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A REVIEW ARTICLE

Innovations in Biomaterials, Scaffolds, and Artificial Intelligence JUSTIFY

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Abstract

Over the past two decades, tissue engineering and regenerative medicine have been among the fastest growing scientific disciplines, driven by the integration of biomaterials, stem cells, scaffolding technologies and artificial intelligence (AI) to reconstruct tissues and restore their function. Natural biomaterials offer a rich environment for biosignals but are limited in structural applications due to poor mechanical stability. Synthetic material, on the other hand, offer flexible control over mechanical properties and degradation rates, but with limited inherent biocompatibility, making hybrid biomaterials a promising option. Electrospinning and 3D and 4D bioprinting technologies have contributed to the development of scaffolds that mimic the extracellular matrix, although challenges related to deep porosity, mechanical stability, and uniform printing persist. Mesenchymal Stem Cells (MSCs) are the most common clinical choice, while induced pluripotent stem cell (iPSCs) hold potential in personalized medicine, despite concerns about genomic integrity. Exosome based therapy represent a safe and effective alternative to whole cell therapy. AI enables the prediction of biomaterial and cell behavior, enhances bioprinting, and allows for virtual model testing via digital twins. However, widespread clinical use is hampered by a lack of regulatory standards and data, as well as the difficulty in understanding the models. Challenges in tissue engineering include blood supply, immune response and ethical and legal issues. Research underscores the need for coordinated, multidisciplinary research efforts. This integration represents the foundation for a new generation of regenerative medicine capable of overcoming current obstacles and restoring vital functions with precision and sustainability.

1. Introduction

One of the best-known cutting-edge research trends is tissue engineering and regenerative medicine (TERM), which aims to address traumatic or chronic tissue damage by creating sustainable bioremediation solutions that combine biomaterials, scaffolding technologies, stem cells and sophisticated computational methods. Increasing the efficiency of bioremediation scaffolds, creating new, more biocompatible materials, increasing the efficiency of stem cell differentiation, and introducing artificial intelligence technologies have all been the subject of numerous studies over the past 20 years, which have completely transformed the field [1,2].

This article does not contain direct experimental data as it is a review. Rather, it compares the existing scientific literature and assesses the merits and shortcomings of all aspects of tissue engineering in order to evaluate, critique, and understand current research trends. Scientific overviews are important because they help researchers identify research questions, fill knowledge gaps and guide future use of animal resources by integrating diverse information into a coherent framework. According to recent research, the true integration of multiple disciplines, including materials science, molecular biology, computer science, and deep learning systems, in addition to advances in biomaterials, is responsible for the rapid progress of this field. For example, artificial intelligence (AI) has created analytical and predictive systems that can optimize the properties of biomaterials before they are produced, reducing the need for expensive and time-consuming experiments, while 3D and 4D bioprinting technologies have made it possible to produce extremely precise scaffolds that adapt to the patient's anatomical shape [3].

Furthermore, research indicates that biomaterials have evolved from basic, traditional platforms to advanced intelligent biomaterials capable of interacting with biological systems and responding to external stimuli such as pH, temperatures, and enzymes. Adult stem cells (MSCs) and induced

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pluripotent stem cells (iPSCs) have made great strides in the field of stem cells for regenerative medicine; yet, issues with biosafety, heterogeneity, and differentiation control still exist.

In addition, there is a growing trend in the field towards personalized regenerative medicine (PRM), which combines predictive computer models with a patient's genetic and functional data to create customized treatment plans and precisely designed scaffolds based on the patient's biological characteristics.

This review provides of the four primary topics that are helping tissue engineering to move forward: (1. Biomaterials: the different kinds, their qualities, and the problems they cause. 2. Tissue-derived scaffolds, bioprinting, and electrospinning are all ways to make scaffolds. 3. Different kinds of stem cells, where they are used, and the problems they cause in the clinic. 4. AI in TERM: Artificial intelligence in regenerative medicine Its role in bioprinting and image analysis optimization and design that predicts the future). The essay also looks at the most important problems that still make it hard to go from research in the lab to clinical use on a broad scale. These constraints encompass commercialization, regulatory approval, and ethical considerations, with challenges associated with artificial intelligence, like the interpretation of deep learning-based models and the absence of comprehensive datasets [4].

2. Biomaterials, Scaffold and Stem Cell-Based Regeneration

2.1. Using biomaterials for tissue engineering

Biomaterials are the basis of tissue engineering and regenerative medicine. They are used to grow cells and make new tissue. For a regenerative system to work, the biomaterial must be able to reproduce the structural and functional properties of the extracellular matrix (ECM) while also being mechanically stable, biocompatible, and able to interact with cells and the environment in a dynamic way.

In recent years, the design and development of both synthetic and natural biomaterials has made a lot of progress. New methods have come up that try to combine the best features of both types of biomaterials into hybrid biomaterials [5].

2.1.1. Biological materials that come from nature

Some natural biomaterials are collagen, gelatin, fibrin, hyaluronic acid, silk fibroin, and chitosan. They are different because they come from living things. These materials are getting a lot of attention because they are very comparable to the (ECM) and can help cells stick together, move around, and heal themselves naturally [6].

Natural biomaterials have advantages such as having natural integrin binding sites; • Excellent biocompatibility; • Ability to induce angiogenesis in poorly vascularized tissue; • Capable of promoting cell differentiation through its intrinsic biosignals. For example, one of the most popular biopolymers is collagen, especially in the development of skin, cartilage and bone. It provides a fibrous network of support that allows cells to grow like natural tissue [7].

However, natural materials have several disadvantages, the most important of which are: (1. Large variation between batches 2. Insufficient mechanical strength in contrast to synthetic materials 3. Rapid and uncontrolled degradation by the body 4. Possibility of immunological reactions, especially when animal sources are used). As a result, modern methods have been developed to improve their properties, including: (Chemical modifications, such as GelMA (gelatin methacryloyl), Cross-linking engineering to increase stability; Addition of synthetic polymers to natural materials to improve mechanical resistance), [2]. When the goal is to improve biocellular interactions such as in skin engineering, nerve healing, cartilage growth support and microvascular engineering, natural materials remain the preferred choice despite technical barriers.

2.1.2. Artificial biomaterials

A wide variety of polymers, such as PLA, PGA, PLGA, PCL and PEG, as well as smart polymers and cutting-edge nanomaterials, are included in synthetic biomaterials. Due to their great stability, ease of large-scale production, and the ability to precisely control their mechanical and chemical properties, these materials have become essential in tissue engineering design[8] . The primary benefits of synthetic biomaterials encompass: (1. Complete authority over the degradation

rate. 2. Continuous repeatability 3. Suitable for structural purposes 4. Ability to convey biological processes through chemical modification).

Polycaprolactone (PCL) is a notable polymer that degrades slowly, making it suitable for extended bone and cartilage regeneration. (PCL) is a notable substance distinguished by its remarkably slow breakdown, making it suitable for extended bone and cartilage formation. Polyethylene glycol (PEG) is a polymer that is hydrophilic and is commonly employed to produce hydrogels that demonstrate excellent biocompatibility and may be modified to incorporate active elements that improve cell adhesion [9].

Even so, synthetic materials may exhibit certain disadvantages: (The lack of natural biosignals reduces cellular adhesion, decomposition might yield acidic waste products, including PLA/PGA, specific polymers demonstrate increased stiffness, obstructing cellular growth, complex alteration processes are required to improve bioactivity). To overcome these restrictions, techniques such as: (RGD peptides for surface functionality are utilized, integration of nanoparticles to augment mechanical or biological qualities; Integrating multiple polymers provides optimal properties [10]. It offers support for bones, joints, cartilage, and tendons while enabling precise control over the rate of deterioration. Synthetic materials are the ideal choice for providing strong mechanical support.

2.1.3. Comparative assessment of synthetic and natural materials

According to the assessment of current research, the main difficulty in creating biomaterials is to find a balance between mechanical strength and bioactivity. While synthetic materials are strong but lack bioactivity, natural materials provide an excellent cellular environment but are mechanically weak. As a result, hybrid biomaterials have been created by combining artificial engineering control with natural biological structure. Combinations of collagen and PCL and hydroxyapatite and gelatin are two examples of these systems. Hydrogel print on strong mechanical support. The table1. below shows the basic differences between natural, synthetic biomaterials.

These systems have demonstrated success in the following areas: multilayer skin regeneration; bone engineering; ligament and cartilage engineering; and tissue interface fabrication [9].

Table 1. illustrate the comparisons between biomaterials in details, providing a critical overview of material choice for different tissue engineering applications

Feature	Natural biomaterials (collagen, gelatin, fibrin, silk, hyaluronic acid)	Synthetic biomaterials (PLA, PGA, PCL, PEG)	Hybrid composites	Ref.
Origin	Derived from biological tissues	Chemically synthesized polymers	Blend of natural and synthetic	[5,7]
Bioactivity	High_mimic ECM,support adhesion and migration.	Low_ require functionalization	High (combined signaling and strength)	[7]
Mechanical strength	Low _ variable	High _ tunable	Balanced (dependent on ratio)	[6]
Degradation	Rapid, enzymatic: may lack control	Predictable, tunable via chemistry	Tunable via hybrid design	[5]
Scalability and reproducibility	Limited due to biological variability	Excellent_ consistent production	Moderate: process dependent	[7]
Immunogenicity	Possible (xenogeneic sources)	Minimal	Reduced (when natural fraction is human derived)	[6,7]
Applications	Skin, cartilage, vascular scaffolds	Bone, load bearing tissues	Multi-layer composites, hybrid ECMs	[4,5]

2.2. Construction techniques for scaffolding

An important structural element in tissue engineering, scaffolds structurally support cells, regulate cell migration, direct differentiation processes and promote the growth of new tissue. The ability of the scaffold to recreate the natural structure of the extracellular matrix (ECM) in terms of porosity, structural gradient, mechanical properties and biocompatibility determines how well the regeneration process works. Scaffold fabrication methods have advanced significantly over the last ten years, making it possible to create precision-engineered structures suitable for some clinical applications [11].

This chapter reviews the most popular scaffolding methods in tissue engineering, with an emphasis on: (1. Electrospinning 2. Bioprinting in three and four dimensions 3. Decellularization and comparative analysis). Table 2. below.

2.2.1. Electrospinning

One of the most popular techniques for creating nanofibers that resemble the fibrous tissue of the extracellular matrix is electrospinning. This is accomplished by creating microfibers that come together to create nanonetworks by delivering a high voltage to a polymer solution. This approach is suitable for applications related to skin, nerves, microvascular systems, and basement membranes, as it may generate fibers with diameters between 50 and 500 nm [12]. The benefits of electrospinning encompass a wide range Surface area that promotes cell adhesion, notable resemblance to the extracellular matrix, the ability to integrate molecules such as growth factors, regulation of fiber positioning (aligned versus random fibers), and the potential to encapsulate pharmaceuticals inside the fibers. A recent study demonstrates that coaxial electrospinning can generate core-shell fibers that release medications or growth hormones in a regulated manner, hence providing dual therapeutic potential for scaffolds [13].

major obstacles

Electrospinning does have certain benefits, but it also has some serious drawbacks: (1. Cell migration is hindered by a lack of suitably deep porous in the scaffold comes with rough fibers. 2.Making three-dimensional tissues incorrectly. 3The sensitivity of the process to production characteristics such as electrical capacity, viscosity, and humidity.4. Difficulties associated with the implementation of bigger scaffolds in clinical environments). As a result, improved methods have been developed, such as: melt electrospinning writing (MEW) to create microfibers with high-precision 3D writing capability; Cryogenic electrospinning to increase porosity and Incorporation of electrospun nanofibers with macroscaffolds made by other methods [14].

2.2.2 Technology for 3D bioprinting

By allowing the creation of highly tailored microstructures based on the layer-by-layer deposition of bioink – which may contain cells, polymers, ECM components or growth factors – 3D bioprinting has completely transformed tissue engineering. By simulating the natural structural gradients of organs, including interfaces between bone, cartilage, skin and tissue, this method enables the creation of structures with different properties [15]. The most popular methods of 3D bioprinting are: (1. Extrusion-based printing is ideal for hydrogels and works well with large-format spacers. 2. Inkjet Bioprinting, excellent resolution, suitable for materials with low viscosity. 3. UV-based stereolithography (SLA) bioprinting provides high micron resolution (10–50 μm).

Advantages

The ability to make abutments that are particular to each patient; • The ability to accurately design graded porosity; • The ability to directly integrate cells throughout the process; • The ability to make complex tissue interfaces, such as osteochondral tissue; • A quicker development time compared with traditional methods.

Some of the problems include that bioinks need to have both mechanical and biological properties, soft gels don't hold up well mechanically, cells are sensitive to fluid shear during printing, and making intricate vascular tissues is hard. 3D bioprinting can evaluate and turn data from CT and MRI pictures into stents that fit anatomically, which is why it is still one of the most promising technologies for the near future. 3.3 4D Bioprinting Technology

The next phase of bioprinting is represented by 4D Bioprinting, which uses intelligent materials that react to heat, pH, humidity, and enzymes.mThus, stents are manufactured that can change their shape or properties over time in response to the body's environment [16].

Important uses for 4D bioprinting include: self-expanding implants; gradually hardening bone implants; shrinking or expanding tissues; time-controlled medication delivery; and self-forming vascular systems. Biocompatible smart materials are few; predicting the dynamic behavior of materials is challenging; and obtaining enough printing precision is difficult.

2.2.3. Decellularization

Decellularization is one of the most advanced ways to make implants out of real tissues. It involves extracting cellular components from tissues or organs while preserving the original biomechanical gradient, related growth factors, and the natural structure of the extracellular matrix [17]. This approach employs chemicals, enzymes, and mechanical processes to get rid of cells without damaging the tissue microstructure too much.

Decellularized scaffolds have these benefits: • Very good at driving differentiation; • Cell adhesion is much stronger than synthetic scaffolds; • Architecture is very similar to that of real tissue; and • Good for organ-level engineering (heart, lung, liver).

Problems

• Quality varies depending on the tissue source; • It might produce significant immune responses; • It's hard to scale up for industrial application; • It's hard to get all the cellular components out without damaging the extracellular matrix. Nonetheless, the emergence of partial decellularization techniques that reduce immunogenicity while maintaining aspects of the extracellular matrix makes this technology one of the most promising avenues for therapeutic applications.

2.2.4. Comparative Evaluation of Various Technologies

every technology has a set of advantages and disadvantages, according to literature analysis: technology advantages restrictions electrospinning similar to ecm, nanofiber synthesis deep porosity's weakness bioprinting in three dimensions accurate geometry and customized design strong bioinks are required. bioprinting in 4d intelligent materials and dynamic performance restricted compatibility decellularization differentiation guidance and natural ecm complete cell eradication is difficult. current trends include combining many technologies, such as: adding electrospun nanofibers to bioprinted structures; using 3d printed layers to reinforce decellularized scaffolds modifying scaffolds after implantation using 4d materials.

Table 2. reveal the differences and applications of scaffold fabrication methods

Fabrication technique	Advanteges	Limitations	Key applications	Recent advantages	Ref.
Electrospinning	ECM like nano fibers, high surface area	Poor pore interconnectivity, scalability issue	Skin, nerve, vascular grafts	Coaxial spinning, meltelectrospinning writing (MEW)	[12,13]
3D Bioprinting	Precise spatial control, customizable bioinks.	Bioink formulation limits, resolution tradeoffs.	Bone, cartilage, vascular tissues	Multi material printing, hybrid scaffolds	[18]
4D Bioprinting	Dynamic responsiveness, adaptive implants	Material limitations, early-stage development.	Shape memory implants	Smart polymer integration	[16]
Decellurization	Native ECM preservation, strong bioactivity	Donor variability, incomplete decellurization	Heart, lung, liver scaffolds	Partial decellurization hybrid ECMs	[17]
Hybrid fabrication	Combines nanoscale and macroscale architectures	Complex and work flow	Organ level scaffolds	Electrospun + bioprinted composites	[9]

2.3. Regenerative Medicine Utilizing Stem Cells

Stem cells are essential in tissue engineering and regenerative medicine because of their extraordinary capacity for self-renewal and multiple lineage differentiation, thus enabling them to rebuild diverse tissues when cultured under appropriate conditions. Recent breakthroughs in molecular biology and biotechnology have facilitated more precise and effective regeneration therapies by improving our comprehension of cellular kinetics and how they interact with materials and biological substrates [19] This article examines the four principal kinds of stem cells utilized in regenerative applications: Mesenchymal Stem Cells (MSCs) and Pluripotent Stem Cells (iPSCs), among others. Embryonic Stem Cells (ESCs) Adipose-derived MSCs (AD-MSCs) provide the advantages of each treatment, presenting benefits in many situations and potential opportunities for further investigation.

2.3.1. Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) are extensively employed in regenerative medicine owing to their easy accessibility, varied origins (such as bone marrow, adipose tissue, and umbilical cord), and distinctive immunological properties.

that promote the modulation of inflammatory responses and improve healing. Mesenchymal stem cells exhibit distinctive immunological properties that allow them to regulate the inflammatory response and facilitate recovery. They can be readily obtained from various sources, including bone marrow, adipose tissue, and umbilical cord [20].

Essential characteristics of MSCs encompass the generation of exosomes rich in growth factors, the ability to distinguish into osteogenic, chondrogenic, and adipogenic lineages, and immunomodulatory properties that alleviate inflammatory reactions. Dynamic alteration of the scaffold's environment for modern applications Research suggests that MSCs may promote: Cartilage restoration utilizing collagen-derived hydrogels or GelMA; Bone regeneration via the integration of hydroxyapatite or β-TCP frameworks; Therapy of ligaments and tendons. Cardiac procedures following myocardial infarction

Recent research appears to indicate that nanomodifications of the scaffold can influence cell differentiation by altering nano topography [21].

Substantial challenges: Despite their widespread application, mesenchymal stem cells exhibit some intrinsic problems: considerable donor-to-donor variability; reduced efficacy with prolonged exposure; challenges in predicting clinical outcomes; and the necessity for universally defined methods. The use of exosomes produced from mesenchymal stem cells is progressively preferred as an effective alternative to transplantation of cells.

2.3.2. (iPSCs), or Induced Pluripotent Stem Cells

Since their discovery, iPSCs have revolutionized the field of regenerative medicine. By integrating specific genetic components, adult somatic cells can be reprogrammed to a pluripotent state, enabling their differentiation into nearly any tissue [22].

Since their introduction, induced pluripotent stem cells have constituted a significant advancement in regenerative medicine. The benefits of iPSCs include: • Production of patient-specific cells; • Avoidance of ethical issues related to embryonic stem cells; • Development of organoids and organoid-like structures; • Improvement of illness models; and • Modern applications.

These days, iPSC-derived cardiomyocytes are used to make cardiac stents, while iPSC-neurons in hydrogels are used to model brain disorders. Producing chondrocytes to cure cartilage damage and creating three-dimensional models of the musculoskeletal system. Research from 2024 suggests that AI-guided bioreactors might be used to enhance iPSC differentiation efficiency and minimize unwanted alterations [23].

2.3.2.1. Challenges

Difficulty in generating pure cell populations; Need for exact and regulated differentiation techniques; Potential carcinogenicity risk owing to chromosomal instability; Expensive and intricate technology. However, one of the most promising approaches for attaining complete individualized regenerative medicine is still iPSCs.

2.3.3. ESCs, or embryonic stem cells

ESCs have a very high pluripotency and are one of the oldest and most differentiated sources of stem cells. Hepatocytes, cardiomyocytes, and neurons are among the functional cell types that they have successfully produced [24]. ESCs have the following benefits: • High ability for proliferation; • Effective differentiation into all three germ layers; • Perfect model for researching embryonic development

2.3.3.1. Limitations and Challenges

Risks associated with teratoma formation; Stringent regulatory barriers; Challenges in widespread clinical implementation; Ethical controversies with cell procurement.

The Current Role of ESCs

ESCs remain a prevalent resource for understanding despite these limitations: Differentiation processes; performance evaluation against MSCs and iPSCs; advancement of improved differentiation techniques; assessment of newly developed biomaterials.

2.3.4 Adipose derived stem cells or, AD-MSCs

Techniques such as liposuction and adipose-derived mesenchymal stem cells offer a direct and efficient solution.characteristics of ad-msc: • superior stability with collagen scaffolds and biogels; • substantial ability to incite angiogenesis; • enhanced tolerance to hypoxic conditions; • superior cellular yield in comparison with bone marrow mesenchymal stem cells.

2.3.4.1. USES

Maxillofacial regeneration, deep wound healing, cartilage and soft tissue regeneration, and bone support with hydroxyapatite/AD-MSC composite scaffolds are among recent uses [25].
Limitations include: • insufficient long-term differentiation of some strains; • Variation between patients; and • the need for precise cell isolate purification. As a result, the use of exosomes produced from AD-MSCs in wound healing and bone regeneration applications is becoming more and more popular.

3. Detailed Analysis of Sources of Stem Cells

The following will be compared in the table: Source; Advantage; borders; Ideal application; and level of clinical acceptance. The nature of the regenerative application, the necessary degree of complexity, and ethical and legal restrictions all have a role in the stem cell type selection, as this chapter emphasizes. Because of their immunomodulatory qualities, MSCs are appropriate for applications involving bone and cartilage, whereas iPSCs provide a wide range of opportunities for customized regenerative medicine despite safety concerns Table 3.
Although AD-MSCs are a suitable option for short-term therapeutic uses, ESCs remain a crucial reference model for understanding differentiation biology. Recent research indicates that combination medications integrate smart scaffolds, advanced biomaterials, enhanced stem cells, and artificial intelligence algorithms that predict biological activity. This enables a new era of high-precision regenerative medicine.

Table 3. comparison of stem cell sources in tissue engineering: advantage, limitation, origin and applications.

Stem cell type	Source	Advantage	limitations	Main applications	Ref.
MSCs (Mesenchymal Stem Cells)	Bone marrow, adipose, umbilical cord.	Multipotent, immunomodulatory	Donor variability, limited proliferation	Bone,cartilage,tendon	[20]
iPSCs (Induced Pluripotent Stem Cells)	Reprogrammed somatic cells	Pluripotent, patient specific	Genetic instability, tumorigenic risk	Cardiac, neural, cartilage models	[22,23]
ESCs (Embryonic Stem Cells)	Blastocyst inner cell mass	Unlimited self-renewal, full pluripotency	Ethical concerns, teratoma formation	Neural, hepatic, cardiac research.	[1,24]
AD_MSCs (Adipose Derived MSCs)	Subcutaneous fat	Ease harvest, angiogenic resilient	Donor variability, limited yield	Maxillofacial, bone, soft tissue	[25,26]

4. The Role of Ai in Tissue Engineering and Regenerative Medicine

Recent developments in artificial intelligence have made it very important to bioengineering studies, especially those that have to do with regenerative medicine and tissue engineering. Applications have moved on from basic models that use old-fashioned statistics to intricate systems that use machine learning (ML) and deep learning (DL), [23]. These systems are now able to do a wide range of tasks, such as predicting cellular behavior, analyzing complicated biological data, designing biomaterials and scaffolds, and changing bioprinting methods. AI is helping regenerative medicine in four main ways that we will look at in this chapter: (1. Making Scaffold Design Better 2. Predicting the Future of Stem Cells Section 3: Looking at Pictures and Histology 4. Getting Better Bioprinting Results).

4.1. Ai for Optimizing Scaffold Design

Surfaces chemistry, permeability, mechanical characteristics, and biocompatibility are intricate elements that must be meticulously matched to develop an optimal scaffold. Progress has been impeded and expenses have escalated due to the reliance on conventional methods. rely on trial-and-error experimentation. Algorithms for deep learning and machine learning have transformed numerous processes by: • Correlating cell adhesion with microarchitecture • Forecasting mechanical efficiency using industrial characteristics and material composition • Producing optimal designs with generative design algorithms. • Simulating the behavior of the support in a biological setting prior to production. Recent research indicates that the degradation rate of biomaterials, biocompatibility index, tensile strength, and mechanical behavior depending on porosity can be forecasted with the application of machine learning alongside biomaterial data [28]. The Integration of AI with 3D and 4D Printing,The bioprinting landscape is rapidly evolving to incorporate AI, which is helping with: Optimal printing parameters can be identified and problematic printing issues can be mitigated. • Evaluate porosity and the final configuration of the support throughout the printing process; • Examine variations on a layer-by-layer basis. According to reports from 2023–2024, integrating AI with digital twins creates a system that may mimic support behavior within the body prior to transplantation [29]. Figure1. below explains the integration between the four fields, AI, biomaterials, trials and scaffolds.

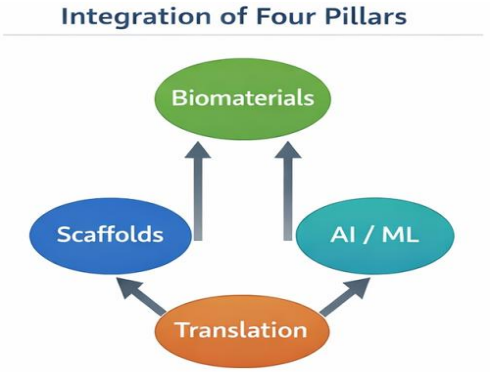

Figure 1. The integration between, AI, biomaterials, trials and scaffolds.

4.2. Artificial Intelligence for Forecasting the Behavior of Stem Cells

Modeling Stem Cell Behavior Predictively: One of the biggest scientific problems in regenerative medicine is the capacity to precisely direct stem cell development. This is because cells are sensitive to chemical gradients, nanotopography, stiffness, 3D microenvironment, and genetic background.

What is the contribution of AI?

Hundreds of experimental variables can be combined using machine learning algorithms like Random Forests, Support Vector Machines, and Neural Networks to create a prediction model that can: Osteogenic, chondrogenic, and neurogenic differentiation pathway prediction. Linking the cellular response to the scaffold pattern. identifying minute details in pictures that are not apparent to the human eye [21].

Recent uses consist of: Using the nature of the scaffold to predict the effectiveness of MSCs in bone regeneration. Using DL to analyze the morphodynamics of stem cells. Bioreactor-AI systems for improving iPSC differentiation methods. DL may also be used to time-lapse data, according to literature published in 2024. Ging enables the identification of early indicators of differentiation before to their functional manifestation [23].

4.2.1 Artificial Intelligence in Engineering and Histology Image Analysis (AI for Histology and Imaging)

An essential component of assessing scaffold effectiveness and cell culture performance is image analysis. The following technologies are employed: Histology (H&E, Masson's Trichrome); Immunofluorescence; Micro-CT; MRI; SEM;

AI's contribution

Convolutional Neural Networks (CNNs) may be used to classify cells (proliferating, differentiating, necrotic), measure extracellular matrix (ECM) density, calculate porosity with high accuracy, analyze

angiogenesis inside scaffolds, and compare the fidelity quality of 3D prints. AI is preferable to conventional manual analysis due to its excellent accuracy in identifying histological alterations [30].
Extra Benefits High-throughput screening tests for stents and cells are supported; sample assessment is accelerated; human error is decreased; thousands of pictures may be analyzed in minutes. According to recent research, combining AI with Micro-CT allows for the evaluation of the stent's deterioration profile without destroying it. [31].

4.2.2 Artificial Intelligence in Automation and Optimization of Bioprinting

Several factors must be precisely controlled in bioprinting processes: Nozzle temperature; extrusion pressure; bioink viscosity; and crosslinking kinetics. AI has become a crucial component of contemporary printing systems since manually manipulating these factors increases the likelihood of inaccuracy.

4.2.3. Applications of Artificial Intelligence

1. Optimization in real-time: Reinforcement learning techniques are used to alter printing parameters while the machine is operating.
2. intelligent bioink selection (suggests the best bioink combination based on the required application.) Third, using predictive failure detection, printing errors may be caught in the early stages. or the orientation of multimaterial printing ensures that the distribution of material and cells within layers is coordinated. Research done in 2025 found that when AI is used in conjunction with digital twins for bioprinting, design efficiency is increased by 30-45% [32].

4.2.4. Artificial Intelligence's Difficulties

Though AI has come a long way, there are still several major problems:

1. Database Limitations: Most data from tissue engineering projects are small-scale and non-standard, which diminishes the accuracy of the models [27].
2. The "Black Box" Problem: Many DL models don't explain their decisions, which makes them hard to adopt in clinical settings [4].
3. Clinical Usage Rejection: In the absence of a definitive method for analyzing the data, numerous clinicians exhibit hesitance in employing AI technologies.
4. The Necessity for New Regulations: Implementing Artificial Intelligence for Cellular Prediction. The manufacture of stents is devoid of explicit regulatory guidelines like Table 4.

Table 4. representation of AI applications in tissue engineering: predictive stem cell modeling, scaffold design, bioprinting optimization and imaging analysis.

AI domain	Target process	AI model _ method	Outcomes	Advantages	Ref.
Scaffold design optimization	Predict material performance	ML regression, neural networks	Predict strength, porosity degradation	Faster design cycles, coast reduction	[29,32]
Predictive modeling of stem cell fate	Forecast linage commitments	Random forest, CNN, SVM	Predict differentiation outcome	Standardized protocols, improved reproducibility	[21,32]
Imaging and histological analysis	Analyze scaffold cell interactions	CNNs, deep segmentation	Automated feature extraction	High accuracy, reduced bias	[30,33]
AI in bioprinting	Process parameter optimization	Reinforcement education, generative models	Minimize printing errors	Improved fidelity and scalability	[29]

5. Difficulties And Restrictions in Regenerative Medicine and Tissue Engineering

The broad application of novel technologies from the laboratory to clinical practice is still hampered by a number of technological, biological, ethical, and regulatory issues, despite the fast advancements in tissue engineering and regenerative medicine. It is necessary to be aware of these challenges in order to pinpoint information gaps and guide research toward practical and applicable solutions. Four primary groups of difficulties are addressed in this review: (1. Clinical and Biological

Difficulties 2. Manufacturing and Biomaterials Difficulties 3. Ethical and Regulatory Difficulties 4. AI-Specific Difficulties).

5.1. Clinical and Biological Difficulties

1. The problem of vascularization:
   The inability to establish sufficient vascularization within stents is one of the main problems in tissue engineering. The inability of cells in cultivated tissues to survive further than a few millimeters from an oxygen supply results in necrosis, biointegration failure, and impaired extracellular matrix synthesis [34]. Creating an efficient vascular network is still very difficult, despite efforts to: • Incorporate growth factors (like VEGF); • Co-culture with endothelial cells; and • Bioprint microvascular channels.
2. Immune response:
   After decellularization, natural scaffolds may still contain immunostimulatory protein residues. Likewise, depending on the patient's condition, stem cells, including MSCs, may vary in their ability to modulate immunity [17].
3. Uncontrolled differentiation of cells:
   Critical problems with pluripotent stem cells include: • high sensitivity to the microenvironment; • Teratoma development; • Differentiation instability .[1]
4. Variability between patients:
   Individual differences in cell and scaffold response are based on: • genetic background; • age; • serious illness; • Inflammatory conditions, clinical outcomes are very difficult to predict.

5.2. Biomaterials and Production Difficulties

1. Finding a balance between biocompatibility and mechanical strength: Synthetic materials are mechanically strong but biologically poor, while natural materials are good in terms of bioactivity but mechanically weak. Development of hybrid solutions is currently underway [35].
2. Limited porosity by electrospinning: The microfiber networks generated are distinguished by: poor deep porosity and good surface porosity that prevents cell penetration [5].
3. Disadvantages of 3D/4D bioprinting: The shear rate during printing affects the cells, and most hydrogels used in printing are not mechanically strong enough to support the weight of the tissue.
4. Inadequate decellularization: Excessive cell elimination can result in loss of natural growth factors and damage to the extracellular matrix. However, partial decellularization causes mild immunological activation [17].
5. Absence of real-time quality control systems: Because feedback mechanisms are often absent in bioprinting and scaffold manufacturing processes, there is a greater likelihood of: • Layering errors. Variation in porosity and poor uniformity [36].

5.3. Regulatory and Ethical Difficulties

Because regenerative medicine is hybrid (biologic + device), it has more regulatory hurdles than conventional medical devices.

1. Absent a specific regulatory category, regenerative goods are "in between": • Medical equipment • Cell therapies • Tissue products for this type of product there are no established international standards [37].
2. Ethical difficulties with stem cells; ESC ethics controversy; problems with genome editing; and induced polymorphic stem cell ownership.
3. Expensive: Due to their high cost, regenerative solutions – especially those based on iPSC or 4D printing – can only be used on a small scale.
4. Inadequate representation of human animal models: Due to variations in ECM, immunology and physiology, preclinical research often fails to predict human response.

5.3.1. Cost-benefit analysis:

The optimal design of traditional scaffolding and biomaterials requires repeated experimentation to achieve the ideal result, leading to wasted money, time, and resources. Integrating

artificial intelligence (AI) and utilizing it in simulation experiments significantly reduces the need for initial testing, provides insight into the ideal materials and conditions for successful experimentation, and consequently minimizes wasted time and materials.

McKinsey estimates that AI will be heavily integrated into the healthcare sector by 2030, contributing up to $15 trillion to the global economy, with the global market reaching $521.9 billion by 2028, according to biomedical engineering market reports, [38].

5.3.2. AI-Specific Difficulties*:*

Despite being a powerful complement to tissue engineering, artificial intelligence (AI) has some fundamental hurdles to overcome:

1. Restrictions on data the majority of tissue engineering datasets are small, sourced from different labs, and do not have: • Consistency • More accurate labeling [27].
2. "Black-Box" problems DL models often fail to explain how decisions are made, which hinders: • Acceptance in medicine. • Building user trust and achieving regulatory approval [4].
3. The need for explainable AI (XAI): Develop models that: • can explain their results; • Offer molecular-mechanical explanations; and • support for therapeutic options is the current approach.
4. Doctors' resistance to intelligent systems: Clinicians are cautious about relying too heavily on digital tools, especially in delicate applications such as differentiation monitoring, stent evaluation, and transplant decisions.

5.3.3. Clinical Data and Success Rates:

A large number of AI-powered biomaterial design applications are still in the preclinical stages, with some initial trials showing improvements in predicting biomechanical properties. Despite rapid scientific advancements, the translation of successful prototypes into clinical applications remains limited due to the difficulty of reconciling the biological and biomechanical domains, and the relatively recent emergence of AI. However, with further trials, significant success and change are undoubtedly on the horizon and next years, figure 2. below as estimated timeline for the integration of smart biomaterial in medical field,[39].

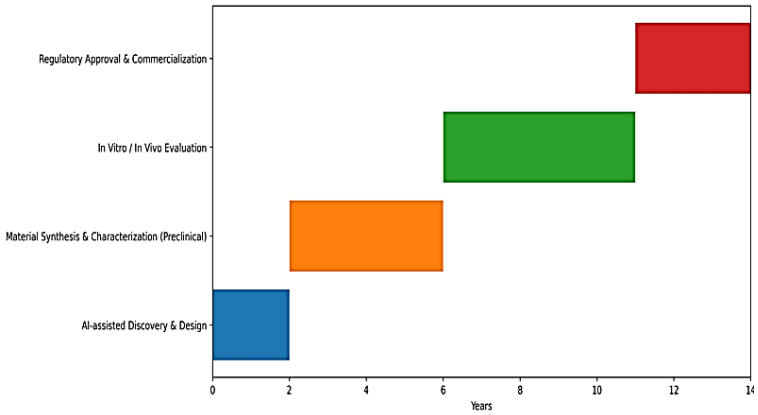

Figure 2. Estimated development timeline for smart biomaterials and scaffolds.

5.3.4. A critical overview of current problems:

It is clear from recent research that the difficulties are not only technical, but overlap at several levels: Problem areas: Critical concerns. Biology Immunology, hematopoiesis and uncontrolled differentiation, production: insufficient porosity, unstable hydrogel and uneven production. Regulatory: The debate on embryonic cells and the absence of a defined legal framework. Artificial intelligence: Insufficient information, inadequate analysis, etc. Method of planning. According to current trends, the solution will be integrated rather than unilateral, including the integration of: smart biomaterials; multi-layer scaffolding; cells with regulated growth; explainable predictive AI models; And new rules designed specifically for regenerative medicine.

6. Conclusion

Over the past 20 years, one of the scientific disciplines that has changed most rapidly is tissue engineering and regenerative medicine (TERM). Advanced biomaterials, scaffolding technology, stem cells and artificial intelligence have all worked together to create an integrated framework that can rebuild tissues and restore their functions. Despite enormous progress, there are still many obstacles to overcome, opening up great opportunities for research that requires coordinated, interdisciplinary efforts.

1. *Biomaterials:* The intersection between engineering design and nature: Natural biomaterials, including collagen, fibrin, and hyaluronic acid, have been demonstrated in the literature to provide an environment rich in biosignals necessary for cell growth and differentiation. Nevertheless, their employment in structural applications is hindered due to their weak mechanical stability and heterogeneity. On the other hand, synthetic materials such as PLA, PCL and PEG lack inherent biocompatibility, but offer considerable flexibility in tuning mechanical properties and degradation rates [8]. As a result, hybrid biomaterials - blending technical precision with intrinsic biocompatibility - are the way of the future.
2. *Scaffold technology:* The development towards smart scaffolds Electrospinning, 3D/4D bioprinting and decellularization technologies have made it possible to create scaffolds that accurately replicate the extracellular matrix (ECM) in a number of ways. While 4D bioprinting has added dynamic capabilities that allow the scaffolds to respond to the biological environment, 3D bioprinting has made it possible to produce personalized and geometrically interconnected scaffolds [16]. However, achieving deep porosity, improving mechanical stability, and promoting uniform printing are still important issues to be solved in the future.
3. *Stem cells:* great potential and current limitations Due to their availability and immunocompatibility, mesenchymal stem cells (MSCs) are still the most popular choice in clinical applications; Nevertheless, despite genomic safety concerns, induced pluripotent stem cells (iPSCs) have particular potential in personalized medicine. Although exosomes provide a special biological model for stem cell differentiation research, their application is limited due to ethical issues [1]. According to recent developments, exosome-based therapy is being adopted as a safe and effective alternative to whole-cell therapy.
4. *Artificial intelligence:* The new engine for regenerative medicine. Powerful tools for predicting the behavior of biomaterials and cells, evaluating images, improving bioprinting, and creating scaffolds before production are made possible by machine learning and deep learning systems. By combining AI with digital twin technologies, biological models can be tested virtually before real-world applications, reducing errors and increasing efficiency [23]. However, widespread clinical use is still hindered by the lack of defined regulatory criteria, lack of data and difficulties in understanding the models. 5. Future difficulties: Need for systematic integration. Research shows that the difficulties in TERM are not only technical, but also include the following problems: hemovascularization; mechanical stability; immunological response; Ethical and legal issues.

Analyzing AI models, it emphasizes the need for coordinated research efforts across the following fields to advance tissue engineering: molecular biology, artificial intelligence, biomedical engineering, materials science, physicians and regulators. Prospects for the future Given recent developments, the future seems to be moving in the direction of: 1. Intelligent materials that respond to mechanical and biological stimuli. 2. Multilayered scaffolds that recreate the hierarchical structure of tissues. 3. Using exosomes instead of whole cells. 4. Incorporate AI into all stages of analysis and design. 5. Creation of new regulatory frameworks especially for regenerative medicine.

A new generation of regenerative medicine that can overcome current barriers and fully exploit tissue engineering will result from achieving this integration. Regenerative medicine is therefore on the verge of becoming a therapeutic norm that safely, accurately and permanently restores functional capacity to many people.

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مراجعة الابتكارات في المواد الحيوية والهياكل الداعمة والذكاء الاصطناعي

الملخص

على مدى العقدين الماضيين، برزت هندسة الأنسجة والطب التجديدي كأحد أسرع التخصصات العلمية نموًا، مدفوعةً بتكامل المواد الحيوية والخلايا الجذعية وتقنيات السقالات والذكاء الاصطناعي لإعادة بناء الأنسجة واستعادة وظائفها. توفر المواد الحيوية الطبيعية بيئة غنية بالمؤشرات الحيوية، إلا أنها محدودة في التطبيقات الهيكلية نظرًا لضعف استقرارها الميكانيكي. في المقابل، توفر المواد الاصطناعية تحكمًا مرنًا في الخصائص الميكانيكية ومعدلات التحلل، ولكن مع توافق حيوي محدود، مما يجعل المواد الحيوية الهجينة خيارًا واعدًا. ساهمت تقنيات الغزل الكهربائي والطباعة الحيوية ثلاثية ورباعية الأبعاد في تطوير سقالات تحاكي المصفوفة خارج الخلوية، على الرغم من استمرار التحديات المتعلقة بالمسامية العميقة والاستقرار الميكانيكي والطباعة المنتظمة. تُعد الخلايا الجذعية الوسيطة الخيار السريري الأكثر شيوعًا، بينما تحمل الخلايا الجذعية المستحثة متعددة القدرات إمكانات واعدة في الطب الشخصي، على الرغم من المخاوف المتعلقة بالسلامة الجينية. يمثل العلاج القائم على الإكسوزومات بديلاً آمنًا وفعالًا للعلاج بالخلايا الكاملة. يُمكّن الذكاء الاصطناعي من التنبؤ بسلوك المواد الحيوية والخلايا، ويُحسّن الطباعة الحيوية، ويُتيح اختبار النماذج الافتراضية عبر التوائم الرقمية. مع ذلك، يُعيق الاستخدام السريري الواسع النطاق نقص المعايير التنظيمية والبيانات، فضلاً عن صعوبة فهم النماذج. تشمل تحديات هندسة الأنسجة إمداد الدم، والاستجابة المناعية، والقضايا الأخلاقية والقانونية. تُؤكد الأبحاث على الحاجة إلى جهود بحثية مُنسقة ومتعددة التخصصات. يُمثل هذا التكامل أساسًا لجيل جديد من الطب التجديدي قادر على تجاوز العقبات الحالية واستعادة الوظائف الحيوية بدقة واستدامة.

الكلمات المفتاحية: هندسة الأنسجة، الطب التجديدي، الدعامات، المواد الحيوية، الذكاء الاصطناعي، الخلايا الجذعية.