

Editorial

Regulation of bone regeneration

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Bone regeneration after injury is a complex but well-orchestrated process that evolves in three major stages. As ‘hallmarks’ of this process can be considered *i*) hematoma formation at the site of injury, *ii*) hypoxia, *iii*) inflammation and innate immune response in the early initial stage, *iv*) periosteal response, *v*) formation of cartilaginous callus, *vi*) its mineralization and replacement by primary bone in the reparative, healing or anabolic stage, and *vii*) cartilage resorption, *viii*) angiogenesis, revascularization, and *ix*) formation of secondary bone with regeneration of the original structural features and reestablishment of marrow space and hematopoietic tissue in the remodeling or catabolic stage [1]. Since an intensive scientific examination of fracture healing and bone regeneration both in humans and in animals has been started early in the last century, with, exemplarily, only mentioning the work of August Bier [2–4], knowledge of the capillarization, the cell types and the panoply of biochemical mediators involved has grown tremendously [1, 5]. This in turn has stimulated intensive research into new methods of improving fracture healing by adjuvant use of molecular stimuli addressing cells, signaling pathways and crosstalks. In this regard, widely examined therapeutical approaches use bone morphogenetic proteins and parathyroid hormone [1]. Other strategies focus on the development and exploration of novel osteoconductive and osteoinductive small molecule drugs for adjuvant therapeutic approaches for both local and systemic application. Among other things, this led to a more critical examination of the effects of drugs that are used specifically to treat pain after bone fractures. Moreover, targeted and pleiotropic effects of approved and widely used drugs, for example those used for treatment of chronic diseases such as hypertension, diabetes or lipid disorders as well as anticancer agents also were considered more intensively [6]. Most recently, selectively targeted drugs, hybrid compounds, drug combinations, and biomaterial-based drug delivery systems became a specific focus of interest.

In this issue, a self-contained series of three review articles comprehensively deals with recent trends and perspectives in adjuvant drug-assisted bone healing, with emphasis on critical bone defects. The latter lead to a high socio-economic burden and their successful treatment poses a particular

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clinical challenge. The authors have critically analyzed recent preclinical and clinical work on the use of inflammation-, angiogenesis- and metabolism-modulating small molecule agents as adjuvants to improve bone healing [7–9]. Therefore, literature was selected from a PubMed database search using the key words and phrases *agonists, anabolic, angiogenesis, antagonists, anti-resorptive, drugs, inflammation, inhibitors, local, small molecule compounds, and systemic* linked to the key words *critical bone defect, fracture, and healing*. Taken together, these articles highlight current concepts attempting to use small molecule drugs and intelligent drug delivery methods to enhance osteogenesis and bone healing. The main conclusions result in an evaluation of the modulation of angiogenesis and microcirculation as a very promising concept. The modulation of inflammation, on the other hand, has been assessed as critical with respect to the beginning and duration of therapy, whereby targeted modulation of bone metabolism, use of bi-functional or hybrid compounds, suitable drug combinations and delivery systems are expected to provide novel solutions.

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