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Review

Bone targeting for the treatment of osteoporosis

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ABSTRACT

Osteoporosis represents a major public health burden especially considering the aging populations worldwide. Drug targeting will be important to better meet these challenges and direct the full therapeutic potential of therapeutics to their intended site of action. This review has been organized in modules, such that scientists working in the field can easily gain specific insight in the field of bone targeting for the drug class they are interested in. We review currently approved and emerging treatment options for osteoporosis and discuss these in light of the benefit these would gain from advanced targeting. In addition, established targeting strategies are reviewed and novel opportunities as well as promising areas are presented along with pharmaceutical strategies how to render novel composites consisting of a drug and a targeting moiety responsive to bone-specific or disease-specific environmental stimuli. Successful implementation of these principles into drug development programs for osteoporosis will substantially contribute to the clinical success of anti-catabolic and anabolic drugs of the future.

Contents

1. Osteoporosis is a major health burden

Osteoporosis and arthrosis are the most prevalent disorders affecting the skeleton. Age related loss in bone mass is a normal process typically commencing beyond an age of 40 years, at which humans typically attain their peak bone mass. Osteoporosis is a disease pattern, within which the decline in bone mass is beyond of what is normal as a function of sex, race and height. The disease typically leads to reduced bone strength and in turn a higher probability to fractures and it is these fractures which drive patient disability and economic burden of health care systems [1]. Approximately 15% of Caucasian women older than 65 years suffer from osteoporosis [2], while other

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sources estimate 55% of subjects being 50 years of age and older are at risk for osteoporosis and fractures in the US [3]. More than 3 million osteoporotic fractures are expected in 2025 in the US alone with associated costs rising to approximately $25.3 billion [3]. Osteoporosis is often progressive, degenerative and may affect the entire skeleton, however, often to a different degree at different skeletal sites. Typical, most frequently affected sites of an osteoporotic fracture are the hip, spine and wrist, which accounted for 297,000 hip fractures, 547,000 vertebral fractures, 397,000 wrist fractures, 135,000 pelvic fractures and 675,000 fractures at other sites in the US alone and in 2005 — osteoporosis was the main cause for all femoral neck fractures of the hip [4] for about those 293,000 Americans of age 45 who experienced it in 2005 [3]. Treatment of these fractures is particularly costly [5] and associated with substantial morbidity as reflected by the estimation that only 15% of patients who suffered from a hip fracture can walk across a room unaided within 6 months after the event [3]. Symptoms following osteoporotic fractures include pain and particular complications may arise for fractures of the spine and hip which require hospitalization. Hospitalization is the main driver of the mortality rate of the disease, caused by embolism and pneumonia. Treatment of osteoporosis, therefore, targets at reducing the fracture rate by means of increasing bone strength, a parameter driven by bone mineral density (BMD) and bone quality. Whereas BMD is frequently assessed as a predictor for fracture risk (and used as a surrogate endpoint in many clinical trials for osteoporosis) through dual energy X-ray absorptiometry (DXA), bone quality is more of an umbrella term for such factors as bone microarchitecture, mineralization, or bone turnover. It has been estimated, that BMD accounts for approximately 60–85% of bone strength and is, therefore, a good predictor for fracture risk [6].

2. Bone cells and their function

Only 2% of the overall organic bone mass is cells and it is these cells from which the entire structure is built and remodeled. Osteoblasts are cells of approximately 20 μm in diameter with a solitary, excentric nucleus. These cells are of mesenchymal origin and can display an enormous production of osteoid, the organic phase which is subsequently calcified to form mineralized tissue. Osteoblasts require an endosteal, periosteal or trabecular surface for the deposition of osteoid and control the mineralization of this matrix by excessive release of alkaline phosphatase, an enzyme which prepares the osteoid for calcification. As a result of their continuous production of osteoid, the osteoblasts immure themselves and they become osteocytes, a phenotype which cannot divide anymore. These cells are typically oval and 20–60 μm long. They reside in lacunae (approximately 30×10 μm) deep within the mineralized matrix of bone and carry numerous processes (Processus osteocyti; length up to 200 μm and 150 nm thin), which are in contact with processes of other osteocytes or endothelial cells through gap junctions. These processes run in approximately 400 nm thin channels or canaliculi (Canalculi ossis). The osteocyte network is nourished by interstitial fluid flow through these canaliculi and, therefore, diffusion dependent. Deformation of the skeleton by mechanical stress induces pressurization of the interstitial fluid [7]. It is hypothesized that this pressure difference is sensed by bone cells, which express mechanosensitive ion channels [8], mechanosensitive connexin hemichannels [9] and primary cilium as putative mechanosensors [10]. These cells secrete autocrine/paracrine factors impacting bone formation through osteoblasts and bone resorption through osteoclasts and, thereby, bone turnover and remodeling. Bone targeting of the osteocyte network, particularly those cells residing deeper within the bone, will be an exciting challenge in the future, a research field, which has not been systematically established yet. Osteoclasts serve the main function of bone degradation. Osteoclasts are large, polynucleated cells (up to 100 μm) which are rich in lysosomal enzymes and acid phosphatase. At sites of bone resorption, they display a ruffled cell membrane (Limbus microplicatus), which seals of a cavity into which the osteoclast is secreting chloride and hydronium, thereby causing a pH drop and dissolution of the hydroxyapatite [2].

The etiology of osteoporosis is manifold; however, all causes lead to an imbalanced remodeling mechanism of bone, either by decreased activity of osteoblasts or increased activity of osteoclasts or both. As this balance is critically impacted by factors released by the osteocyte network, this third class of mechanoresponsive bone cells play an important role in bone homeostasis and offer some novel and exciting new treatment paradigms targeting signaling molecules released from the osteocyte network.

3. Treatment options of osteoporosis — where would targeting translate into advanced medication?

Current therapeutic intervention in osteoporosis target resorptive events – such as the bisphosphonates (BPs), cathepsin K inhibitors, receptor activator of NF-κB ligand (RANKL) inhibitors, strontium ranelate, calcitonin, or selective estrogen receptor modulators (SERM) – and anabolic events (such as parathormone (PTH) fragments and analogs) and sclerostin (SOST) inhibitors (in clinical phase).

3.1. Anti-resorptive therapy

Oral BPs dominate the osteoporosis market in terms of sales and are prescribed across the whole spectrum of the disease manifestation in spite of the fact that some of these compounds are associated with complicated dosing regimens challenging patient compliance and from a safety perspective by particularly gastric side effects, which can be avoided by using injectable bisphosphonates. These compounds are derivatives of naturally occurring diphosphate carrying a C–P–C backbone, and share a poor oral bioavailability and – for those who contain nitrogen – a strong affinity to mineralized tissues (see Section 5.2.1). BPs reduce osteoclastic activity through inhibition of farnesyl diphosphate synthase which leads to a loss in guanosine triphosphate (GTP) binding proteins. These proteins are key to osteoclastic activity and it is this interference within the mevalonate pathway which halts osteoclastic activity and, therefore, bone resorption [11]. Osteoclasts interfere strongly with osteoblasts and the apoptosis of osteoclasts as a result of bisphosphonate exposure ultimately slows osteoblastic activity and, therefore, bone formation. It is this inherent targeting pattern of BPs to mineralized tissues, which has motivated their use as bone targeting moiety (BTM) when coupled to other drugs (cargo), which has been nicely reviewed before [12]. We address the use of BPs as BTM in Section 5.2.1. The use of some BPs has been clearly connected to osteonecrosis of the jaws, particularly nitrogen-containing BPs. The molecular mechanisms of this adverse event are still a matter of debate, leading to increased bone turnover as the primary mechanism of osteonecrosis. A major risk factor is infections of the jaw and the use of BPs in patients with this morbidity should only be very cautiously used or be avoided. The risk of development of osteonecrosis of the joint seems to be higher after long term use and among other risk factors, dental extraction in elderly multiple myeloma patients has been particularly identified [13,14]. In spite of these adverse events, the BPs demonstrate an overall good tolerability along with good efficacy. This challenges the need for additional targeting for this compound class, *e.g.* by additional decoration with recognition sites for tissue/cell specific epitopes. In addition, the market saturation of this compound class is significant such that new BPs with a more selective targeting pattern beyond of what has already been achieved is probably not leading to new development programs and ultimately medication, more particularly as generic erosion is going to continue with *e.g.* risedronic acid, ibandronate and zoledronic acid running out of patent protection.