelatin, alginate, chitosan, fibrin, and hyaluronic acid. The biological polymers are inherently bioactive and biocompatible due to which the cells grow and migrate on these hydrogels and even create tissues. Owing to their natural origin, they are good candidates for regeneration although they lack mechanical strength and cannot be degraded in a controlled manner; therefore, they need to be improved upon (55).

1.7.8 Synthetic Hydrogels

Synthetic hydrogels are prepared by using synthetic polymers, such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), PLA, PLGA, and polycaprolactone-based polymers. They allow us to control the mechanical and degradation properties of these hydrogels. Because of these properties, these polymers have found applications in tissue engineering and drug delivery (56).

1.7.9 Stimuli-responsive Hydrogels

Stimuli-responsive or "smart" hydrogels respond to environmental changes, which include temperature, pH, enzyme, optical and magnetic fields. The smart hydrogels provide opportunities for targeted drug release and regulation of cellular processes through intelligent design (57).

1.8 Nanotechnology-Based Systems

Through the introduction of the precise control in terms of design and delivery of therapies in Nano scale, nanotechnology has contributed immensely towards improving the capabilities of biodegradable and regenerative platforms (58).

1.8.1 Nanoparticles

They consist of nanomaterials made from biodegradable polymers such as PLGA, PLA, and chitosan and can be utilized in drug delivery, gene delivery, and growth factors. The small size enables these particles to deliver therapy and achieve cellular absorption (59).

1.8.2 Nanofibers

They consist of biomimetic structures resembling the fibrous structure of natural extracellular matrix. Due to the large surface area presented by these fibres, they stimulate the process of cell attachment and tissue integration, making them useful in regeneration (60).

1.8.3 Nano gels

Nano gels are hydrogel particles at the nano-scale that have the ability to encapsulate various therapeutics, such as proteins, nucleic acid, and growth factors. High loading capacity, biocompatibility, and responsiveness of these particles are promising traits for regenerative therapies (61).

1.8.4 Lipid-Based Biodegradable Carriers

Lipid-based biodegradable particles are known as liposomes, solid lipid nanoparticles, and lipid-polymer hybrid nanoparticles. They are very good biocompatible vehicles used for efficient drug delivery due to their protective ability for sensitive therapeutic compounds (62).

1.9 Controlled Drug and Growth Factor Delivery Systems

Controlled drug delivery systems are now considered vital for regenerative medicine owing to their capacity to achieve localized, sustained, and specific delivery of biological molecules that control tissue formation and regrowth. Such biological molecules include growth factors, cytokines, genes, and therapeutic medicines. These biological molecules act in the process of cellular proliferation, cell differentiation, vascularization, and extracellular matrix remodelling. However, direct application of these molecules leads to their rapid degradation, reduced biological lifetime, poor localization, and adverse effects on other body organs (63).

1.9.1 Need for Controlled Delivery

Tissue regeneration demands the timely presentation of biological cues. The release of signalling factors in natural tissues occurs under stringent control conditions, ensuring that each process within the healing sequence is properly coordinated. Traditional drug delivery techniques often fall short in reproducing such physiological patterns, which results in decreased effectiveness of therapy. The use of controlled delivery systems can solve these issues by providing a sustained supply of the treatment agent at the site of application while limiting its effects on the rest of the body. Controlled delivery technologies may increase bioavailability, decrease the frequency of treatments, ensure the stability of sensitive molecules, and provide targeted actions on the affected organ (64).

1.9.2 Growth Factor Delivery

Growth factors are potent signalling proteins that regulate cellular activities essential for tissue regeneration. Biodegradable biomaterials serve as effective carriers for their localized and sustained delivery (65).

1.9.2.1 Vascular Endothelial Growth Factor (VEGF)

VEGF is an important regulator in angiogenesis and vascular remodelling. It causes the proliferation, migration, and production of new vessels through endothelial cells, which contribute to their ability to deliver oxygen and nutrients to areas undergoing regeneration. Controlled release of VEGF has been shown to be highly beneficial in the treatment of wound healing, cardiac tissue regeneration, and engineered tissues (66).

1.9.2.2 Bone Morphogenetic Proteins (BMPs)

Amongst the group of growth factors that play a significant role in the process of bone induction, the Bone Morphogenetic Proteins (such as BMP-2 and BMP-7) rank highest in effectiveness. These growth factors stimulate the differentiation of mesenchyme stem cells to osteoblasts. Many studies have been conducted in this area involving bone grafts made of BMPs (67).

1.9.2.3 Transforming Growth Factor-Beta (TGF-β)

This factor plays an important role in the formation of cartilage, production of extracellular matrix and tissue remodelling. Controlled release of this factor significantly increases chondrogenic differentiation and cartilage regeneration, thus being highly beneficial in cartilage defects and osteoarthritis treatment (68).

1.9.2.4 Platelet-Derived Growth Factor (PDGF)

This factor participates in the wound healing process due to its simulative effect on fibroblasts, collagen production, angiogenesis and tissue remodelling (69).

1.9.3 Biodegradable Delivery Vehicles

Various biodegradable systems have been designed to facilitate the controlled release of growth factors and drugs.

1.9.3.1 Microspheres

The use of biodegradable microspheres produced from polymers like PLGA allows for sustained and site-specific delivery of proteins, peptides, and growth factors. The modifiable nature of their size and biodegradability allows for a prolonged action of therapeutics while preventing the decomposition of loaded biomolecules (70).

1.9.3.2 Nanoparticles

Nanoparticles have advantages like high surface area, effective cellular internalization, and target specificity. These carriers at the Nano scale level are able to deliver drugs, genes, and growth factors selectively to target tissue or cell, which provides greater efficiency for drug administration (71).

1.9.3.4 Hydrogels

Hydrogels constitute an extremely hydrated polymer structure with the ability to integrate biological compounds and cells into the gel framework. As hydrogels are very similar to extracellular matrix, hydrogels are regarded as the perfect material for controlled release in biomedical applications (72).

1.9.4 Controlled Release Mechanisms

Release of pharmaceutical agents in biodegradable systems is regulated by different mechanisms that could be customized in accordance with the desired results (73).

1.9.5 Diffusion Controlled Release

Diffusion-controlled release occurs as a result of diffusion of therapeutic agents through the matrix/pores of the polymeric matrix into the surrounding tissue (74).

1.9.6 Degradation-Controlled Release

Degradation-dependent release systems depend upon gradual degradation of the degradable carrier. The gradual degradation of the biomaterial results in a constant delivery of the drugs into the system. The application of this technique is especially effective in regenerative therapies (75).

1.9.7 Stimuli-Dependent Release

In stimuli-dependent release systems, the release of therapeutic factors takes place in response to external stimuli like pH, temperature, enzymes, magnetic fields, and light. This sophisticated method can be used in targeted therapy and represents one of the most advanced directions in personalized regenerative therapy show in table.1 (76).

Controlled systems for delivering drugs and growth factors to tissues have revolutionized the field of regenerative medicine by providing a way to deliver biological signals to the site of regeneration continuously, locally, and in a biologically meaningful fashion. Further advancements in the development of biodegradable carrier materials and release technology are anticipated to promote tissue regeneration and the advancement of future generations of regenerative therapies.

1.9.8 Stem Cell Engineering and Biodegradable Systems

Biotechnology techniques involving stem cells have proven effective for developing regenerative therapies because of the self-renewal, proliferation, and differentiation capabilities of stem cells into specialized cell populations. In addition to the biological properties of stem cells, an ideal therapy would include a biodegradable system capable of promoting the survival and proper functioning of the stem cells in the area of tissue damage. By imitating the extracellular matrix (ECM), biodegradable materials enable stem cell interaction with the material and the formation of new tissue as the material decomposes (78).

1.9.8 1 Stem Cells in Regenerative Medicine

Various types of stem cells have been used in regenerative applications as a result of their biological properties and therapeutic potential.

Table 1. Common Growth Factors Delivered Using Biodegradable Systems for Tissue Regeneration (77)

Growth Factor	Function	Target Tissue	Delivery System
VEGF	Promotes angiogenesis and vascularization	Vascular tissue	Hydrogel
BMP-2	Stimulates osteogenesis and bone formation	Bone	Scaffold
TGF-β	Enhances chondrogenesis and cartilage repair	Cartilage	Nanoparticles
PDGF	Accelerates wound healing and tissue remodelling	Skin	Microspheres

1.9.8.2 Mesenchyme Stem Cells (MSCs)

Adult mesenchyme stem cells are the most extensively researched due to their multipotent ability to differentiate and immunomodulatory functions. Adult stem cells like MSCs are known to give rise to oestrogenic cells, chondrogenic cells, adipogenic cells, and myogenic cells and are therefore useful in the reconstruction of bones, cartilages, skin and cardiovascular tissues. Besides, mesenchyme cells also produce different types of growth factors and cytokines which are involved in healing and angiogenesis (79).

1.9.8.3 Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells are formed as a result of reprogramming of adult somatic cells into pluripotency cells. iPSCs have the potential to differentiate into almost all types of cells just like ESCs do but they overcome many problems and ethical issues which are normally associated with embryonic stem cells.

1.9.8.4 Embryonic Stem Cells (ESCs)

The advantages of embryonic stem cells include their unlimited ability to divide infinitely and form all cells which originate from all germinal layers. This property makes them very useful in tissue engineering and organ regeneration. Ethical, immune incompatibility and teratoma risks are limiting the use of ESCs (80).

1.9.8.5 Cell–Scaffold Interactions

The interaction between cells and scaffolds is crucial in the success of any regenerative therapy treatment. Biodegradable scaffolds offer both physical and biochemical cues which facilitate cell adhesion, proliferation, migration and differentiation. Characteristics such as the scaffold's chemistry, porosity, stiffness and degradability will influence the fate of stem cells and overall tissue regeneration. Biomimetic scaffolds with characteristics similar to those of the natural extracellular matrix will improve cellular function and aid in effective tissue regeneration (81).

1.9.8.6 Stem Cell Delivery Platforms

There have been many types of biodegradable delivery platforms designed for improved stem cell transplantation and regenerative purposes. Injectable matrices have been designed for easier transportation and transplantation of stem cells at specific locations. Injectable matrices are highly malleable to accommodate the deformities of the body tissue and thus provide a conducive microenvironment for cell retention and effectiveness. In addition, three dimensional bio printing has been developed to aid in the fabrication of precisely constructed biodegradable cell-laden scaffolds.

1.9.8.7 Enhancing Cell Survival

A significant limitation with the use of stem cells for therapy is the inability of transplanted cells to survive due to factors such as inflammation, hypoxia, and improper vasculature at the injured area. Modern biodegradable scaffolds have overcome these challenges by incorporating factors such as growth factors, bioactive agents, oxygen delivery agents, and antigens to optimize the local environment. In addition, the use of strategies like cell adhesion enhancement via surface modification techniques, controlled delivery of bioactive substances, and bio mimicry have improved stem cell engraftment. Overall, these approaches have greatly increased the effectiveness of using stem cells for tissue repair. Stem cell engineering in combination with biodegradable materials provides strong treatment platforms with great potential to facilitate tissue repair. Future developments in biomaterial engineering and bio printing will lead to further advancements in the field of regenerative medicine (82).

1.10 Tissue-Specific Regenerative Applications

Versatility of bio-degradable biomaterials has allowed their use in many fields of regenerative medicine. They provide physical support for cell adherence, deliver therapeutic molecules, mimic the native extracellular matrix and help repair and restore tissues. Many biomaterials and scaffolds are selected based on the needs of different tissues with respect to mechanical and physiological properties. Thus, the development of tissue-specific regeneration strategies has become one of the main concerns of modern regenerative medicine (83).

1.10.1 Bone Tissue Engineering

Bone is a highly plastic tissue that possesses strong regenerative ability, but sometimes bone defects that can be caused by trauma, infections, congenital disorders and even removal of tumours exceed its regenerative ability. Biodegradable biomaterials stimulate bone regeneration through oestrogenic action (84).

1.10.1.1 Osteoconductive Systems

Osteoconductive materials assist in promoting bone formation through acting as a scaffold on which the cells can anchor themselves, migrate, and proliferate. Biodegradable polymers such as PLA, PCL, and PLGA are popular due to their favourable degradation characteristics and mechanical properties. The degradation occurs in conjunction with cellular infiltration, vascularization and formation of new bone tissue. Growth factors like BMPs are introduced within the scaffold to further stimulate osteogenesis and tissue repair (85).

1.10.1.2 Bio Ceramic Composites

Bio ceramics including hydroxyapatite, β-TCP, and bioactive glass share close resemblance with the mineral composition of natural bones. Bio ceramic composite scaffolds incorporating biodegradable polymers exhibit improved mechanical properties and osteoconductivity. This combination assists in improving mineral deposition, cell differentiation and long term bone tissue regeneration (86).

1.10.2 Cartilage Tissue Regeneration

The limited self-repair potential of articular cartilage due to its avascular and hypo cellular nature makes the regeneration of cartilage challenging. Cartilage defects and diseases such as osteoarthritis are thus serious clinical problems. Biodegradable scaffolding materials are promising in addressing this problem (87).

1.10.3 Hydrogel-Based Approaches

Hydrogels have been extensively studied as cartilage tissue engineering materials due to their high water content, which mimics the cartilage matrix. Natural hydrogels composed of collagen, gelatin, alginate, and hyaluronic acid form a suitable environment for cell growth and matrix synthesis. Artificial hydrogels exhibit mechanical and degradation properties that permit tissue formation control. Moreover, hydrogels can also release growth factors like transforming growth factor-beta (TGF-β), thus inducing chondrogenesis (88).

1.10.3.1 Chondrocyte Delivery

Cartilage repair can be performed using a chondrocyte delivery technique involving the use of biodegradable matrix scaffolds, in which the chondrocytes can stay, proliferate, and secrete an extracellular matrix. Hydrogels loaded with stem cells are additional methods for cartilage tissue engineering that continuously produce new cartilage-forming cells (89).

1.10.4 Skin and Wound Healing

Skin damage due to burns, ulcers, injury, or surgery should be effectively repaired using regenerative techniques to ensure skin integrity and avoid infection. The use of biodegradable biomaterials has led to significant changes in wound treatment, allowing not only for wound protection but also for drug delivery (90).

1.10.5 Smart Dressings

The latest trend in biodegradable wound dressings involves their active participation in the healing process, as opposed to passive coverage. For example, smart materials that react to various environmental stimuli (e.g., pH, temperature, moisture levels, bacteria presence) allow the release of therapeutic substances in response to these changes. Hydrogels, nano-fibrous matrizes, and bioactive films are often used to ensure a moist environment on wounds to facilitate re-epithelialization and tissue remodelling (91).

1.10.6 Antimicrobial Biomaterials

Infections are among the key barriers to wound healing. The antimicrobial biodegradable materials usually feature antimicrobial components, such as silver nanoparticles, antimicrobial peptides, chitosan, and antibiotic-based coatings, which help prevent colonization of the wounded site by pathogenic microorganisms (92).

1.10.7 Cardiovascular Regeneration

Despite numerous advancements, cardiovascular disorders are still the leading cause of death across the globe. Due to the lack of regenerative capacity of myocardial tissue, biodegradable materials are used to restore the proper function of heart and repair vascular injuries (93).

1.10.7.1 Cardiac Patches

The use of biodegradable cardiac patches helps promote the regeneration of injured myocardium after an infarction. It is possible to create cardiac patches from various natural or artificial biopolymers, as well as introduce growth factors or stem cells into these scaffolds.

1.10.7.2 Vascular Grafts

Biodegradable polymer-based vascular grafts with small diameters have drawn substantial interest due to their potential applications as substitutes for synthetic vascular grafts. Such biomaterials can promote endothelialisation, vascular remodelling, and tissue ingrowth. Modern biodegradable vascular grafts strive to minimize thrombosis, inflammatory response, and complications and normalize vascular function.

1.10.8 Neuro-tissue Engineering

Neuroregeneration is an extremely challenging issue, considering the complexity and poor regenerative capabilities of the central and peripheral nervous systems. Biodegradable biomaterials create favourable conditions for the guidance and restoration of the function of nerve tissue (94).

1.10.8.1 Nerve Conduits

Biodegradable nerve conduits imply tubular structures of biodegradable nature designed for bridging a segment of damaged tissue and facilitating axonal regeneration at a point of nerve damage. Many biocompatible substances are currently under study for use as nerve conduits. They include such materials as collagen, chitosan, PLGA, and PCL.

1.10.8.2 Neuro-active biomaterials

The recent progress in the sphere has made it possible to develop neuroactive biomaterials that can deliver neurotrophic, neuroelectric, and neuroprotective stimuli promoting neural regeneration. Bioactive compounds, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), promote neural cell survival, differentiation, and axonal elongation. Also, conductive biomaterials and nanotechnological approaches to neurorehabilitation are being considered (95).

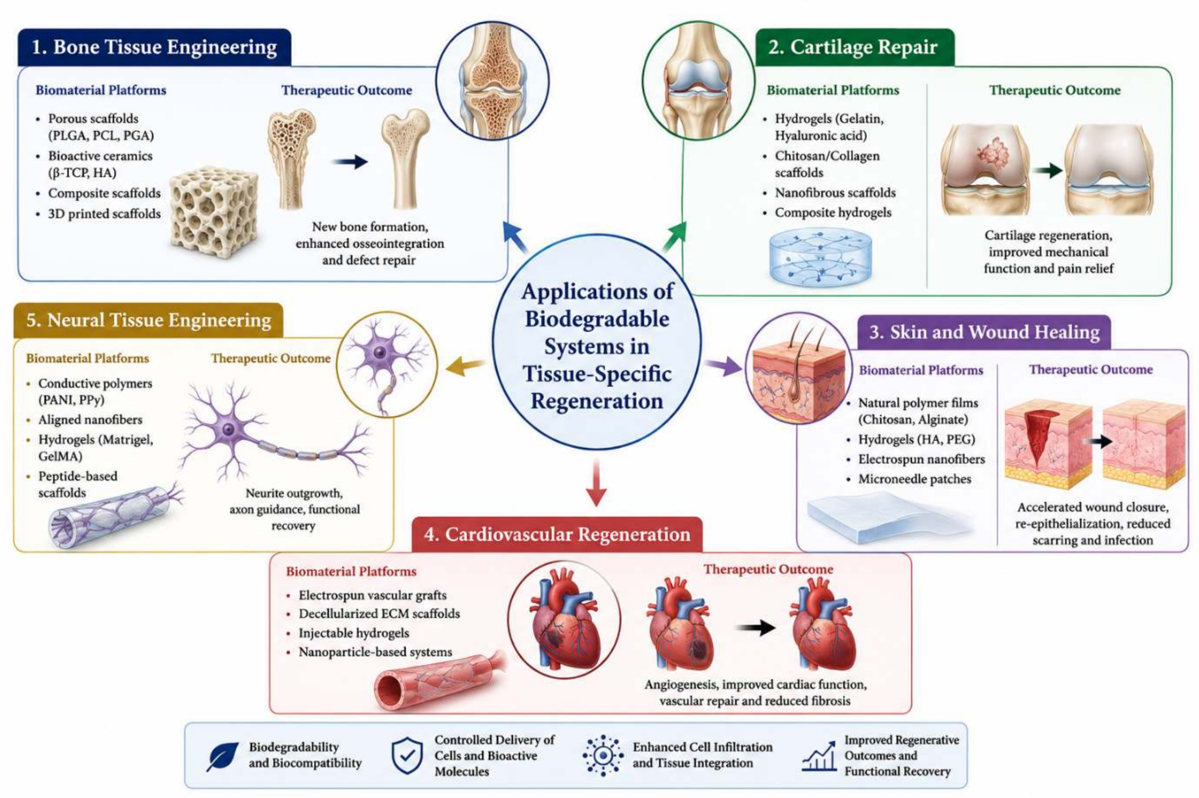

Fig. 2: Illustration depicting major regenerative applications of biodegradable biomaterials such as bone tissue engineering, cartilage repair, skin and wound healing, cardiovascular regeneration, and neural tissue engineering, along with respective biomaterials used and therapeutic outcomes achieved.

1.11 Emerging Technologies & Next Generation Systems

Emerging technologies in material science, bioengineering, artificial intelligence, and additive manufacturing are driving rapid advancements in the field of next generation biodegradable systems for regenerative therapeutics. The objective is to achieve enhanced biological performance and therapeutic precision through personalized treatment strategies based on advanced responsive biomaterials and their fabrication (96).

1.11.1 Responsive Biodegradable Biomaterials

Responsive biodegradable biomaterials exhibit dynamic response in relation to various physiological cues resulting in regulated therapeutic action and tissue regeneration process.

1.11.1.1 pH Responsive Systems

pH responsive biodegradable systems react differently with change in pH levels in inflamed or infected tissues leading to targeted drug delivery without any systemic adverse effects.

1.11.1.2 Temperature Responsive Systems

Biodegradable temperature responsive systems show reversible changes upon exposure to physiological or external temperatures changes. These biomaterials are especially suitable for injectable systems.

1.11.2 Enzyme-Responsive Materials

Enzyme-responsive biomaterials break down selectively in response to specific enzymes present in target tissues, which allows for controlled release of drugs and timing of degradation processes with tissue remodelling mechanisms.

1.11.2.1 D Bio printing

The advent of three-dimensional bio printing has completely transformed tissue engineering by providing an ability to produce complex biological constructs with controllable architecture and cell arrangements.

1.11.2.2 Bioinks

Bioinks are made from degradable polymers, live cells, growth factors, and other bioactive ingredients. They enable production of tissue-like constructs by printing. Hydrogel-based natural and synthetic bioinks are widely used because of biological advantages associated with them.

1.11.2.3 Customized Scaffolds

It is possible to use bio printing techniques to generate customized scaffolds that have pre-programmed structure, mechanical properties, and biological functions.

1.11.2.4 Patient-Specific Implants

Medical imaging data allows for designing implants using three-dimensional bio printing techniques that match anatomy of individual patients.

1.11.2.5 4D Printing in Regenerative Medicine

This technology improves on conventional three-dimensional printing by adding time dependence in behavior to degradable constructs.

1.11.3 Shape-Memory Biomaterials

Such biomaterials can change their shape in response to some external stimulus, such as a change in temperature, moisture content and pH.

1.11.3.1 Dynamic Tissue Constructs

The main feature of the 4D-printed constructs is that they can change their shape upon implantation in order to more closely resemble the developmental processes taking place in the native tissue.

1.11.3.2 Biological Fabrication and Organ Engineering

Biological fabrication involves the use of biomaterials, cells, growth factors, and engineering technology in order to produce biological constructs. The development of tissue substitutes for engineered organs that can imitate certain parts of the native organs has already been achieved in recent years. Although at present full-fledged organs are not produced, research in the area of vascularization and stem cells will eventually make it possible (97).

1.11.3.3 Artificial Intelligence in Designing Biomaterials

Artificial intelligence is now being considered as one of the major tools to accelerate biomaterial development. Machine learning algorithms will help analyse the existing data sets on certain characteristics of materials, such as their degradation process and their influence on regenerative functions (98).

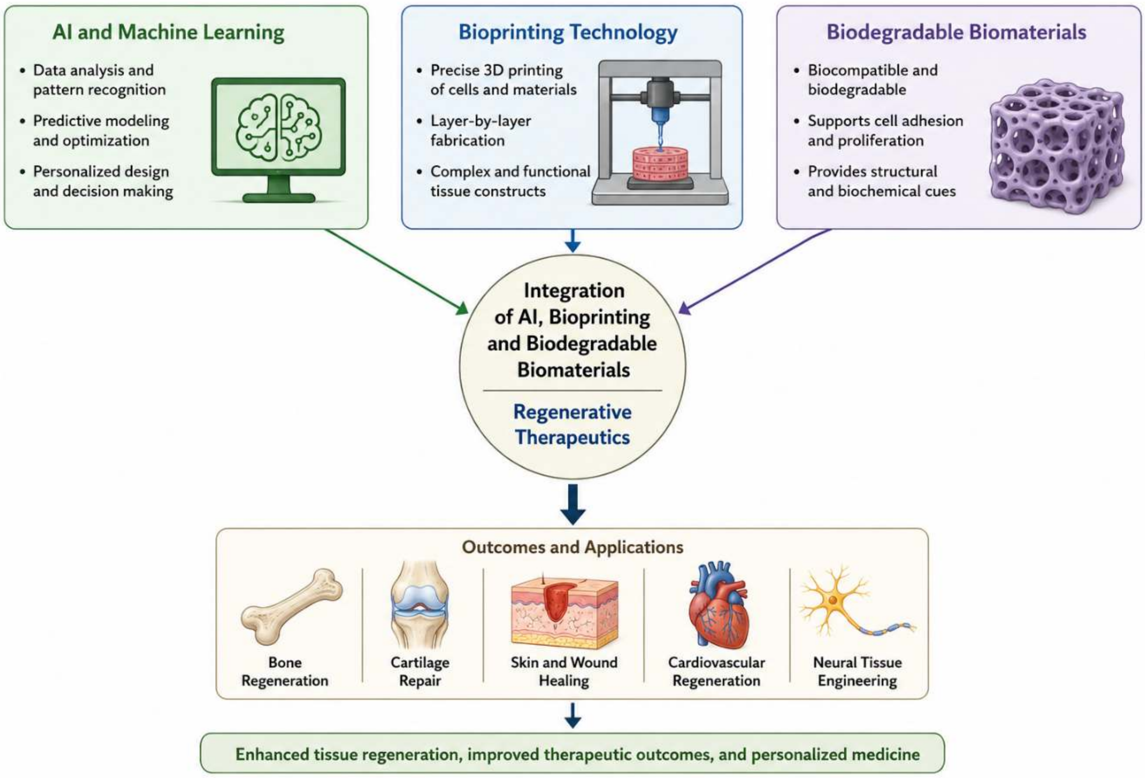

Figure 3. Incorporation of AI technology, bio printing and biodegradable biomaterials into regenerative therapies.

1.12 Clinical Applications and Regulatory Issues

Even with all of the recent progress that has been made in biodegradable regenerative therapy technologies, there remain many scientific, manufacturing, regulatory and even ethical issues that must be overcome before effective translation can be realized (99).

1.12.1 Presently Available Clinical Products

Several biodegradable biomaterials have found their way into clinical applications and even to market. Examples of FDA-approved biodegradable technologies include biodegradable sutures, orthopedic bone fixators, tissue engineered skin replacements, drug delivery implants and other bioresorbable structures. Commercialized regenerative therapies make increasing use of biodegradable polymers, hydrogels, and cell delivery matrices (100).

1.13 Manufacturing Challenges

1.13.1 Up-Scale Manufacturing

The scaling-up of laboratory scale biomaterials for production as clinical products is necessary to meet both demand and efficacy requirements for commercialization.

1.13.2 Quality Control

Quality control must be extremely stringent to guarantee the safety and efficacy of the product. Divergences in chemical composition, degradation rates, porosity, and mechanical properties may have significant implications for the clinical outcomes. Accordingly, complete characterization and standardized tests need to be performed during all stages of manufacturing.

1.13.3 Reproducibility

Reproducibility still continues to be an issue with biologically-derived materials and cell-based products. It affects both biological performance and regulatory approval of the product. Consequently, standardized methods of production are important here.

1.13.4 Regulatory Guidelines

Implementation of biodegradable regenerative products in the clinical setting is subject to strict regulatory requirements.

1.13.5 FDA Regulations

The FDA assesses biodegradable biomaterials according to criteria such as biocompatibility, toxicity, degradation rate, mechanical characteristics, and clinical efficiency. Extensive research, both preclinical and clinical, may be required for the approval of the product.

1.13.6 EMA Regulations

The EMA regulates advanced therapy medicinal products, including tissue engineering and regenerative medicine products. The process of regulating involves an assessment of manufacturing process, safety, biological activity, and long-term results.

1.13.7 ISO Standards

ISO provides internationally accepted guidelines that regulate the assessment of biomaterials. The standards cover biomaterial characterization, biological evaluation, sterilization, and risk assessment.

1.13.8 Safety and Ethical Considerations

There are a number of issues that affect the safety of biodegradable regenerative treatments, which include things like degradable product types, immunogenic reactions, toxicity, and the reactions within tissues. It is essential to conduct full testing before these products can be used for clinical treatment because there may be risks that need to be avoided. There are particular ethical concerns associated with stem cells, genetic engineering, and personal regenerative therapy.

1.14 Challenges and Future Perspectives

The area of biodegradable biomaterials has seen tremendous advances in recent decades in the area of regenerative therapeutics and tissue engineering. Nonetheless, there are some challenges that need to be addressed in order to further improve upon biodegradable technologies and ensure clinical success in the future. Integrating new technology solutions will play a key role in addressing the following scientific challenges.

1.14.1 Scientific Challenges

Most biodegradable materials are made to be biocompatible and non-immunogenic; however, adverse immune reactions could still occur due to material composition, surface characteristics, and other factors that trigger an immune response. The excessive activation of such responses could result in an inefficient process of tissue formation. Thus, the development of biomaterials with the ability to modulate the host's immune system is needed.

1.14.2 Incomplete Tissue Integration

The successful integration between implanted biomaterials and existing tissues plays an important part in the process of regeneration. Inadequate vascularization and poor interactions between cells and the biomaterial could prevent effective tissue integration and restoration.

Efficient communication with engineered materials and tissues is considered to be the biggest challenge faced in regenerative medicine.

1.14.3 Variable Degradation Rates

Degradation characteristics of biodegradable materials tend to vary as a function of their implantation location, physiological environment, and patient variability. If scaffolding degradation does not correspond with the growth of tissues, this can lead to too early degradation of structures, as well as delayed elimination of biomaterials from a living organism. Fine control of the rate of material degradation is still needed.

1.14.4 Technological Issues

1.14.4.1 Scalable Fabrication

Many biodegradable technologies have shown good results in preclinical trials. However, translating these discoveries into practice is difficult because they involve issues related to mass production, cost efficiency, quality control, and reproducibility of materials and cells used to generate them. Scaling up complex biodegradable technologies is difficult to achieve in practice.

1.14.4.2 Long-Term Performance

The behaviour of biodegradable systems in a living body is still poorly understood. Factors including stability of scaffolds, potential toxicity of degradation by-products, and possible long-term inflammatory response require further studies.

1.14.5 Personalized Regenerative Medicine

1.14.5.1 Precision Biomaterials

Improvements in biomaterials engineering are resulting in the emergence of new biomaterials that can be developed to address patients' specific biological and pathological needs. It is possible to develop such materials to suit individuals based on their age, biological state, genotypic makeup, and special tissue requirements.

1.14.5.2 Patient-Specific Therapies

Patient-specific therapies have been developed as a result of the combination of stem cell technology, use of artificial intelligence and imaging techniques, as well as the development of new manufacturing processes. The potential for developing patient-specific scaffold and tissues is significant in regenerative therapy while overcoming problems of immune response.

1.14.6 Future Perspectives

1.14.6.1 Multifunctional Biomaterials

New biodegradable systems are likely to be multifunctional, and include such functions as being a scaffold structure, providing drug delivery, having immunomodulatory properties, having antibacterial effects, and even self-monitoring capabilities. Thus, new multifunctional biodegradable systems can enhance regeneration.

1.14.6.2 Self-Healing Biodegradable Systems

Biodegradable self-healing materials can be considered an entirely new category of regenerative platforms that will have the ability to repair themselves structurally after implantation.

1.14.6.3 Biomimetic Regenerative Platforms

Future regenerative technologies are likely to incorporate elements of mimicry of native biological structures, mechanics, and biochemistry. Platforms that mimic the structure and properties of the extracellular matrix and microenvironment are expected to offer considerable improvement in the performance of cells, as well as in tissue integration and regeneration.

Conclusion

Biodegradable systems have been identified as key components of the future of regenerative medicine, contributing innovative approaches to repair, replace, and regenerate tissues and organs affected by trauma and disease. Through the creation of temporary scaffolding, delivery of therapeutic agents in a controlled manner, and generation of a bioactive environment that mimics the native extracellular matrix, biodegradable biomaterials have improved the efficiency of tissue engineering and regenerative medicine. The combination of biodegradable materials with other advanced technologies including stem cell engineering, delivery of growth factors, nanotechnology and bio fabrication techniques has made it possible to achieve regeneration not only in bones but also in various tissues including cartilage, skin, cardiovascular and nervous tissue. Some novel concepts involving the use of stimuli-responsive biomaterials, 3D and 4D bio printing, artificial intelligence and customized regeneration platforms have already started transforming the regenerative therapeutics field. However, despite tremendous progress in the area, some hurdles still need to be overcome. These include difficulties related to achieving precise control over degradation kinetics, improved tissue integration and safety as well as scaling up production and regulatory issues. Overcoming the obstacles ahead would require cooperation from scientists, engineers, doctors and regulatory bodies working in the field. In the years ahead, the development of multifunctional, self-healing and biomimetic biodegradable materials is likely to make an important contribution to advancing the state-of-the-art even further. Indeed, as material sciences, biotechnology and artificial intelligence continue to advance at breakneck pace, novel generation of biodegradable platforms will gain increasing prominence in personalized regenerative medicine.

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