SEMA4D in osteoporosis

By Lauren Martz, Staff Writer

Researchers from the **Tokyo Medical and Dental University** have shown that inhibition of the protein semaphorin 4D increases bone formation in a mouse model of osteoporosis.¹ By directly promoting bone formation, a semaphorin inhibitor could be more effective than existing osteoporosis therapies that work by preventing bone loss.

The semaphorins are a large class of membrane proteins that play a role in the CNS as axon guidance molecules. Semaphorins also have been implicated in immune cell function, tumor progression and tumor angiogenesis.²⁻⁴

In addition, studies have suggested that one of the semaphorins, semaphorin 4D (SEMA4D), plays a role in signaling between osteoclasts and osteoblasts,⁵ the two cell types that drive bone resorption and bone formation.

Thus, Hiroshi Takayanagi and colleagues at the Tokyo Medical and Dental University hypothesized that targeting SEMA4D could have a therapeutic effect in osteoporosis, which is caused by an imbalance in the activity of osteoclasts and osteoblasts. Takayanagi is a professor in the Department of Cell Signaling.

The researchers first looked at semaphorin expression in the osteoclasts and osteoblasts of healthy mice and found that *Sema4d*

levels were greater in osteoclasts than levels of other semaphorin family members.

Based on that finding, the researchers created *Sema4d* knockout mice to better understand the function of the protein in bone remodeling. In those animals, bone volume, trabecular thickness and bone strength were higher than those in wild-type mice, suggesting that the presence of *Sema4d* in osteoclasts serves to suppress bone formation.

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—Atsushi Kumanogoh,
Osaka University Graduate School
of Medicine

Subsequent mouse studies fleshed out a mechanism: osteoclast-derived *Sema4d* binds its receptor, plexin B1 (PLXNB1), on osteoblasts, which then decreases osteoblast motility and ultimately inhibits bone formation (see Figure 1, “SEMA4D released by osteoclasts blocks osteoblast formation”).

The real question for the researchers was whether blocking *Sema4d* would trigger bone formation and treat osteoporosis. In an ovariectomized mouse model of postmenopausal osteoporosis, an

Figure 1. SEMA4D released by osteoclasts blocks osteoblast formation. Whereas most osteoporosis drugs on the market work by curbing the destruction of bone, inhibiting semaphorin 4D (SEMA4D) could go a step further and promote bone growth.

SEMA4D is expressed on osteoclasts as a transmembrane protein, which is released upon activation by proteolytic cleavage [a]. Active SEMA4D binds plexin B1 (PLXNB1) on the osteoblast surface [b]. PLXNB1 forms a complex with HER2 (EGFR2; ERBB2; neu), causing ERBB2 autophosphorylation and activation. ERBB2 activation then causes PLXNB1 phosphorylation (P).

Rho guanine exchange factors (RhoGEFs) bind to and are activated by phosphorylated PLXNB1 [c]. RhoGEFs activate Ras homolog gene family member A (RHOA), which induces RHOA-Rho-associated coiled-coil containing protein kinase (ROCK) signaling [d]. The activated RHOA-ROCK pathway inhibits phosphorylation of insulin receptor substrate 1 (IRS1) by the insulin receptor (INSR), which prevents downstream synthesis of insulin-like growth factor-1 (IGF-1) and ultimately prevents osteoblast differentiation and proliferation [e]. Activated proteins are indicated by an asterisk.

anti-Sema4d mAb protected against bone loss by promoting bone formation compared with saline control. The antibody was given both prophylactically and therapeutically.

Results were published in *Nature Medicine*. The paper also included researchers from **The University of Tokyo**, the **Mount Sinai School of Medicine** and **The University of Western Australia**.

“Existing strategies to treat bone loss are indirect—they suppress functions of osteoclasts, which absorb bone, resulting in increased bone mass,” said Atsushi Kumanogoh, professor and chair of the Department of Respiratory Medicine, Allergy and Rheumatic Diseases at the **Osaka University Graduate School of Medicine**. By contrast, he said, blocking SEMA4D promotes the activity of osteoblasts, which form bones, directly increasing bone mass. “Therefore, it is expected that blocking SEMA4D would be a direct and efficient way to treat bone loss.”

The only marketed osteoporosis drug that acts by increasing bone formation rather than preventing bone loss is parathyroid hormone (PTH). **Eli Lilly and Co.** markets Forteo teriparatide, an injectable recombinant PTH fragment.

Takeda Pharmaceutical Co. Ltd.’s **Nycomed** subsidiary markets Preotact recombinant PTH (NPSP558) in Europe. The hormone is in registration in the U.S. under the name Preos by **NPS Pharmaceuticals Inc.**, which developed the drug and licensed rights to Nycomed.

Good to the bone

Takayanagi said his team plans to study anti-SEMA4D antibodies in arthritis and bone metastasis. He added that the researchers will look closely at any side effects related to the immune system.

“SEMA4D plays important roles in the immune system, and a lack of SEMA4D results in immunodeficiency. Therefore, too much blocking of SEMA4D may affect the immune system,” said Takayanagi.

He noted that SEMA4D is recognized by a different receptor, CD74, in immune cells than in osteoblasts, which have PLXNB1. “It may be a good strategy to develop antibodies or small molecules that specifically block the interaction between SEMA4D and plexin B1,” he said.

Takayanagi told *SciBX* that the Tokyo Medical and Dental University has filed a patent application for bone-forming agents targeting

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SEMA4D and PLXNB1. The IP is available for licensing.

Vaccinex Inc. has a humanized anti-SEMA4D mAb in Phase I testing in cancer, and the company plans to begin an additional Phase I study in multiple sclerosis (MS) next year.

“The Vaccinex anti-SEMA4D antibody has been shown to have potent anti-inflammatory as well as antiangiogenic and antimetastatic activity in animal disease models,” said

President and CEO Maurice Zauderer. “Extending development to osteoporosis is an interesting opportunity, which, because of the need to score relatively low-frequency bone fractures as the major clinical endpoint, would be a major undertaking.” He said that based on the endpoints, a large clinical trial would be required in order to accrue a significant number of events.

Zauderer said the company does not have current plans to move into osteoporosis.

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COMPANIES AND INSTITUTIONS MENTIONED

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Mount Sinai School of Medicine, New York, N.Y.
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