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BONE DISEASES

# MST1R inhibitor prevents bone osteolysis

Bone osteolysis occurs in patients with metastatic cancer or osteoporosis and can lead to an increased risk of fracture as well as pain. Now, Andrade *et al.* have found that inhibiting macrophage-stimulating protein receptor (MST1R; also known as RON) blocks bone destruction in mice with metastatic breast tumours or that have undergone ovariectomy. An MST1R inhibitor also decreased bone turnover in a phase I clinical trial that included postmenopausal women.

MST1R is a receptor tyrosine kinase that is expressed in osteoclasts and other tissues (including macrophages) and serves as the receptor for macrophage-stimulating protein (MSP; also known as hepatocyte growth factor-like protein). Previously, this group had shown that expression of MSP in mouse mammary tumours led to spontaneous osteolytic bone metastasis.

> “genetic deficiency of MST1R or pharmacological inhibition … protected mice from bone loss”

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To further investigate the role of MSP, Andrade *et al.* studied MST1R-deficient mice. They found that these mice are resistant to osteolysis, including following tumour cell transplantation in immunodeficient mice, which suggests that MST1 has a role in the bone rather than the tumour. Pharmacological inhibition of MST1R by oral gavage with either OSI-296 or BMS-777607 (both of which also inhibit the related receptor, MET) had similar effects. OSI-296, but not BMS-777607, also reduced tumour growth in the bone.

Next, the authors set out to explore the downstream effects of MST1R activation. Denosumab is a receptor activator of nuclear factor κB ligand (RANKL) antagonist that is approved by the US Food and Drug Administration (FDA) to treat bone metastasis and osteoporosis. Stimulation of either RANKL or MST1R results in SRC activation, so the authors investigated whether these pathways overlap. In their model, an anti-RANKL antibody fragment (muRANK-Fc) had effects that were distinct from those of the MST1R inhibitors: although muRANK-Fc decreased osteolysis in mouse tumour models, this treatment was not effective if the tumour cells overexpressed high levels of MSP. In osteoclasts *ex vivo*, both MSP and RANK increased osteoclast survival and activation, but only RANK promoted osteoclast differentiation. Furthermore, MSP and RANK stimulation resulted in the phosphorylation of different tyrosine residues on SRC. So, MST1R and RANKL are likely to activate SRC through different mechanisms.

In ovarectomized mice, a model of osteoporosis, genetic deficiency of MST1R or pharmacological inhibition with BMS-777607 every other day for 28 days protected mice from bone loss.

In a phase I clinical trial of BMS-777607 in patients with cancer, 13 out of 21 individuals treated with BMS-777607 showed decreased levels of cleaved bone-derived collagen in plasma, which is a marker of bone turnover. Approximately two-thirds of these patients had large enough drops to meet Mayo Clinic guidelines for a response to bone antiresorptive therapies. The best results were seen in women, most of whom were over 50 years old and are therefore expected to have increased bone turnover as a result of menopause.

These data suggest that MST1R inhibitors could be used to prevent bone loss in patients with advanced cancers or osteoporosis, possibly in combination with existing treatments, such as RANKL inhibitors. The authors highlight that MSP is also selectively overexpressed in multiple myeloma and lung cancer, so MST1R inhibitors could be particularly useful in those tumour types as well.

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**ORIGINAL ARTICLE** Andrade, K. *et al.* RON kinase: a target for treatment of cancer-induced bone destruction and osteoporosis. *Sci. Transl Med.* **9**, eaai9338 (2017)