RANKLing non-skeletal tumors

By Michael J. Haas, Senior Writer

Research presented by **Amgen Inc.** suggests that inhibiting RANKL could help treat breast and other non-skeletal tumors—thus adding to the range of indications that Prolia denosumab, the company's anti-RANKL antibody, could potentially target.

Receptor activator of NF- κ B ligand (RANKL; TNFSF11) is important in the formation of osteoclasts, which are responsible for bone resorption in osteoporosis. In metastatic cancer, tumor cells can set up a vicious cycle of bone destruction by RANKL-activated osteoclasts, thereby making space in bone tissue for the metastatic tumors to grow and proliferate (see Figure 1, "RANKL's role in bone metastases").

Thus, RANKL-inhibiting therapies are in development to treat osteoporosis and cancers that metastasize to the bone. The most advanced is Prolia, which is under FDA review to treat and prevent postmenopausal osteoporosis and to treat and prevent bone loss due to hormone ablation therapy for breast and prostate cancer.

The antibody, which is partnered with **Daiichi Sankyo Co. Ltd.** and **GlaxoSmithKline plc**, also has completed Phase III testing to prevent bone metastasis-related skeletal complications in patients with breast and prostate cancer, multiple myeloma (MM) and other solid tumors. According to Amgen spokesperson Lisa Rooney, the company expects to file these data with U.S. and EU regulatory agencies in 2Q10.

Prolia also is in Phase III testing to delay the onset of bone metastases in men with prostate cancer and as an adjuvant to chemotherapy to prevent disease recurrence, in the bone or in any other part of the body, in women with early stage breast cancer.

Mounting evidence has suggested that the effects of RANKL and its receptor go beyond the bone and play a role in mammary tumorigenesis, according to William Dougall, scientific director of oncology research at Amgen. "The thrust of our current study was to see whether there was a beneficial effect of inhibiting RANKL on non-skeletal tumors," he said.

First, his team showed that mice overexpressing Rankl developed mammary tumors earlier and in greater numbers than did wild-type controls. Also, Rankl was upregulated in abnormally growing mammary epithelial cells and adenocarcinomas in the wild-type models of mammary cancer compared with levels in healthy controls.

Wild-type models of mammary cancer treated with a RANKL-inhibiting fusion protein called RANK-Fc had delayed tumorigenesis and fewer tumors than did animals receiving either Zometa zoledronic acid or no treatment.

Prolia denosumab, a human mAb targeting RANKL from **Amgen Inc.** (NASDAQ:AMGN) and partners **Daiichi Sankyo Co. Ltd.** (Tokyo:4568; Osaka:4568) and **GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), completed Phase III to prevent bone metastasis-related skeletal complications in patients with breast and prostate cancers, multiple myeloma (MM) and other solid tumors, and is in Phase III to delay the onset of bone metastases in prostate cancer patients and to prevent recurrence of primary tumors and/or metastasis in breast cancer patients. ALX-0141, a nanobody against RANKL from **Ablynx N.V.** (Euronext:ABLYX), in Phase I to treat osteoporosis and bone disorders. CEP-37251, a decoy receptor targeting RANKL from **Cephalon Inc.** (NASDAQ:CEPH), in preclinical testing to treat bone cancer.

Figure 1. RANKL's role in bone metastases. Tumor cells can stimulate signaling between receptor activator of NF- κ B ligand (RANKL; TNFSF11) and its receptor, tumor necrosis factor (TNF) receptor superfamily member 11a (TNFRSF11A; RANK; CD265), to induce a vicious cycle of bone destruction that gives metastatic bone tumors room to grow.

Metastasizing tumor cells (TC) can secrete growth factors (GFs) and bone morphogenetic proteins (BMPs) that [a] induce differentiation of osteoblasts, which in turn express RANKL (♦). RANKL [b] signals RANK (Y) on osteoclasts to activate [c] their capacity to destroy bone cells. Tumor cells [d] take up residence in the resulting bone lesions and [e] perpetuate the cycle of bone destruction as the metastatic tumor grows.

Lastly, the team showed that fusion protein-treated models had lower bone resorption and higher bone mineral density than untreated controls. Animals receiving Zometa had similar reductions in bone resorption.

The team used RANK-Fc as a substitute for Prolia, which does not inhibit mouse Rankl. **Novartis AG's** Zometa, an IV bisphosphonate osteoclast inhibitor, is approved in the U.S., EU and elsewhere to treat bone metastases, bone complications in cancer patients, and osteoporosis.

Amgen presented the data last month at the American Association for Cancer Research (AACR) meeting in Washington, D.C.

Although the precise mechanism of Prolia action in breast cancer is unknown, Dougall said Australian and Japanese researchers may have provided clues in a newly published report. The April paper in *Nature* showed that RANKL promoted the proliferation of mammary stem cells in response to signaling by estrogen and progesterone—hormones associated with increased risk of breast cancer.¹

“While that study included no cancer data, the speculation is that RANKL inhibitors could treat breast cancer” by blocking hormone-induced mammary stem cell proliferation, he said. “We know that mammary stem cells are a likely target to block mammary tumorigenesis, so it would be logical to link the *Nature* findings with RANKL inhibition” to reduce tumorigenesis—a link that Dougall said Amgen might want to investigate in future studies.

Beyond bone and breast

Amgen is now testing the effects of RANKL inhibition in more mammary tumor models, and Dougall said the company also plans to investigate whether RANKL inhibition affects non-skeletal tumors besides breast tumors.

“There is some published evidence in cancer cell lines that other tumor types respond to RANKL signaling” for growth and survival, he told *SciBX*. For example, RANKL has been shown to increase the invasiveness of prostate tumor cell lines.

Dougall added: “We wouldn’t want to limit ourselves to just prostate cancer, but it’s a likely first step.”

Amgen declined to disclose the IP status of the findings reported in its AACR presentation.

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REFERENCES

1. Asselin-Labat, M.-L. *et al.* *Nature*; published online April 11, 2010; doi:10.1038/nature09027

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