Delivery of small molecules for bone regenerative engineering: preclinical studies and potential clinical applications

Cato T. Laurencin[1,2,3,4], Keshia M. Ashe[1,2,4,5], Nicole Henry[4], Ho Man Kan[1,2,5] and Kevin W.-H. Lo[1,2,3,6]

[1] Institute for Regenerative Engineering, University of Connecticut Health Center, School of Medicine, Farmington, CT 06030, USA
[2] The Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Sciences, University of Connecticut Health Center, School of Medicine, Farmington, CT 06030, USA
[3] Department of Biomedical Engineering, University of Connecticut, School of Engineering, Storrs, CT 06268, USA
[4] Department of Chemical, Materials and Biomolecular Engineering, University of Connecticut, School of Engineering, Storrs, CT 06268, USA
[5] Department of Orthopedic Surgery, University of Connecticut Health Center, School of Medicine, Farmington, CT 06030, USA
[6] Department of Medicine, Division of Endocrinology, University of Connecticut Health Center, School of Medicine, Farmington, CT 06030, USA

Stimulation of bone regeneration using growth factors is a promising approach for musculoskeletal regenerative engineering. However, common limitations with protein growth factors, such as high manufacturing costs, protein instability, contamination issues, and unwanted immunogenic responses of the host reduce potential clinical applications. New strategies for bone regeneration that involve inexpensive and stable small molecules can obviate these problems and have a significant impact on the treatment of skeletal injury and diseases. Over the past decade, a large number of small molecules with the potential of regenerating skeletal tissue have been reported in the literature. Here, we review this literature, paying specific attention to the prospects for small molecule-based bone-regenerative engineering. We also review the preclinical study of small molecules associated with bone regeneration.

Introduction

Regenerative engineering is an emerging interdisciplinary field at the convergence of life sciences, engineering technology, and physical sciences. Laurencin *et al.* defined regenerative engineering as 'the integration of tissue engineering with advanced material science, stem cell science, and areas of developmental biology' (Fig. 1) [1]. Developmental biology research has uncovered pro-regenerative biological protein-based factors that have the capabilities to modulate stem cell activity towards a final outcome of regenerating injured, damaged, or otherwise impaired tissue [2]. The use of growth factors, such as bone morphogenetic protein-2 (BMP-2), for bone repair and regeneration has been widely researched [3–7]. However, growth factors have significant drawbacks that have so far hindered their practical applications [6,8–12]. Small molecules with osteoinductive potential have been proposed as promising alternatives because they are able to minimize or overcome many of the problems associated with protein-based growth factors [11–18]. For instance, in general, small molecules are often too small in molecular size (<1000 Da) to induce unwanted immune responses in the host [19]. In addition, unlike protein-based growth factors, structural integrity is usually not required for the bioactivity of small molecule compounds [10,11,20]. With the advent of high-throughput screening (HTS), a large number of small molecules with osteoinductive potential have been discovered over the past decade [21–26]. A literature survey for osteogenic small molecules based on a search of electronic databases over the past 10 years (Fig. 2) clearly indicates the increasing interest in the application of small molecules for bone repair and regeneration: a total of 80 relevant publications appeared in electronic databases from January 2013 to October 2013 versus only one article in 2003.

Considering the growing number of osteoinductive small molecules that have been reported in the literature, some of them might represent the next generation of therapies for clinical bone repair and regeneration. In this review, we focus on the prospective future of small molecule delivery to bone tissue as well as on

Corresponding authors:. Laurencin, C.T. (laurencin@uchc.edu), Lo, K.W.-H. (wlo@uchc.edu)

1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2014.01.012

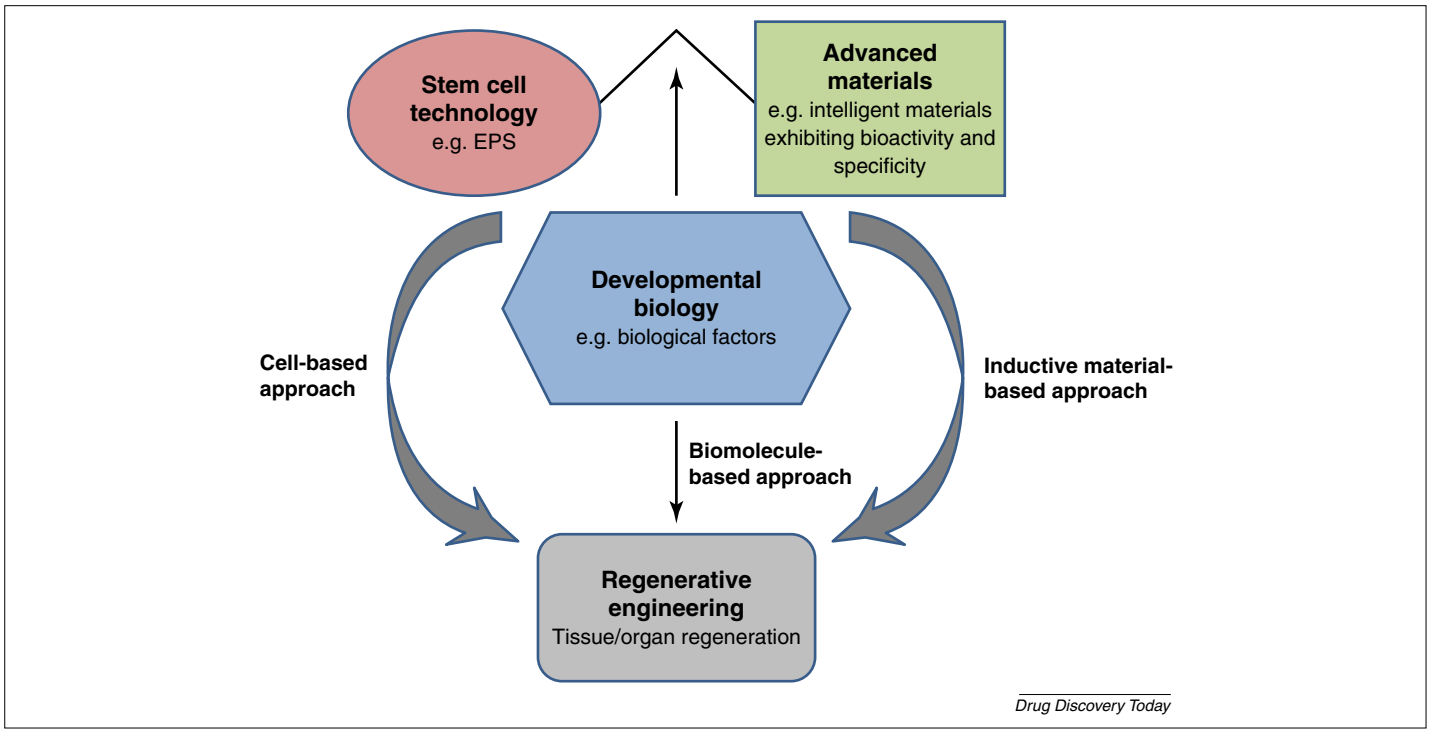

FIGURE 1

A schematic representation of the emerging field of 'regenerative engineering'. Advanced materials, stem cells, and biological factors alone or in combination have important roles in regenerating tissue. *Abbreviations*: EPS, embryonic stem cells.
Adapted, with permission, from [18,94].

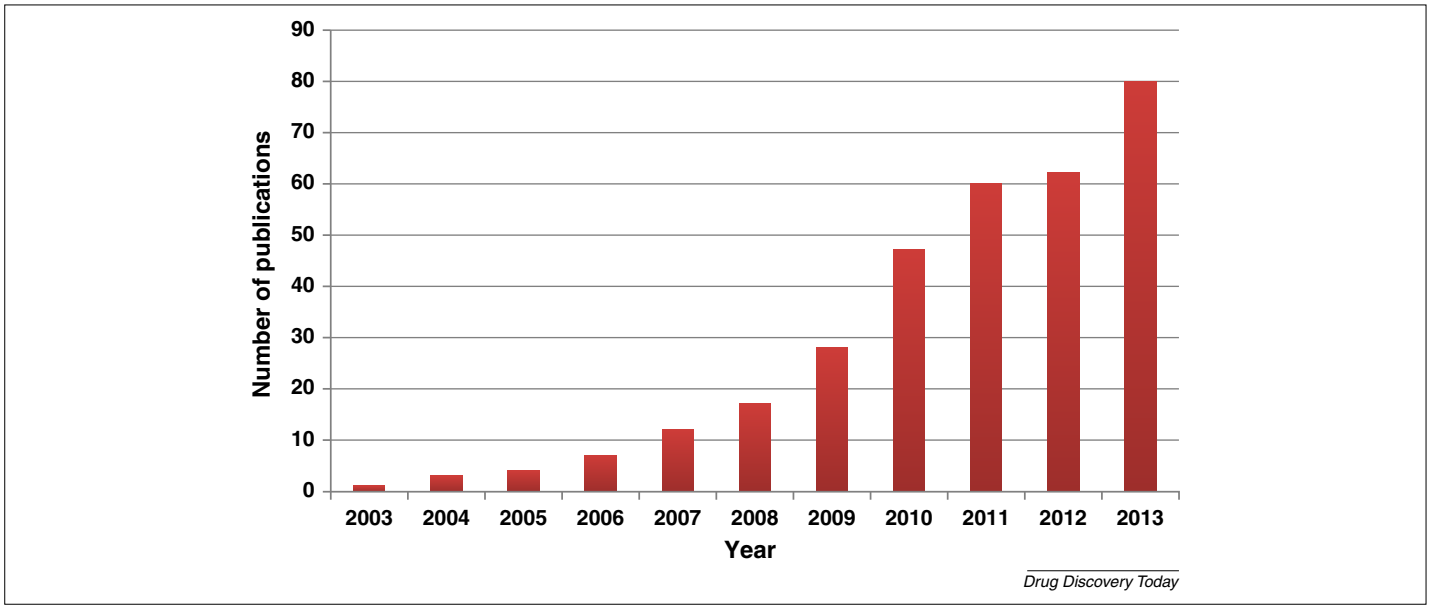

FIGURE 2

A research survey conducted using different keywords, such as 'osteogenic small molecules' or 'small molecules and bone tissue engineering' shows an increasing number of publications relating to small molecule application for bone regenerative engineering over the past 10 years.

current preclinical studies associated with small molecules for bone repair and regeneration.

Delivery of small molecules

Despite the fact that emerging small molecules show promise in various orthopedic applications, their use is limited by nonspecific adverse effects on nontarget tissues and organs [11,27]. The key to success with utilizing small molecules for bone regeneration is designing suitable delivery systems to localize and sustain the controlled release of small molecules to target sites. Although many types of biomaterials, from biologically derived constructs to those of synthetic origin, have been developed to address this need, constructs that are biocompatible and biodegradable are of the utmost interest. Biodegradability is of particular importance