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# Biomimetic approaches in bone tissue engineering: Integrating biological and physicomechanical strategies

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#### ABSTRACT

The development of responsive biomaterials capable of demonstrating modulated function in response to dy- 21 namic physiological and mechanical changes in vivo remains an important challenge in bone tissue engineering. 22 To achieve long-term repair and good clinical outcomes, biologically responsive approaches that focus on repair 23 and reconstitution of tissue structure and function through drug release, receptor recognition, environmental responsiveness and tuned biodegradability are required.

Traditional orthopedic materials lack biomimicry, and mismatches in tissue morphology, or chemical and me- 26 chanical properties ultimately accelerate device failure. Multiple stimuli have been proposed as principal contrib- Q6 utors or mediators of cell activity and bone tissue formation, including physical (substrate topography, stiffness, 28 shear stress and electrical forces) and biochemical factors (growth factors, genes or proteins). However optimal 29 solutions to bone regeneration remain elusive. This review will focus on biological and physicomechanical considerations currently being explored in bone tissue engineering.

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Abbreviations: HA, hydroxyapatite; GAG, glycosaminoglycan; PG, proteoglycan; ECM, extracellular matrix; VEGF, vascular endotelial growth factor; HIF- $1\alpha$ , hypoxia-inducible factor-1 alpha; PDGF, platelet-derived growth factor; IL-1, interleukin 1; TNF, tumor necrosis factor; TGF- $\beta$ , transforming growth factor beta; IGF, insulin-like growth factor; ROS, reactive oxygen species; COX-2, cyclooxygenase 2; MAPK/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinases; RUNX2, runt-related transcription factor 2; MSC, mesenchymal stem cells, non-steroidal anti-inflammatory drug, NSAID; LPS, lipopolysaccharides, macrophage colony-stimulating factor, M-CSF; PGE2, prostaglandin E2; BMSCs, bone marrow stromal cells; CaP, calcium phosphate; CVD, chemical vapor deposition; BMP-2, bone morphogenetic protein-2; MRSA, methicillin-resistant straphylococus aureus; SDF-1, stromal derived growth factor-1; c-di-GMP, Bis-(3'-5')-cyclic dimeric guanosine monophosphate; RGD, arg-gly-asp; FN, fibronectin, OCN, osteocalcin; PGF, placenta growth factor.

This review is part of the Advanced Drug Delivery Reviews theme issue on "Scaffolds, Cells, Biologics: At the Crossroads of Musculoskeletal Repair".

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#### 1. Introduction

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Bone tissue regeneration remains an important challenge in the field of orthopedic and craniofacial surgery. Traumatic injuries and various pathological diseases, including osteoporosis, osteoarthritis, osteogenesis imperfecta and Paget's disease, can impair normal bone functions and lead to bone fractures non-unions, immobility, severe pain and deformity. As such the demand for bone grafts is considerable, and represents the second most common tissue transplantation procedure after blood, with over 2.2 million bone graft procedures conducted worldwide annually in orthopedics and dentistry [1]. Current clinical treatments for large defects are challenging, and despite the natural capacity of bone for healing, if an injury is beyond a critical limit (critical size defect), it cannot heal by regeneration. (See Tables 1–3.)

Harvesting bone from autologous or allograft donor sites is an expensive and painful procedure, which is linked with added health risks associated with additional surgical procedures in elderly patients, increased risk of infection or disease transmission or rejection from donors [2,3]. Novel solutions are required to overcome the limitations of current bone grafting approaches and in vitro strategies, through tissue engineering or regenerative medicine approaches, which are promising strategies for treating bone diseases and reconstructing bone defects.

Tissue engineering approaches involve the combination of cells, biomaterial scaffolds and specialized culture conditions incorporating biochemical and physical stimuli to encourage in vitro bone formation. The development of responsive biomaterials capable of producing modulated function in response to the dynamic physiological and mechanical environments in vivo remains an important challenge in bone tissue engineering to achieve long-term repair and good clinical outcomes [4]. Despite considerable progress in the understanding of the biological and physicomechanical properties of organs and tissues, relatively few orthopedic biomaterials designed with biomimetic and bioresponsive characteristics have been translated into clinical solutions to date [5]. Nevertheless, according to the EU-Report on Nanotechnology, the global market for 'smart biomaterials' reached \$47 billion in 2009 and will rise to \$113 billion by 2025 [6].

Most current orthopedic technologies draw on simple or composite building blocks, yet next-generation tissue-engineering strategies in bone regeneration must combine multiple functions such as drug release, receptor recognition, environmental responsiveness and tuned biodegradability [7]. Furthermore, traditional medical devices lack biomimicry, and mismatches in tissue morphology, or chemical and 118 mechanical properties ultimately accelerate implant failure [8,9]. In par-119 ticular, current scaffold and implant designs are not biochemically, or 120 physically specific to a particular patent, and long-term or permanent 121 implants are not ideal for many applications, due to risks of stress 122 shielding [10,11] and implant loosening [12]. Biomimetic approaches 123 to biomaterial design enable molecular, structural and biological com- 124 patibility similar to that of the tissue being replaced to facilitate the re- 125 generation of complex tissues [13-15]. Multiple stimuli have been Q10 proposed as principal contributors or mediators of cell activity and 127 bone tissue formation, including physical (substrate topography, stiff- 128 ness, shear stress and electrical forces) and biochemical factors (such 129 as growth factors, genes or proteins). However, next-generation scaf- 130 folds and tissue engineered constructs need to be driven by a personal 131 medicine approach and must integrate a range of biological and physical 132 properties for optimal bone regeneration.

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#### 2. Structural and functional elements of bone tissue

Bone tissues can be understood as a nanocomposite 3D scaffold of 135 nano-HA and type-I collagen and can be principally defined as either 136 cortical or cancellous bone, dependent on the structural organization, Q11 porosity and mechanical properties. Cortical bone (<20% porosity) con- 138 sists of close packets of osteons, cylindrical (Haversian) systems with a 139 central channel that consists of a blood vessel surrounded by concentric 140 rings (lamellae) of bone matrix. The mechanical properties of this sys- 141 tem are anisotropic, being a function of the direction of applied force 142 (E = 20 GPa along the Haversian system and E = 8 GPa along the transverse axis) [16,17]. In contrast, cancellous bone is less dense (>90% po- 144) rosity) and is structured in plates (trabeculae) offering a larger surface 145 area to mass ratio, making it an effective structure for ion exchange (ho- 146 meostasis), hematopoiesis, and imparting flexibility in load-bearing 147 bones (E = 100 MPa) [18]. Within the osteon and cancellous bone matrices are complex networks of canalilculi, which connect bone cells (os- 149 teocytes) and are believed to play an important role in traducing 150 mechanical stresses, arising from every day from physical loading, into 151 a cellular biochemical process to regulate bone remodeling a process 152 known as mechanostransduction [19,20].

Bone tissue is a highly specialized and hierarchical connective tissue 154 with structural, cellular organization and component material proper- 155 ties that direct bone function. The bone architecture is under continuous 156

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