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Local and targeted drug delivery for bone regeneration

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While experimental bone regeneration approaches commonly employ cells, technological hurdles prevent translation of these therapies. Alternatively, emulating the spatiotemporal cascade of endogenous factors through controlled drug delivery may provide superior bone regenerative approaches. Surgically placed drug depots have clinical indications. Additionally, noninvasive systemic delivery can be used as needed for poorly healing bone injuries. However, a major hurdle for systemic delivery is poor bone biodistribution of drugs. Thus, peptides, aptamers, and phosphate-rich compounds with specificity toward proteins, cells, and molecules within the regenerative bone microenvironment may enable the design of targeted carriers with bone biodistribution greater than that achieved by drug alone. These carriers, combined with osteoregenerative drugs and/or stimuli-sensitive linkers, may enhance bone regeneration while minimizing off-target tissue effects.

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Introduction and motivation

Trauma, osteoporosis, and genetic disease cause approximately 6 million fractures in the United States annually [1]. Between five and ten percent of fractures result in delayed union or non-union, with age, smoking, and diabetes as common comorbidities of poor healing [1,2]. Successful bone regeneration requires a complex and orchestrated cascade of cells and growth factors [3–6]. To emulate this complex cascade, regenerative strategies often employ cell transplantation and/or growth factor delivery. While each of these approaches has yielded different levels of success clinically, there are still significant technological challenges.

To achieve translation of cell-based therapies, there are many hurdles to overcome. For bone regeneration, mesenchymal stem cells (MSCs) are commonly used, as they can differentiate to cells required for bone healing (osteoblasts and chondrocytes). However, other cells (e.g., inflammatory cells, endothelial cells) that play important roles in bone regeneration may also be included. A challenge to the use of any cell type is assurance of cellular uniformity. With MSCs as an example, the International Society for Cellular Therapy (ISCT) issued three criteria for identifying MSCs: plastic adherence, specific cell surface marker expression, and tri-lineage potential [7]. Additional gains in uniformity have been achieved through GMP-compliant isolation procedures [8], culture conditions [9,10], and cryopreservation techniques [11,12]. There are now Food and Drug Administration GMP-approved facilities (the NIH BMSC Transplantation Center and the Upstate New York Stem Cell cGMP Facility) that generate MSCs for clinical investigations [13•]. However, cell-based therapies require significant lead-time to achieve cell quantities necessary for many regenerative approaches [14]. Further, these approaches still may fall short due to inconsistent and/or unpredictable outcomes resulting from donor-to-donor and batch-to-batch variability of cells. For example, it has been shown that patients with many comorbidities, such as age, osteoporosis, genetic defects, infection, obesity, diabetes, and smoking, exhibit reduced MSC potency and number resulting in poor bone regeneration [15]. While it is possible to transplant regenerative cell types, including MSCs or MSCs pre-conditioned with small molecule drugs [16] or augmented with genetic manipulations [17] to encourage osteogenesis or microenvironmental modulation [18], to date no MSC-based regenerative strategy is approved for clinical use [19••].

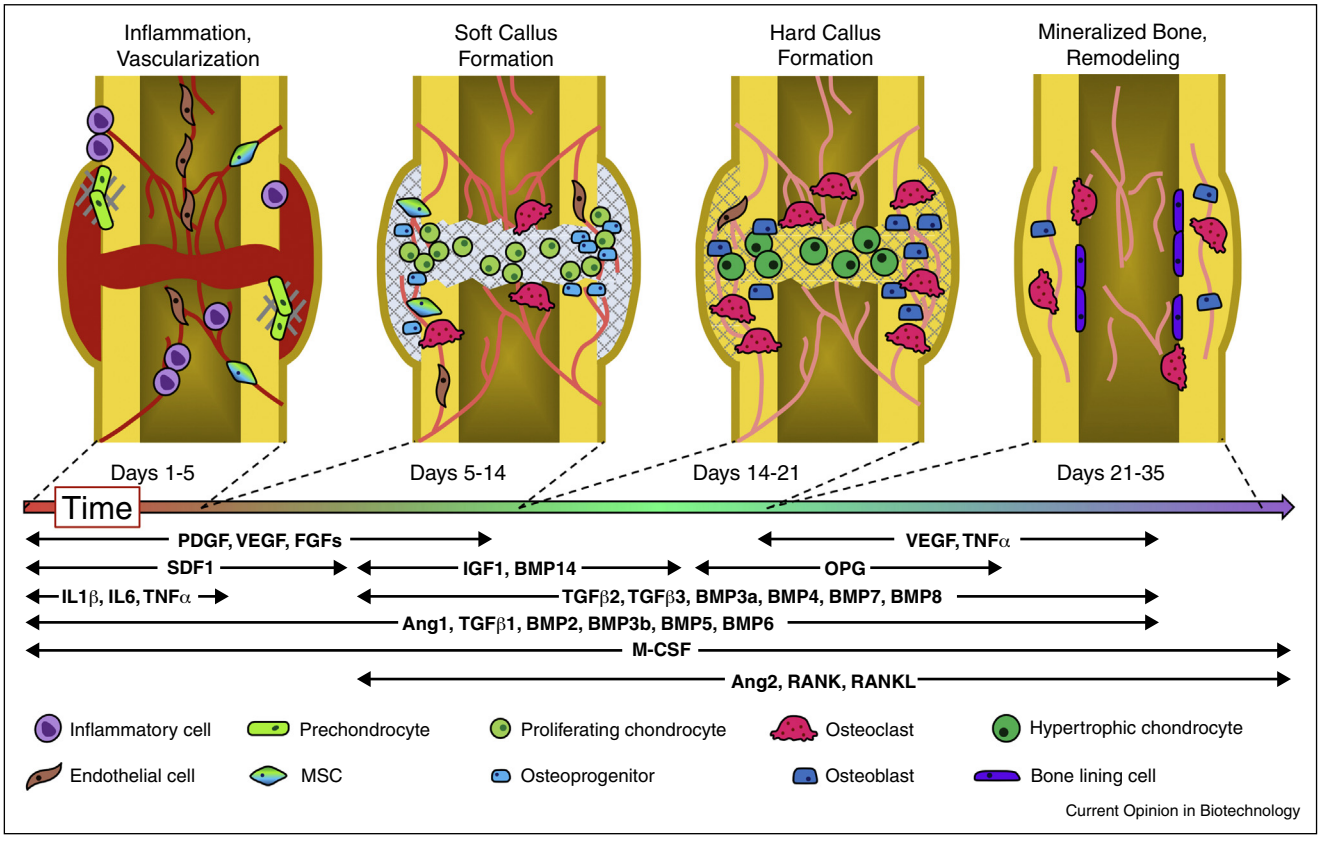
Nevertheless, nearly 20% of the approximately 100 MSC-based clinical trials registered in the United States National Institutes of Health database are for bone and cartilage regeneration [20]. However, there is still a nascent understanding of long-term safety and efficacy of MSC-based therapies as most trials are in Phase I or Phase I/II. Interestingly, for the ~33% of trials completed, there is evidence to suggest MSCs have therapeutic benefits that are not aligned with typical tissue engineering outcomes (e.g., tissue-specific differentiation and tissue production), such as enhancing vascularization in patients with osteonecrosis of the hip [21]. Additional therapeutic effects include attenuating inflammation and stimulating proliferation, suggesting these effects are due

to MSC production of cytokines and growth factors that exhibit paracrine and/or autocrine effects [22].

Ultimately, cell phenotype and function are coordinated by a myriad of spatiotemporally regulated growth factors to realize bone regeneration. These factors include transforming growth factors (TGFs), bone morphogenetic proteins (BMPs), stromal cell-derived factor 1 (SDF1), and osteoprotegerin (OPG) (Figure 1). Based on these factors, a variety of drugs, including BMPs, other growth factors, hormones, and monoclonal antibodies, have been explored for bone regenerative effects [20,23•]. Common strategies focus on BMP therapy, as canonical BMP signaling is integral to bone formation [13•,24•]. In fact, drug delivery approaches that increase the availability of factors such as BMP2 have been proven safe and efficacious for bone regeneration (e.g., INFUSE^{TM} [6]); however, protein (e.g., antibodies, growth factors) half-lives are only on the order of an hour [25], necessitating local delivery of supra-physiological doses to achieve desired pharmacodynamics.

As an alternative to BMP, small molecule drugs such as statins that induce BMP signaling [26] and osteoregenerative agents that act on BMP-convergent pathways may also enhance bone remodeling [27•,28]. These convergent pathways, including parathyroid hormone (PTH) and Wnt, stimulate osteogenesis and preserve osteoblasts when activated (Figure 2). Activated PTH receptor initiates Wnt signaling by complexing with low density lipoprotein receptor-related protein 5 and 6 (LRP5/6) [28], and Wnt signaling regulates targets common to BMP signaling [29]. Teriparatide (PTH 1-34), which is approved to treat osteoporosis, is used off-label in normal bone fractures, delayed bone fractures [30], and non-unions [31], and patients demonstrate accelerated healing. Lithium, a Wnt signaling agonist that negatively regulates glycogen synthase kinase 3 beta (GSK3β) [32•], and a monoclonal antibody that inhibits the Wnt-inhibitory protein sclerostin [33] accelerate fracture healing since Wnt signaling is critical for fracture repair [34]. Wnt, PTH, and BMP play key roles in specific stages of fracture repair [35,36], but they can also be inhibitory if activated without proper spatiotemporal control [37].

Figure 1



A spatiotemporal cascade of multiple endogenous factors controls normal bone regeneration during fracture repair in four stages. PDGF = platelet derived growth factor; VEGF = vascular endothelial growth factor; FGF = fibroblast growth factor; TNF = tumor necrosis factor; SDF = stromal cell-derived factor; IGF = insulin-like growth factor; BMP = bone morphogenetic protein; OPG = osteoprotegerin; IL = interleukin; TGF = transforming growth factor; Ang = angiopoietin; M-CSF = macrophage colony stimulating factor; RANK = receptor activator of nuclear factor κB; RANKL = RANK-ligand.