

Highlights of the molecular pharmacology of bone and cancer-related bone diseases

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Over recent years, our understanding of the mechanisms that drive bone disorders has dramatically increased, supported by advances in technology that facilitate the dissection of the cellular and molecular crosstalk that underpins disease pathogenesis. This has translated to the clinic, with new treatment modalities emerging, alongside research efforts to optimise existing therapies. This BJP themed issue focussing on the molecular pharmacology of bone and cancer-related bone diseases arose from a conference held at St Catherine's College in Oxford in 2018 entitled "The 8th International Workshop on Advances in the Molecular Pharmacology and Therapeutics of Bone and other Musculoskeletal Diseases" and the "Cancer and Bone Society 2018 Meeting". The themed issue contains a number of in-depth review articles across a spectrum from basic science through to patient care, all addressing key advances in musculoskeletal research.

Osteoporosis is one of the most prevalent diseases in our society, with a worldwide impact on more than 200 million patients, who suffer from reduced bone mass and fractures. Pharmacological approaches target either bone resorption, bone formation, or both. These different mechanisms of action result in different clinical responses. For example a greater response in BMD is observed in patients with severe osteoporosis receiving treatments that stimulate bone formation such as parathyroid hormone or romosozumab (anti-sclerostin antibody) as compared to anti-resorptives, such as bisphosphonates or denosumab (anti RANK-ligand antibody). The review article by Bente Langdahl provides a comprehensive overview of the currently available osteoporosis treatments and discusses unmet medical

needs and the move towards a personalised or optimised approach to such treatments to achieve maximum benefit (Langdahl, 2020).

For patients with skeletal malignancies, cancer-induced bone disease is a major clinical feature, increasing fracture risk and causing severe bone pain in patients with solid tumour metastases, such as in breast and prostate cancer with bone metastases. In the haematological malignancy, multiple myeloma, the osteolytic bone disease is exacerbated by suppression of bone formation. This has a major clinical impact, since the majority of patients present with bone disease, treatment with anti-resorptives can be effective to prevent further bone loss but is unable to repair existing bone loss. As such, an improved understanding and clinical targeting of osteoblast suppression are imperative. This is elegantly discussed by Marino et al., describing the underlying cellular mechanisms that are dysregulated and current anti-resorptives, followed by a detailed discussion of the potential for bone anabolic agents and novel approaches that are emerging in the preclinical setting and show promise for translation to the clinic (Marino, Petrusca & Roodman, 2019). The challenge of repairing existing bone lesions is a key area within the cancer-induced bone disease, with the potential to have a huge impact on patient quality of life.

One of the key mechanisms driving cancer-induced bone disease is well known to be parathyroid hormone -related protein. This protein is expressed by late-stage cancer cells that upregulate RANKL and drives the osteolytic component of cancer-induced bone disease. Interestingly, more recently, parathyroid hormone-related protein has been found to have multiple roles including a protective effect in early breast cancer and a role in tumour dormancy. Mechanistic studies have identified multiple mechanisms, involving canonical signalling through the parathyroid-1 receptors, and non-canonical, mediated through distinct parathyroid hormone -related protein domains. Martin & Johnson provide an in-depth review of these distinct mechanisms and roles of parathyroid hormone -related protein at different disease stages, so expanding our traditional way of thinking and opening up new avenues for targeting this molecule (Martin & Johnson, 2019). For the majority of patients, bone metastases are ultimately fatal and so increasing our understanding of the mechanisms underlying this metastatic progression is vital to develop new therapeutic approaches. Noncoding RNAs represent one such approach, while they were first identified in the 1990s,

their importance as biological regulators were not recognised until the early 2000s. There is increasing evidence to demonstrate the importance of non-coding RNAs (including long ncRNAs, microRNAs and circular RNAs) in bone remodelling and bone metastasis, as detailed by Puppo et al. (Puppo, Taipaleenmaki, Hesse & Clezardin, 2019) Furthermore, they not only represent potential therapeutic targets but also biomarkers. The ability to predict those patients at greatest risk of fatal bone metastases is currently challenging, and as such, the prognostic potential for noncoding RNAs is incredibly exciting.

Primary bone tumours, such as osteosarcoma, chondrosarcoma and Ewings sarcoma, while rare, have a high morbidity and mortality rate, with treatment largely consisting of surgical resection and chemotherapy. The emergence of anticancer immunotherapy has revolutionised the treatment of many cancers, with increasing evidence for the potential of immunotherapies to target primary bone tumours. Heymann et al. discuss not only the basic science underlying the role of the immune system in such bone tumours but also the clinical evidence. They also highlight the challenges that remain, such as the low immunogenicity of paediatric tumours, providing a comprehensive overview of the rationale for and potential of immunotherapy in primary bone tumours (Heymann, Schiavone & Heymann, 2020).

One of the major clinical features of all bone diseases is that of bone pain, and this is one of the most challenging areas to address. Bisphosphonates are well known as antiresorptive agents, widely used in osteoporosis and cancer-induced bone disease. Interestingly, there is increasing evidence for the potential for bisphosphonates in the treatment of pain, both in animal models and evidence of clinical efficacy. However, the underlying mechanisms and so the potential to exploit this remains unclear. Thomas Tzschentke describes the evidence for anti-nociceptive and analgesic effects of bisphosphonates, with a detailed discussion of potential mechanisms of action (Tzschentke, 2019). Aligned with this, Sliepen et al. investigate nociceptin/orphanin FQ receptor agonists, demonstrating the potential for this system for the treatment of cancer-induced bone pain (Sliepen et al., 2019). Bisphosphonates have been in use for decades for the treatment of osteoporosis and cancer-induced bone disease, and as is evident throughout this editorial, are one of the most widely studied classes of drugs in musculoskeletal research. It is exciting to see their potential being explored in other areas, such as pain and also for improving efficacy of current therapeutic

approaches. The power of bisphosphonates stems at least in part from their bone-homing ability. In contrast, the bone microenvironment is a challenge to other therapies, resulting in drug toxicities or limited efficacies. Combining bisphosphonates with other therapeutic approaches offers the potential to alleviate these challenges, by exploiting the unique bone-homing properties of bisphosphonates. Such drug-design strategies are described by Sun et al. (Sun et al., 2020), raising the exciting potential for bisphosphonates to revolutionise drug-design for bone disease.

Over recent years, there have been many exciting advances in musculoskeletal research. Notably, it has always been the case that this research community maximises new discoveries, with a rapid translation of new ideas and pharmacological approaches towards different diseases, facilitated by collaborative meetings, cross-cutting disciplines, where such ideas are shared and discussed. The future for musculoskeletal disease looks promising, including novel and personalised therapies, effective pharmacological targeting to the bone, and improved treatment of bone disease and pain.

References

- Heymann MF, Schiavone K, & Heymann D (2020). Bone sarcomas in the immunotherapy era. *Br J Pharmacol.* doi:10.1111/bph.14999
- Langdahl BL (2020). Overview of treatment approaches to osteoporosis. *Br J Pharmacol.* doi:10.1111/bph.15024
- Marino S, Petrusca DN, & Roodman GD (2019). Therapeutic targets in myeloma bone disease. *Br J Pharmacol.* doi:10.1111/bph.14889
- Martin TJ, & Johnson RW (2019). Multiple actions of parathyroid hormone-related protein in breast cancer bone metastasis. *Br J Pharmacol.* doi:10.1111/bph.14709
- Puppo M, Taipaleenmaki H, Hesse E, & Clezardin P (2019). Non-coding RNAs in bone remodelling and bone metastasis: Mechanisms of action and translational relevance. *Br J Pharmacol.* doi:10.1111/bph.14836
- Sliepen SHJ, Koriath J, Christoph T, Tzschentke TM, Diaz-delCastillo M, Heegaard AM, *et al.* (2019). The nociceptin/orphanin FQ receptor system as a target to alleviate cancer-induced bone pain in rats: Model validation and pharmacological evaluation. *Br J Pharmacol.* doi:10.1111/bph.14899

Sun S, Tao J, Sedghizadeh PP, Cherian P, Junka AF, Sodagar E, *et al.* (2020). Bisphosphonates for delivering drugs to bone. Br J Pharmacol. doi:10.1111/bph.15251

Tzschentke TM (2019). Pharmacology of bisphosphonates in pain. Br J Pharmacol. doi:10.1111/bph.14799