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Trends in the naturally derived biomedical polymer and programmable biomaterials for bone regeneration; developments and challenges, future prospects

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Abstract: The advancement of tissue engineering has significantly benefited from the use of biomedical polymers, which offer essential characteristics such as mechanical strength, biocompatibility, and biodegradability. These polymers, both natural and synthetic, serve as scaffolds for tissue regeneration, supporting cellular processes and degrading in synchrony with tissue formation. Natural polymers such as collagen, gelatin, and chitosan exhibit excellent biocompatibility and mimic native extracellular matrices, though they may have limited mechanical strength. Synthetic polymers, including polyesters and polycarbonates, offer controlled degradation and tunable mechanical properties but may lack inherent biological activity. The integration of programmable biomaterials capable of responding to environmental stimuli and adapting over time marks a promising direction in regenerative medicine. These smart materials can dynamically regulate biological responses to support bone repair, addressing inflammation, remodeling, and regeneration. This review discusses the different natural and programmable biomaterials and their technological applications in tissue engineering, highlighting their role in creating next-generation solutions for bone regeneration.

Keywords: Scaffold, Natural biomaterials, polymers, programmable biomaterials, biocompatibility

1. Introduction

The development of tissue engineering, which seeks to produce functional biological substitutes to repair, preserve, or enhance damaged tissues or organs, has been greatly aided by biomedical polymers [1]. Biomedical polymers possess special qualities like mechanical strength, flexibility, and biocompatibility that make them appropriate for a range of tissue engineering applications. The ability of those polymers to break down and even be absorbed by the body over time is one of their most important characteristics. For temporary scaffolds or implants intended to encourage tissue growth before progressively deteriorating as the new tissue develops and matures, this characteristic is essential [2]. A seamless transition from the artificial scaffold to the natural extracellular matrix can be achieved by adjusting the rate of polymer degradation to correspond with the rate of tissue regeneration. Moreover, these polymers are frequently used as a supporting substrate to transfer cells and therapeutic agents to a specific location. They can also be designed into a variety of microstructures to achieve particular performance goals or manufactured into adaptable materials that can replicate the structure and function of native tissues [3]. Therefore, biomedical polymers find application in a number of fields, including osseointegration, bone injury repair, regenerative medicine, tissue engineering, drug delivery systems, biosensors, hemodialysis, and artificial organs [4].

The structure of biomedical polymers is the primary distinction between their natural and synthetic forms. Proteins and polysaccharides are examples of natural polymers that can fold into intricate shapes on their own [5]. Their basic structures, which in turn define their biological functions, are determined by the particular arrangement of amino acids in proteins or the makeup and connections of monosaccharaides in polysaccharides. Among the many benefits of naturally derived polymers are their biocompatibility, biodegradability, biomimicry, and modification potential. Collagen, gelatin, chitosan, and hyaluronic acid are examples of natural polymers that come from biological sources and have outstanding biocompatibility [6]. This indicates that, in contrast to certain synthetic materials, they do not induce inflammation or a strong immune response when inserted into the body. The majority of natural polymers can be broken down and reabsorbed by the body over time as new tissue forms because they are enzymatically degradable under physiological conditions.

For scaffolds used in tissue engineering, this property is beneficial because the material should break down at a pace that corresponds with the formation of new tissue [7]. Natural polymers that closely resemble the cellular microenvironment of native tissues, such as collagen, elastin, and glycosaminoglycan, offer suitable biological cues to direct cell adhesion, proliferation, and differentiation. A high degree of customization is also possible with natural polymers since they can be chemically altered to change their mechanical characteristics and rate of degradation, as well as to add growth factors, medications, or allow for crosslinking [8]. The majority of synthetic polymers, on the other hand, have simpler, more haphazard structures. Examples of these include polyesters, poly (ethylene glycol), and polycarbonates. Moreover, naturally occurring polymers usually interact favorably with biological entities like cells and tissues and decompose in the environment [9]. Their use in biological organisms is limited by their disadvantages, which include poor mechanical qualities, uncontrollable decomposition, and the potential for adverse immune system reactions.

However, despite lacking natural biological activity, synthetic polymers are a promising option for biomedical applications because of their good controllability in terms of composition, structure, mechanical properties, and degradation behavior. Maximizing the advantages of both natural and synthetic polymers in biomedical fields is therefore crucial [1]. To accommodate various tissue engineering applications, biomedical polymers with a broad range of physical and chemical characteristics can be created or altered. For instance, in order to endure the loads and stresses that bones endure, polymers used in bone tissue engineering must possess high mechanical strength and stiffness [10]. On the other hand, polymers for soft tissue engineering, such as skin or blood vessels, require flexibility and elasticity to mimic the natural behavior of these tissues.

Biomedical polymers' surface characteristics and porosity are important for cell adhesion, proliferation, and differentiation. For cells to proliferate and arrange into useful tissues, porous polymeric scaffolds offer a three-dimensional environment [11]. Cell migration, nutrient transport, and vascularization can all be aided by controlling the pore size, interconnectivity, and total porosity. Surface alterations that improve cell-material interactions and direct tissue formation include chemical functionalization and protein coatings. Biomedical polymers can be shaped and arranged in a variety of ways using techniques like solvent casting, 3D printing, and electrospinning. The capacity for adaptation and change makes it possible to create complex support structures that closely resemble the original tissue in terms of shape and design [8]. The ability to customize the shape and makeup of polymeric scaffolds is particularly useful when creating patient-specific implants or tissue constructs. Thanks to technological advancements, biomaterial development has greatly improved, providing a wider range of functionalities to support cellular repair processes and the mechanical stability of bone tissue [12]. The majority of biomaterials, however, only provide a restricted range of functions, concentrating on either mechanical support or particular cellular processes involved in bone repair. Inflammation, repair, and remodeling phases are all part of the intricate, dynamic, and protracted biological process that is bone tissue repair [13]. Since each step is crucial for the proper healing of bone tissue, biomaterials that can adapt to particular needs and respond dynamically to and regulate these biological processes have the most potential for development and clinical use in the field of regenerative medicine.

In response to environmental changes or external stimuli, programmable materials can alter their morphology, physical characteristics, or chemical functions in a preset order [14]. Time-dependent control techniques are made possible by this programmability, which opens up a wide range of potential applications in industries like drug delivery, tissue engineering, regenerative medicine, smart medical devices, and biosensors [15]. According to the natural bone repair process or micro environmental features, implant materials can dynamically respond and regulate on demand to ultimately achieve bone regeneration. The most popular naturally derived biomedical polymers and programmable biomaterials in tissue engineering are reviewed here, along with information on their chemical makeup, physical and chemical properties, and biological roles [16]. The most recent findings in the field of biomedicine are also presented. The article also offers a thorough overview of programmable biomaterials and their salient characteristics.

2. Polymers with natural origins and their derivatives in biological applications.

2.1 Hyaluronic Acids

The extracellular matrix of the body's connective tissues contains a naturally occurring glycosaminoglycan called hyaluronic acid (HA). The compound is made up of a repeating unit of N-acetyl-D-glucosamine and D-glucuronic acid, making it a linear polymer [17]. Due to its exceptional biocompatibility, HA does not cause an immunological reaction when it is inserted into the body. In addition, the body's hyaluronidases naturally break down HA itself. By controlling the rate at which HA degrades, chemical modification enables the production of scaffolds with particular degradation patterns that correspond to the rate at which new tissue develops [18].

The unique viscoelastic and hygroscopic properties of HA can be used to the benefit of tissue engineering structures meant to integrate with host tissues. In 3D cell culture and tissue regeneration, HA can be incorporated into hydrogel scaffolds. HA hydrogels mimic the extracellular matrix found in nature and foster the attachment, proliferation, and specialization of cells [19]. Cell movement, growth, and specialization are among the various cellular processes that are regulated by hyaluronic acid's binding to cell surface receptors such as CD44 and RHAMM [20]. Tissue engineering applications can utilize these interactions to control cell activity. To create delivery systems that allow the controlled release of bioactive substances that aid in the rege, HA can be changed using growth factors, cytokines, or medications [21] .

2.2 Gelatins and Collagens

Gelatin and collagen are proteinaceous materials derived from animals, particularly the connective tissues, bones, and skin of fish, pigs, and cows. Gelatin is a material made from collagen, which is the main protein that gives the body's connective tissues their structure [22]. Gelatin and collagen are particularly well-suited for a variety of biomedical applications because they are both biocompatible and biodegradable. They are extremely valuable in a variety of medical fields, including tissue engineering, wound healing, drug delivery, and other medical applications, due to their unique properties, which include their capacity to form gels, offer structural support, and have minimal potential to trigger an immune response [23][24].

Gelatin is a high-protein material made from demineralized animal bones and the skins of cows and pigs. Many food items, including pastilles, marshmallows, and gummy candy, commonly contain it. A meticulously regulated procedure involving heat and acid or alkaline treatment is used to create gelatin [25]. Through the partial hydrolysis of collagen, it is obtained from animal sources. In many food products, such as candies, desserts, jellies, and some dairy products, it is frequently used as an aging agent [26]. A wide range of industries, including pharmaceuticals, photography, and the production of coatings and capsules, use gelatin extensively.

Collagen is the predominant protein found in mammals, comprising around 25 percent 35 percent of the total protein composition in the body. It is present in connective tissues such as cartilage, bones, tendons, ligaments, and skin, as well as in corneas, blood vessels, the gut, intervertebral discs, and teeth [27]. Made up of amino acids that organize themselves into a triple helix structure called a collagen helix, collagen is a strong and insoluble protein. Maintaining the strength and flexibility of various tissues depends on collagen, which is in charge of giving structural support [28] . Collagen promotes the elasticity of skin and tendons, helps strengthen bones, and speeds up the healing process after an injury. Collagen comes in 29 different forms in the human body, with types I, II, and III making up between 80 and 90 percent of the total collagen content [29].

Figure 1.0: Diagrammatic representation of the origin, structures, manufacturing processes, and uses of naturally derived polymers. The properties of each polymer in tissue engineering will be examined in the following section.

The FDA has approved collagens and gelatins for use in a number of medical products, such as dermal fillers, tissue sealants, hemostatic agents, and wound dressings. For tissue regeneration and cell proliferation, these adaptable biomaterials offer a three-dimensional environment [30]. They can be used in conjunction with growth factors, stem cells, and other bioactive substances to promote the healing process. Clinical applications of collagen-based scaffolds and matrices include tissue engineering and regenerative medicine [31]. These scaffolds are useful for a variety of processes, such as drug and gene delivery systems and the regeneration of skin, bone, cartilage, tendons, and nerves. For example, in clinical trials, gelatin-based hydrogels are being investigated as injectable drug and cell carriers that enable long-term and localized delivery [32].

2.3 Chitosans and Chitins

Derived from the outer shells of crustaceans and the cellular walls of fungi, chitin and chitosan have many advantageous characteristics that make them desirable biomaterials for tissue engineering applications [33]. As biocompatible polysaccharides, chitin and chitosan are suitable for use in biomedical applications because they are typically not toxic or immunologically reactive. Because these materials can undergo biodegradation, they can gradually be broken down and replaced by new tissue under controlled conditions [34]. Because chitin and chitosan can change their shape, they can take on different shapes, including scaffolds, hydrogels, sponges, and nanofibers. This allows three-dimensional structures to be created that closely mimic the extracellular matrix (ECM) present in real tissues. These biomaterials have surface characteristics, porosity, and suitable mechanical qualities that can be altered to satisfy the particular requirements of various tissue types [35]. Specifically, chitosan exhibits antibacterial properties that help prevent fungal and bacterial infections in tissue engineering applications.

Studies have demonstrated that chitin and chitosan both encourage cell attachment, growth, and specialization, which aids in tissue regeneration and restoration. A variety of bioactive substances, such as genes, growth factors, and medications, can be transported by chitin and chitosan [36]. Additionally, in the field of tissue engineering, biomaterials made from chitin and chitosan have demonstrated promise in aiding in the process of wound healing and regenerating a variety of tissues, such as bone, cartilage, skin, and nerve tissue [15]. Their efficacy in a variety of applications is increased by their capacity to promote cell adhesion, proliferation, and specialization as well as to regulate bleeding and fight microbial infections [37].

Research on chitin and chitosan is currently facing challenges in improving extraction and production techniques to increase yield and purity while reducing costs. Along with improving the reproducibility and standardization of chitin-derived products, efforts are also being made to create more effective deacetylation procedures for chitosan. Additionally, a more thorough comprehension of the structure-function relationships of these biopolymers and their derivatives is required [38]. The main problems with chitin and chitosan in tissue engineering are that they don't always work the same way from batch to batch, some forms don't have enough mechanical strength, and some people may have immune reactions to them. Notwithstanding these obstacles, chitin and chitosan have a bright future [39]. Their distinct qualities, biodegradability, and biocompatibility make them desirable for a range of uses, such as food packaging, water treatment, biomedicine, and agriculture.

Research is still being done on developing new chitin-based materials with improved qualities, finding new uses for chitosan in the production of functional nanomaterials, and finding new uses in tissue engineering and drug delivery [39] . The development of green technologies and circular economy solutions may benefit greatly in the upcoming years from the use of chitin and chitosan, which are environmentally friendly and sustainable substitutes for synthetic polymers [40].

3. Programmable biomaterials

This clinical situation has been greatly enhanced by the development of biomaterials, which provide a wider range of functions to support cellular repair processes and the mechanical stability of bone tissue [14]. The majority of biomaterials, however, only provide a restricted range of functions, concentrating on either mechanical support or particular cellular processes involved in bone repair. Inflammation, repair, and remodeling phases are all part of the intricate, dynamic, and protracted biological process that is bone tissue repair [41]. For bone tissue to heal successfully, each step is crucial. Therefore, the most promising biomaterials for development and clinical application in the field of regenerative medicine are those that can dynamically respond to and regulate these biological processes, tailored to specific needs [42].

Programmable materials can respond to external stimuli or changes in their environment by changing their morphology, physical characteristics, or chemical functions in a preset order. This programmability makes time-dependent control techniques possible, which opens up a wide range of potential applications in industries like biosensors, drug delivery, tissue engineering, regenerative medicine, and smart medical devices [43]. When it comes to bone regeneration, it means that implant materials can react and adjust dynamically depending on the natural bone repair process or the properties of the microenvironment, ultimately resulting in the best possible bone repair [44]. Resveratrol (Res) is a polyphenol that has anti-inflammatory, antioxidant, and heart-protective properties. Additionally, it increases the osteogenic potential of bone marrow mesenchymal stem cells (BMSC), which may help treat osteoporosis and promote bone growth. Because of its low water solubility and quick breakdown when exposed to oxygen, liposomes are commonly used to improve the stability and bioavailability of Res [45] .

Additionally, bone norphogenetic protein-2 (BMP-2) can promote the directed differentiation of mesenchymal cells into osteoblasts by stimulating cell replication and deoxyribonucleic acid (DNA) synthesis. It is an essential growth factor for bone regeneration and repair [46]. Despite the fact that BMP-2 is essential for osteogenesis, its short half-life, high cost, and possible adverse effects restrict its clinical use. Cai et al. uses a chemical grafting condensation reaction to create HAMA@HepMA hydrogel microspheres (MS) and chitosan coated resveratrol liposomes (CS-Res@Lipo) using film dispersion and static loading [47]. These systems form a programmed release system by effectively anchoring BMP-2 through non-covalent interactions at MS binding sites.BMP-2 is released gradually to promote bone healing, and Res is used to regulate the immune response. In addition to managing inflammation, this dual-release system promotes osteogenesis, utilizing the coordinated release profiles to optimize bone regeneration results and maximize therapeutic efficacy [48].

Furthermore, the timed release of bioactive factors can be programmatically controlled by a silk fibroin (SF)-based scaffold that mimics cartilage, improving in-situ cartilage regeneration. E7 is first encapsulated in a quickly degrading SilMA/-HAMA coating after transforming growth factor-β1 (TGF-β1) is physically adsorbed into the SF cryogel scaffolds [49] . This configuration facilitates the slow, continuous release of TGF-β1 over a number of weeks and the rapid release of E7 in the early days, which work in concert to promote BMSC recruitment and their chondrogenic differentiation in vitro [50]. The best 3D microenvironment for cartilage reconstruction is provided by these SF scaffolds, which retain exceptional structural integrity and mechanical characteristics akin to cartilage.

Based on the unique requirements of the tissue repair process, programmable biomaterials can be designed to react dynamically to the physiological environment of the injury site, enabling customized therapeutic actions. With their significant clinical benefits in bone repair, these materials offer a promising new direction for regenerative medicine [46]. The study of programmable biomaterials for bone repair is booming and has a lot of promise for the clinic. On the other hand, thorough summaries of the application of these materials for bone healing are currently scarce.

4. How programmable biomaterials are emerging

The advancement of biomaterials has been a persistent pursuit of innovation, progressing sequentially through three significant phases, each characterized by notable scientific breakthroughs and shifts in the principles of materials science. The introductory

period of biomaterials, predominantly utilized from the 1950s to the 1980s, focused on materials that were biologically inactive [51][52]. These encompassed gypsum, various metals, rubber, and cotton. The primary intent during this phase was to develop materials that would not cause adverse responses from biological tissues. However, the inactive nature of these materials frequently resulted in host responses and long-lasting compatibility issues, necessitating more advanced solutions [53]. Despite their limitations, these materials served as the basis for future advancements by defining the essential criteria for biocompatibility.

During the 1980s and 1990s, the second generation saw a move toward bioactive materials. The interdisciplinary approach of this era combined knowledge from physics, biochemistry, materials science, and medicine [54] . Advanced polymer materials science and improved physical testing techniques are two examples of the technologies that have made it possible to create materials that interact favorably with biological tissues. Hydroxyapatite, tricalcium phosphate, polyhydroxy acids, hydroxyethyl methacrylate polymers, collagen, and fibrin are important products from this era [37] [55]. These materials were created not only to be physiologically compatible but also to actively support biological functions like tissue repair and regeneration. New medical application opportunities, such as scaffolding for tissue engineering and more efficient implants, were made possible by the emphasis on bioactivity.

The emergence of the third generation of biomaterials, commencing in the 1990s and persisting to the current era, signified a transformative movement towards materials capable of actively engaging and modifying biological environments [56]. This generation is centered on materials that are responsive to cells, proteins, and genes, essentially constituting biomedical conglomerates intended to augment the body's innate healing and regenerative potential. These materials are a combination of active constituents eliciting physiological reactions and inactive components for regulation and stability [57]. Their design aims to attain an optimal equilibrium between material characteristics and biological functionality. Third-generation biomaterials are distinguished by their capacity to respond to cellular environments, adjust to physiological conditions, and support the body's natural regenerative processes [58]. BMP and other physiologically active substances, which have found widespread use in tissue engineering and regenerative medicine, are examples of representative materials.

Programmable biomaterials constitute a notable and pivotal development, encompassing the convergence of disciplines, such as materials science, biology, and computer science. These biomaterials are designed to incorporate computational principles, like coding and data processing, into their structure and functionality [46]. By employing this innovative method, it is possible to meticulously modify material properties through targeted molecular interactions, strategically designed chemical modifications, and sensitivity to external stimuli. This versatile approach allows programmable biomaterials to adapt their attributes or behavior in response to environmental fluctuations, including variations in temperature, pH levels, or mechanical forces, thereby demonstrating remarkable versatility and responsiveness [47]. The application of programmable attributes within biomaterials has spurred the development of cutting-edge medical technologies. Among these advancements are intelligent drug delivery systems capable of accurately timing and positioning the release of therapeutic agents, as well as intricate tissue engineering scaffolds that can adapt and evolve in sync with healing tissues [59]. These materials are engineered for dynamism, both in terms of structure and functionality, heralding a new epoch in materials science research. Programmable materials respond to specific stimuli in multiple ways. In some instances, a stimulus may trigger changes in non-covalent interactions within the material, resulting in a reversible physical change.

The combination of materials science, biology, and computer science is exemplified by programmable biomaterials, which produce materials that are not only biocompatible but also capable of dynamic interactions with their environment. Biological systems and material properties work in concert to create more individualized and effective medical treatments [60]. It has enormous potential to advance targeted drug delivery systems, regenerative medicine, and other medical specialties, marking the beginning of a new era in healthcare innovation. As programmable biomaterials research and development progress, we can anticipate that these materials will become more and more important in solving challenging medical problems. More complex integration of synthetic and biological components is anticipated in the future of biomaterials, resulting in creative solutions that can instantly adjust and react to the body's demands [61].

The expanding knowledge of the relationships between materials and biological systems is demonstrated by the transition from inert to bioactive and programmable materials. A new era of bio-inspired and bio-integrated materials science is dawning with this evolution [62]. The creation of increasingly intelligent biomaterials that can precisely interact with biological systems while also adapting to self-regulation and repair in particular biological environments as from the understanding of these intricate interactions grows. This will significantly advance the development of regenerative medicine [63][64].Recent developments in programmable materials and related manufacturing technologies are very promising and could have a big influence on both research and industrial applications. The various kinds of programmable biomaterials, their benefits, and their drawbacks are discussed below.

4.1 Electrically responsive biomaterials

The capacity of electrically responsive biomaterials to react dynamically to electrical stimuli, thereby promoting cellular activities essential for osteogenesis, confers substantial benefits in bone regeneration [65]. Conductive polymers, piezoelectric biomaterials, and metal nanomaterials are examples of materials that improve intercellular communication and promote osteoblast proliferation

by means of signaling pathways like calcium/calmodulin. The preciseness of tissue engineering techniques is increased by electrically responsive biomaterials, which allow the controlled and prolonged release of growth factors and bioactive molecules [66]. Electrically responsive biomaterials help to improve bone healing and encourage cellular differentiation by combining electrical and biochemical cues to promote bone tissue regeneration.

4.2 Bioactive scaffolds with programmable properties

Programmable bioactive scaffolds combine dynamic, customized biological functionality with structural support. Because of its programmability, the scaffold can react to various biological stages of healing, guaranteeing that signals are sent at the appropriate moment to boost cellular activity and encourage effective bone repair [57]. Wang and associates. created and produced a number of shape memory/hydroxyapatite biomimetic composite scaffolds. These scaffolds have excellent shape memory capabilities, mechanical properties that can be adjusted, and programmable pore structures with a wide range of parameters and high connectivity [46]. The microstructure and pore configuration of these composite scaffolds can be precisely controlled by varying the amount of hydroxyapatite (HA), which improves the formation of perforated pores even more.

Additionally, altering the HA content can enhance the scaffold's mechanical qualities, melting point, expansion rate, and hydrophilicity, making it more appropriate for use in biomedical applications [67]. The versatility of a magnetic chitosan microscaffold (Mag-C) was demonstrated by its design, which allows for shape and movement adaptation for a range of biomedical applications. Mag-C is made up of surface-attached magnetic particles (MPs) and a chitosan microscaffold (CMS) [15]. Using laser micromachining on a porous chitosan sheet, the CMS is quickly and accurately shaped, utilizing the biocompatibility and biodegradability of chitosan. Magnetic responsiveness is added when MPs are adsorbed onto the CMS surface. This surface alteration improves Mag-C's magnetic actuation and cell adhesion capabilities while preserving the natural qualities of chitosan [38]. Mag-C is appropriate for in vitro biomedical applications because it can carry out distinct functions depending on its shape, allowing for particle manipulation and assembly by loading different cells and magnetic fields.

4.3 Surface-engineered implants for sequential regeneration

A cutting-edge class of materials in materials science and engineering are surface-engineered implants for sequential regeneration. Because of their special ability to change their surface properties in response to particular stimuli, these materials offer specialized functions for a range of applications [68] . Through surface modification of implants or biomaterials, the programmable sequential bone repair function is accomplished. A promising material in orthopedics, poly(aryl-ether-ether-ketone) (PEEK) is renowned for its exceptional mechanical qualities, inherent radiolucency, and biostability [4][69]. Because of its favorable mechanical properties and high temperature resilience, this thermoplastic is widely used in engineering applications. PEEK is a semicrystalline polymer with an aromatic backbone joined to ketone and ether groups within its molecular structure. A high-performance polymer with exceptional chemical stability is PEEK.

4.4 Nanomaterials for targeted bone regeneration

A state-of-the-art combination of bone tissue engineering and nanotechnology is represented by nanomaterials for targeted bone regeneration for bone repair. These materials offer novel ways to support bone regeneration and repair because they are nanoengineered to interact specifically with bone tissues [70]. With substance P (SP) in the shell and alendronate (ALN) in the core, a core-shell structure was created using coaxial electrospinning to create a dual delivery system that ensures a programmed release in line with treatment requirements [71][46].

While ALN was designed to prevent bone resorption and improve implant osseointegration, SP sought to encourage bone regeneration. By effectively regulating the release rates of SP and ALN, the dualdelivery system improved mesenchymal stem cell recruitment and osteogenesis while lowering osteoclast activity [72]. Bone tissue engineering is progressing thanks to new approaches that make use of magnetic nanoparticles (MNPs), magnetic field technology, and stem cells. These novel approaches combine magnetic nanoparticles (MNPs) and scaffolds with magnetic fields and stem cells to dramatically improve osteogenic differentiation, angiogenesis, and bone regeneration.

When compared to the control group, this method has been demonstrated to enhance the effects of bone tissue engineering by two to three times. This method speeds up the process of bone repair by improving the interaction between cells and scaffolds and controlling the local microenvironment with magnetic fields [8]. This encourages the directional differentiation of stem cells and the formation of new bone. These techniques' possible clinical uses greatly enhance the results of bone regeneration and repair. Hydroxyapatite nanowire@magnesium silicate Nano sheet core-shell structured hierarchical nanocomposites, also known as Nano brushes, were created by Sun et al [46]. To create a scaffold, they were incorporated into a chitosan matrix. High performance drug loading and sustained release are facilitated by the large specific surface areas and pore volumes of Nano brushes.

The biological efficacy of the scaffolds was assessed through both in vitro and in vivo methodologies. In vitro analysis revealed that the scaffold improved the attachment and proliferation of rat bone marrow mesenchymal stem cells while also enhancing the expression of genes associated with osteogenic differentiation and vascular endothelial growth factor (VEGF) [73]. In vivo

experiments conducted with a rat bone defect model indicated that the scaffold significantly facilitated bone regeneration and angiogenesis. This capability is linked to the scaffold's ability to create a conducive environment for cell attachment, proliferation, and differentiation, aided by the sustained release of bioactive ions essential for bone tissue regeneration [3]. He et al. engineered core-shell nanofibers intended for the programmed, sequential release of tea polyphenols (TP) and AdipoRon (APR), aimed at managing inflammation and improving bone regeneration [40][74]. These nanofibers, produced via electrospinning, exhibit controlled sequential release properties. The release profiles indicated an initial rapid discharge of TP, succeeded by a prolonged release of APR. This innovative design effectively reduced levels of proinflammatory cytokines and enhanced osteogenic differentiation within an inflammatory microenvironment [72]. Managing pro-inflammatory responses triggered by cytokines and fostering the anti-inflammatory activity of M2 macrophages are vital for osteogenesis during the repair of bone tissue. Zhou et al. utilized 3D printing and electrospinning techniques to create a biomimetic scaffold that replicates the extracellular matrix for bone regeneration [41]. The scaffold features a core-shell architecture that includes dimethyloxalylglycine (DMOG)-loaded mesoporous silica nanoparticles and a 3D-printed structure composed of strontium-enriched hydroxyapatite and polycaprolactone (PCL). This configuration supports the sequential release of DMOG and strontium ions, thereby promoting angiogenesis and osteogenesis. In vitro evaluations demonstrated that the scaffold improved cell attachment, proliferation, and differentiation, significantly upregulating genes associated with osteogenic differentiation [7].

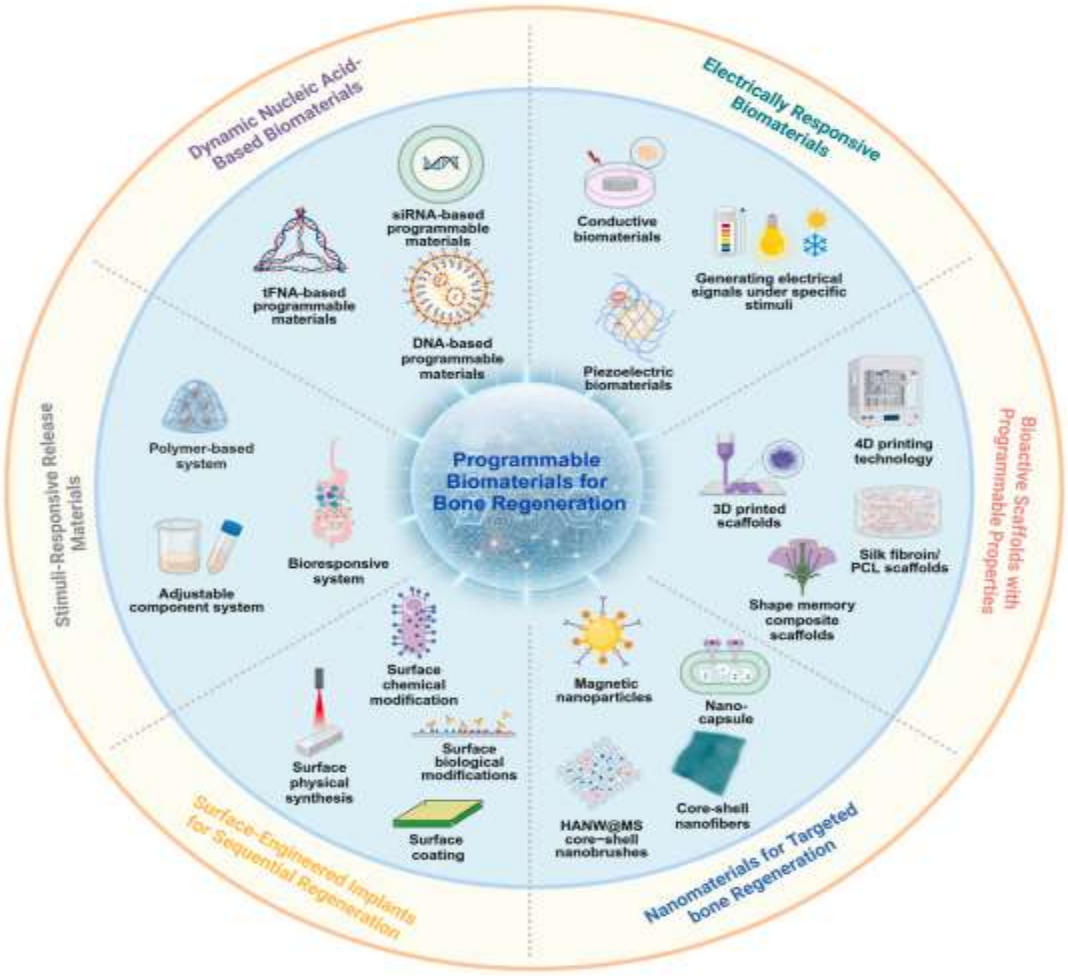

Figure 1.1: Classification of Programmable biomaterials

A novel biomaterial scaffold has been developed, combining alginate matrices with calcium phosphate scaffolding to facilitate a programmed release of growth factors. This scaffold features a carefully formulated mixture of alginate microspheres, alginate hydrogels, and an innovative resorbable calcium phosphate-based cement (ReCaPP) [75]. Within this framework, platelet-derived growth factor (PDGF) and BMP-2 are released in a sequential manner, achieving a targeted three-day overlap where PDGF is delivered prior to BMP-2. Research utilizing a three-dimensional coculture model demonstrated that this specific release sequence of PDGF followed by BMP-2 significantly affected cellular infiltration into the scaffold and the expression of alkaline phosphatase (ALP) [76][47]. These results indicate that the well-timed delivery of PDGF, followed by BMP-2, effectively encourages the

differentiation of human mesenchymal stem cells (hMSCs) into an osteoblast phenotype while simultaneously improving cellular infiltration within the scaffold. Additionally, microcapsules containing various bioactive molecules were affixed to the scaffold surfaces, enabling multimodal activation through physical (such as ultrasound and laser radiation) and biological (enzymatic treatment) stimuli. This configuration allows for the controlled release of the encapsulated agents from the scaffolds [40][77].

3D printing presents remarkable opportunities in the field of biofabrication; however, it encounters difficulties in producing intricate, non-linear geometries and in adjusting the properties of multi-material structures over time. In contrast to 3D bioprinting, 4D bioprinting is capable of creating dynamic structures that closely replicate the inherent dynamics and conformational alterations of natural tissues, thereby fulfilling the increasing demands of biomedical engineering applications [45]. Since the introduction of 4D printing technology in 2013, the discipline has attracted significant interest. Two essential elements for achieving optimal results in 4D printing are smart materials and intelligent design. Smart materials are those that can alter their shape or properties in response to external stimuli, while intelligent design focuses on enabling programmable transformations by thoroughly considering the time-dependent attributes of the printed objects [42]. Looking ahead, advancements in 4D printing technology are anticipated to facilitate the use of biocompatible smart materials, biochemical agents, and living cells, ultimately leading to the creation of dynamic 3D living structures. Programmable active scaffold materials are engineered to not only provide structural support for tissue regeneration but also to engage actively in the healing process [70]. Their "programmability" is characterized by their capacity to respond to biological signals and environmental variations, positioning them as dynamic contributors to tissue regeneration.

Bioactive scaffolds with adjustable properties present considerable benefits for bone regeneration by not only offering mechanical support but also actively engaging in the healing process. Their ability to be programmed enables the controlled and sequential release of bioactive molecules, which can be customized to align with the various stages of bone healing [61]. This approach ensures that growth factors such as BMP-2, IL-10, and PDGF are administered at the most effective times to facilitate osteoblast differentiation, angiogenesis, and immune modulation [32]. Additionally, these scaffolds can be engineered with tailored pore structures and materials that replicate the natural extracellular matrix, thereby improving cellular infiltration, proliferation, and differentiation. The adaptable and responsive characteristics of these scaffolds significantly enhance their effectiveness in regenerating complex bone structures while reducing inflammation and promoting tissue integration [57].

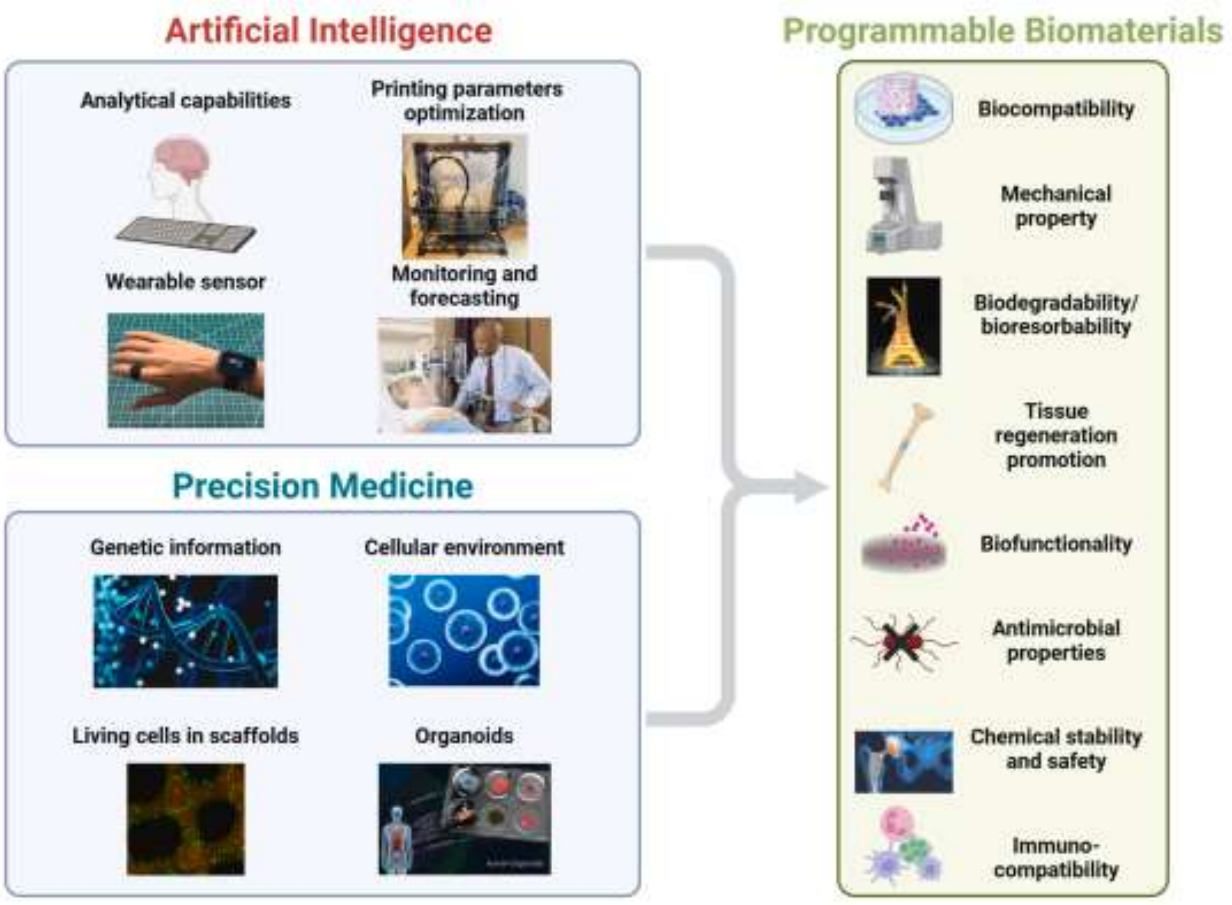

Figure 1.3: Artificial intelligence and precision medicine will drive the development of programmable biomaterials.

5. Conclusion and future perspectives

The utilization of programmable biomaterials in bone regeneration addresses the intricate, multi-stage process of bone healing, which encompasses inflammation, repair, and remodeling. Each category of programmable material fulfills a distinct function in facilitating these phases. For instance, dynamic nucleic acid-based biomaterials are engineered to precisely regulate the expression of osteogenic genes, such as BMP-2, by delivering nucleic acids in a controlled spatiotemporal manner [77]. This targeted gene regulation promotes osteoblast differentiation and enhances bone formation. Bioactive scaffolds with programmable characteristics offer both mechanical support and biological signals to the injury site, thereby encouraging cell adhesion, proliferation, and osteogenesis. These scaffolds can be tailored to release growth factors like VEGF and TGF-β1, which are crucial for angiogenesis and bone repair [75]. Additionally, stimuli-responsive release materials provide a controlled and sustained delivery of bioactive molecules, ensuring that osteoinductive factors remain available throughout the healing process. This regulated release minimizes the initial burst effect and synchronizes the delivery of growth factors with the body's natural healing phases, thereby optimizing bone tissue regeneration [61]. Collectively, these programmable materials effectively address the specific requirements of bone regeneration by dynamically adapting to the microenvironment and supporting the cellular activities necessary for successful bone healing.

The investigation of programmable biomaterials in the realm of bone tissue engineering introduces compelling challenges that require a collaborative approach, integrating biology, chemistry, physics, and engineering. Although these materials hold significant promise across various domains, their development and implementation remain in a phase of ongoing enhancement and refinement [78]. In the context of bone repair, it is essential to maintain precise control over the dosage and release kinetics of growth factors and other bioactive substances. Factors such as the degradation rate of the material, fluctuating environmental conditions, and the specific site of implantation can greatly influence this process, often resulting in unpredictable outcomes [79]. Furthermore, the use of materials like shape-memory polymers (SMP), which necessitate accurate positioning and adaptation to the surgical site through temperature adjustments, imposes greater demands on surgical techniques and medical circumstances.

The long-term stability of biomaterials within the human body is of paramount importance. Ideally, these materials should gradually decompose after fulfilling their role in bone repair, with the byproducts being non-toxic to the body. The materials employed in bone repair must possess adequate mechanical strength to support skeletal reconstruction and endure the stresses imposed by body weight and movement [80]. However, to improve bioactivity, some programmable biomaterials may sacrifice strength and stiffness, potentially failing to meet the required mechanical standards under sustained stress or heavy loads. Additionally, the production and procurement of advanced programmable biomaterials can be costly, limiting their broader application in clinical environments. Integrating multiple independent functions within a single material such as responding to a single stimulus either simultaneously or sequentially, or reacting differently to various stimuli while minimizing functional interference remains a significant challenge[81][14][78]. Consequently, while programmable biomaterials offer promising avenues for bone repair, their practical application is still fraught with complexities.

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