Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Emerging therapies in bone metastasis

Lise Clément-Demange[1,2] and Philippe Clézardin[1,2]

Skeletal lesions contribute substantially to morbidity and mortality in patients with cancer. Emerging treatments for metastatic bone disease have arisen from our understanding of the biology of bone metastases. Tumour cells alter the functions of bone-resorbing (osteoclasts) and bone-forming (osteoblasts) cells, promoting skeletal destruction. Drugs that inhibit osteoclast-mediated bone resorption (denosumab, bisphosphonates) are the standard of care for patients with skeletal metastases. In this review, we describe the progress and future directions of novel bone-targeted therapies that not only focus on osteoclasts, but also on osteoblasts and the bone microenvironment.

Addresses
[1] INSERM, UMR 1033, Lyon F-69372, France
[2] Université Lyon-1, Villeurbanne F-69622, France

Corresponding author: Clézardin, Philippe (philippe.clezardin@inserm.fr)

Current Opinion in Pharmacology 2015, **22**:79–86

This review comes from a themed issue on **Musculoskeletal**

Edited by **James A Gallagher** and **R Graham G Russell**

For a complete overview see the Issue and the Editorial

Available online 14th May 2015

http://dx.doi.org/10.1016/j.coph.2015.04.004

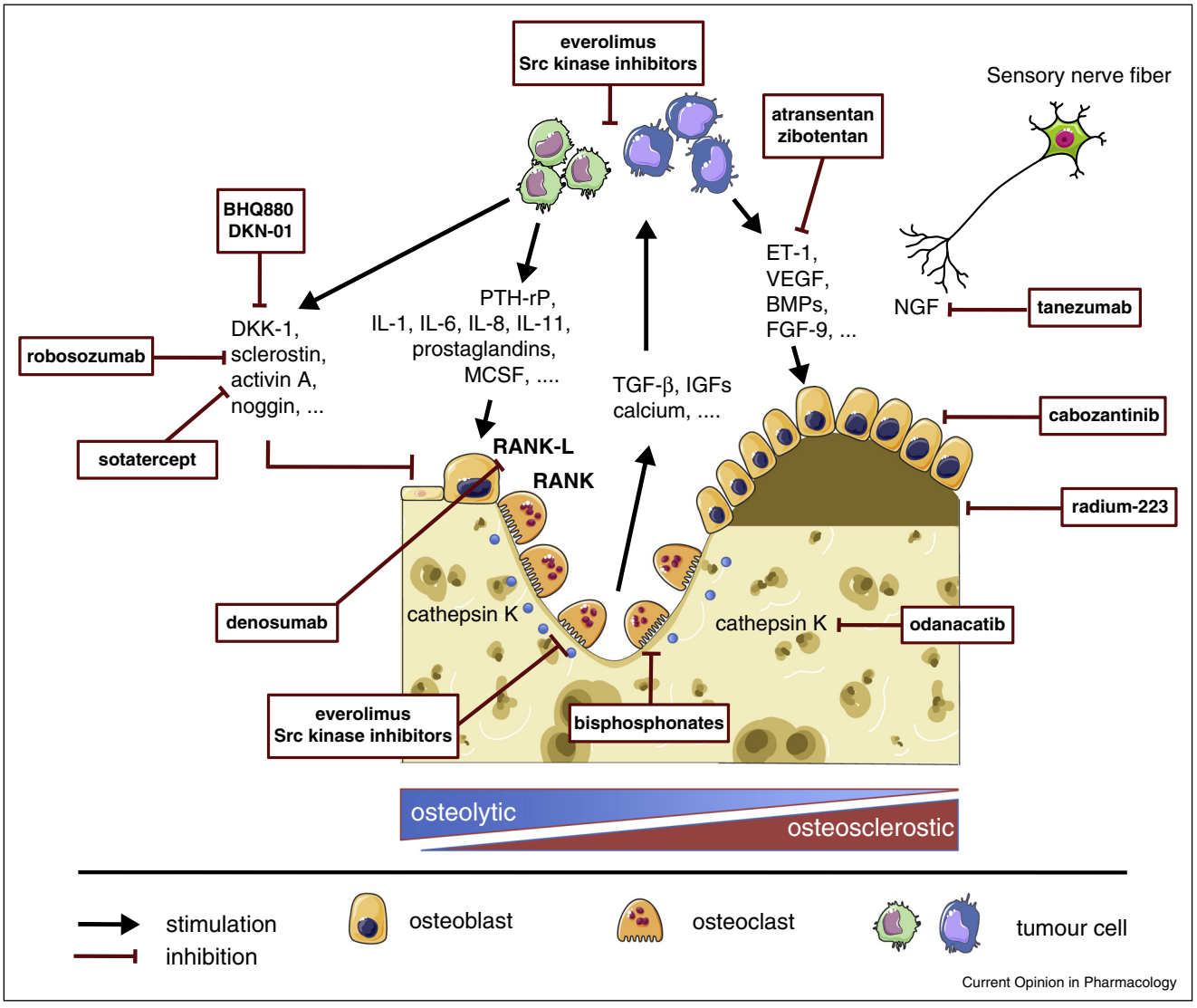
Introduction

Bone disease contributes substantially to morbidity and mortality in patients with cancer. Approximately 70% of patients with myeloma or advanced-stage (stage IV, i.e., metastatic) solid tumours (breast, prostate, lung) are associated with a heavy burden of skeletal disease, with potentially debilitating or life-limiting skeletal-related events (SREs) such as pathological fractures, nerve compression, hypercalcemia, and cancer-induced bone pain [1].

Studies of the biology underlying bone metastasis support the notion that in solid tumours and multiple myeloma, cancer cells alter the functions of bone-resorbing (osteoclasts) and bone-forming (osteoblasts) cells and hijack signals coming from the bone matrix, thereby disrupting the physiological bone remodelling [1]. Indeed, tumour cells residing in the bone marrow secrete factors [parathyroid hormone-related protein, interleukins (IL-6, IL-8, IL-11), prostaglandins, . . .] that stimulate osteoclast activity through the activation of the receptor activator of nuclear factor-κB ligand (RANKL)/RANK pathway, which is the primary mediator of osteoclast-mediated bone resorption [1,2] (Figure 1). Additionally, tumour cells (breast, lung, multiple myeloma) secrete factors [*e.g.*, activin A, dickkopf-1 (DKK-1), sclerostin, noggin] that inhibit osteoblast differentiation and activity [1,2] (Figure 1). This leads to an imbalance between bone resorption and bone formation, resulting in the formation of osteolytic skeletal metastases (Figure 1). Bone metastases may be osteosclerotic (*e.g.*, prostate cancer) or mixed instead, because tumour cells secrete factors [endothelin-1, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-9, bone morphogenetic proteins (BMPs)] that stimulate osteoblast activity [1] (Figure 1). In addition, endothelin-1 and the RANKL inhibitor osteoprotegerin (OPG), which are secreted by tumour cells, inhibit osteoclast activity, thereby contributing to the osteosclerotic feature of cancer-associated bone metastases [1]. As bone is resorbed, growth factors [*e.g.*, transforming growth factor-β (TGF-β) and insulin-like growth factor-I (IGF-I)], that are stored in the bone matrix, are released and stimulate tumour growth [1,2] (Figure 1). Calcium released from bone mineral also stimulates tumour growth through calcium-sensing receptors expressed by tumour cells [1] (Figure 1). The realization that there exists in bone metastasis a cross-talk between bone cells and tumour cells led to the use of inhibitors of osteoclast-mediated bone resorption, such as bisphosphonates and the RANKL inhibitor denosumab, in the treatment of skeletal lesions [2] (Figure 1). These bone-targeted treatments successfully delay the occurrence of bone metastasis and reduce the risk of skeletal complications in patients with malignant bone disease [2]. However, progress in understanding the biology of bone metastases clearly show that not only bone destruction but also inhibition of bone formation is occurring in bone metastases, suggesting that agents which counteract inhibition of osteoblast activity may be of interest in the treatment of bone metastases. Other cell types in the bone marrow microenvironment such as endothelial cells, myeloid cells, immune cells, platelets and sensory nerve fibres are also likely to contribute to the progression of bone metastases and may be promising therapeutic targets [3].

In this review article, we provide an overview of emerging targeted agents that might improve the pharmacologic treatment and prevention of bone metastases. We have classified these agents according to the cellular compartment that they target. Some of these agents are already in clinical development, and are tested in cancer patients with metastatic disease (Table 1).

Figure 1



Present and emerging bone-targeted agents and their respective targets in osteolytic and osteosclerotic bone metastases. Tumour cells secrete osteoclast-stimulating factors as well as factors that inhibit osteoblast activity, leading to the formation of osteolytic lesions. Conversely, tumour cells may promote the formation of osteosclerostic lesions through the production of factors that stimulate osteoblast activity. Bisphosphonates bind to hydroxyapatite and impede osteoclast-mediated bone resorption. Denosumab is a monoclonal antibody that targets RANKL and inhibits osteoclast formation and activity. Both drugs have been approved to treat bone metastases. Several other drugs which target osteoblast activity (BHQ880, DKN-01, sotatercept, robosozumab, cabozantinib), osteoclast activity (odanacatib, everolimus, Src kinase inhibitors), tumour cells in bone (everolimus, Src kinase inhibitors, radium-223) and cancer-associated bone pain (tanezumab) are under development. BMPs: bone morphogenetic proteins; DKK-1: dickkopf-1; ET-1: endothelin-1; FGF-9: fibroblast growth factor-9; IGFs: insulin-like growth factors; IL: interleukin; MCSF: macrophage colony-stimulating factor; PTH-rP: parathyroid hormone-related peptide; RANK: receptor activator of nuclear factor κB; RANKL: RANK ligand; Src: proto-oncogene tyrosine-protein kinase; TGF-β: transforming growth factor-β; VEGF: vascular endothelial growth factor.

Targeting osteoclasts

Cathepsin K inhibitors

Cathepsin K is a lysosomal cysteine protease highly expressed in osteoclasts, which plays a major role in bone resorption [4] (Figure 1). The cathepsin K inhibitor odanacatib decreases bone resorption and maintains bone formation, indicating this compound has an advantage over other antiresorptive agents (bisphosphonates, denosumab) in the treatment of diseases associated with bone loss. In this respect, odanacatib (ODN) is currently investigated in a large phase-III Long-Term ODN Fracture Trial (LOFT) for the treatment of postmenopausal women with osteoporosis [5]. Results regarding its anti-fracture efficacy are expected soon. Pre-clinical experiments