Restoring bone while attacking cancer

By Lauren Martz, Staff Writer

Harvard researchers have shown that blocking activin A induces osteoblast formation, providing a strategy to counter bone loss in a variety of indications including cancer and metastasis.¹ The research also provides a rationale for partners **Acceleron Pharma Inc.** and **Celgene Corp.** to develop their soluble activin receptor decoy for the treatment of osteolytic lesions in multiple myeloma.

Osteolytic bone disease occurs when there is an imbalance between bone-resorbing osteoclasts and bone-producing osteoblasts in the marrow, leading to bone loss. Tumor cells activate osteoclasts when they home to the bone marrow, making bone loss a characteristic of many cancers.²

To date, therapies to treat osteolytic bone disease have focused on antiresorptive agents to slow bone loss. Now, in a paper published in the *Proceedings of the National Academy of Sciences*, Noopur Raje and colleagues suggest that intervening in the activin A pathway goes a step further by stimulating bone regrowth rather than just slowing bone loss.

Raje is assistant professor of medicine at **Harvard Medical School** and director of the Multiple Myeloma Program at **Massachusetts General Hospital**.

“What this team has studied in the paper has been talked about for a long time,” said Jasbir Seehra, CSO, SVP and cofounder of Acceleron, which provided the compound used in the Harvard study. “The question has been: when you target the tumor microenvironment to prevent cancer, can you improve bone quality as well?”

Seehra thinks the Harvard team has answered the question in the affirmative.

“This work shows what the effect of blocking activin A is on the bone microenvironment. It not only forms a hostile environment for the tumor to grow but also repairs the bone that the cancer has damaged,” he told *SciBX*.

Bone loss RAP

Acceleron contributed RAP-011 for the work in the *PNAS* paper. The compound is a fusion protein combining the activin-binding portion of activin receptor type 2a (ACVR2A) with a soluble, murine IgG fragment. Previous work had shown that RAP-011 promoted bone

growth in a mouse model of osteoporosis.³

Raje and her team hypothesized that activin A, a member of the transforming growth factor- β (TGFB; TGF β) family of cytokines, might also play a role in cancer-related bone disease. The team set out to determine whether activin A was specifically involved in multiple myeloma (MM)-associated osteolytic bone disease.

First, in a cytokine screen of bone marrow samples, the researchers showed that activin A levels were significantly higher in MM patients with more than one osteolytic lesion than in patients with one or fewer such lesions ($p=0.03$).

In culture, activin A was specifically secreted by bone marrow cells from MM patients compared with osteoclasts, osteoblasts or MM cells from the same patients. Also, coculture of bone marrow stromal cells (BMSCs) from healthy controls with MM cells stimulated activin A secretion, suggesting that it is contact with the cancer cells that leads to secretion of the cytokine.

Further, the team showed that activin A from BMSCs induced MADH (mothers against decapentaplegic homology; SMAD) phosphorylation, resulting in inhibition of *distal-less homeobox 5* (DLX5) expression and osteoblast differentiation. Directly inhibiting DLX5 also inhibited osteoblast differentiation. This highlighted the link between activin A and bone loss.

In MM-derived BMSCs, treatment with an activin A-neutralizing antibody increased bone mineralization, whereas treatment with RAP-011 restored osteoblast differentiation.

In a mouse model of MM-related bone disease, RAP-011 restored the ratio of bone volume to tissue volume to near normal and increased osteoblast number compared with no treatment.

In the treated animals, the number of bone-resorbing osteoclasts, the amount of MM cell

growth and the tumor cell burden in the bones were decreased, suggesting this strategy might be particularly promising for MM-associated bone disease.

“Researchers in the field have known that activin A is elevated in bone disease, and there has been a lot of data on the effect in osteoclasts but not osteoblasts,” Raje said.

“What has been demonstrated here is that this is a bone anabolic agent—one that actually grows your bones,” said Acceleron’s Seehra. “In diseases such as multiple myeloma, the machinery to generate new bone has been taken apart. But, by targeting activin, the osteoblasts are actually targeted; bone is formed.”

Acceleron’s ACE-011 is the humanized version of RAP-011. According to Seehra, the Harvard work “shows that ACE-011 has a very novel mechanism that has been sought after for some time.”

He said Acceleron was involved in discussions about the studies but the experiments were conducted exclusively in Raje’s lab and the company did not contribute financially.

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**—Jasbir Seehra,
Acceleron Pharma Inc.**

Developmental program

Preliminary data from a Phase IIa Russian trial of ACE-011 in MM patients with osteolytic lesions were presented at the American Society of Hematology conference last November, showing that the compound was well tolerated and that it significantly increased biomarkers of bone formation, improved skeletal metastases, decreased bone pain and had antitumor activity.

Acceleron completed a Phase I study of ACE-011 in osteoporosis in 2008, when it entered its partnership with Celgene.

Under the deal, Acceleron is responsible for preclinical and clinical testing through the two ongoing Phase II trials. All future studies will be conducted by Celgene.

In addition to the osteolysis trial, the biotechs have ACE-011 in Phase II testing in the U.S. and Russia to treat chemotherapy-induced anemia in metastatic breast cancer.

Seehra told *SciBX* that Celgene is planning another clinical study in MM and that the company is in discussions with regulatory agencies to plan the trial.

On the preclinical front, Raje told *SciBX* her next plan is to test RAP-011 in combination with other antimyeloma agents in order to determine the best clinical regimen.

If the studies pan out, activin A blockers could represent a three-pronged strategy against cancer: they could promote bone regrowth after cancer-induced damage, prevent metastatic cancer cell growth in bone in the first place and help reduce chemotherapy-induced anemia (CIA).

Moreover, although the *PNAS* paper provides support for activin A inhibition in MM, Seehra thinks the work could expand the strategy to other cancers.

“With other cancers, including breast cancer, the balance between

bone formation and resorption is also out of whack,” he said. “In cancers such as breast cancer, ACE-011 has obvious potential because the tumors metastasize to the bone, so it would affect tumor growth there.”

Based on this, Seehra said Acceleron and Celgene are considering ACE-011 for other indications in oncology in which there is metastasis to the bone.

He also thinks there might be potential for activin A disruption in solid tumors that don't metastasize to bone, because the cytokine might play a role in cancer cell proliferation as well.

Looking elsewhere in the pathway, Raje thinks DLX5 may be a new target in bone disease, because her team has “demonstrated at the molecular level that activin A leads to bone loss through DLX5 inhibition.” Intervening at this downstream target could provide even more specific effects against bone loss.

Raje said the Harvard team's work is not patented.

Martz, L. *SciBX* 3(10); doi:10.1038/scibx.2010.298

Published online March 11, 2010

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COMPANIES AND INSTITUTIONS MENTIONED

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