Oncostatin's LIFR sentence

By Steve Edelson, Executive Editor

A key challenge in developing osteoporosis therapies that actually promote bone growth—most marketed drugs stop bone loss—is uncoupling the tightly related processes of bone formation and resorption. Now, a group of Australian researchers has found a ligand, oncostatin M, that can elicit bone formation when it binds to a receptor called LIFR or bone resorption when it binds to another receptor called OSMR.¹

The challenge will be to develop small molecules that are selective enough to agonize the interaction between oncostatin M (OSM) and leukemia inhibitory factor receptor- α (LIFR; CD118) without affecting binding between OSM and oncostatin M receptor (OSMR).

OSM is a cytokine that signals through gp130, a pathway with a known role in bone remodeling.² But of all the cytokines that signal through gp130, OSM is unique because of its subsequent bimodal signaling through either LIFR or OSMR³ (see **Figure 1**, “The role of oncostatin M in bone formation”).

“We’ve had a long-standing interest in the cytokine signals of gp130,” said Natalie Sims, a senior research fellow in the bone, joint and cancer unit at **St. Vincent’s Institute**. “Oncostatin M has been known to exist in osteoblasts for a long time,” but the local role of OSM in osteoblast

and osteoclast differentiation has been muddled by the cytokine’s dual signaling.

The first step for Sims’ team was generating *Osmr* knockout mice. Previous studies have shown that mouse *Osm*, unlike human OSM, acts predominantly through *Osmr*.⁴ Thus, the researchers were surprised when they treated the knockout animals with mouse *Osm* and actually saw increases in bone formation, which suggested that mouse *Osm* was also interacting with *Lifr*.

They concluded that agonizing the specific interaction of OSM with LIFR could be a therapeutic approach to treat osteoporosis.

Additional experiments fleshed out OSM’s mechanisms. Cell culture studies showed that when OSM acted through OSMR, it stimulated osteoclast formation by triggering the production of receptor activator of NF- κ B ligand (RANKL). In contrast, when OSM acted through LIFR, it inhibited the production of sclerostin, a known inhibitor of bone formation.

The results were published in *The Journal of Clinical Investigation*.

“LIFR signaling was not expected to happen with mouse *Osm*,” noted Sims, who was corresponding author on the paper. “But it was happening, and the particular downstream gene being affected was sclerostin, which is known to be osteoblast specific and is a drug target that large pharma are looking at.”

Amgen Inc. and **UCB Group** are co-developing AMG 785 (CDP7851), a humanized antibody against sclerostin.

The LIFR side

The Australian team’s findings suggest that OSM’s activity through LIFR can promote bone formation without any compensatory increases in bone resorption. Thus, OSM could be a welcome addition to the small pool of osteoporosis targets involved in bone growth.

Figure 1. The role of oncostatin M in bone formation. Australian researchers have shown that oncostatin M (OSM) is unique among osteoporosis targets in that the cytokine’s effects on bone growth are independent of its effects on bone resorption. Normally the processes are tightly coupled, but OSM is different because it interacts with two receptors and elicits different effects depending on which receptor it binds. When OSM binds to oncostatin M receptor (OSMR), the result is stimulation of receptor activator of NF- κ B ligand (RANKL) production and consequent osteoclast formation [a]. In contrast, when OSM binds to leukemia inhibitory factor receptor- α (LIFR; CD118), the result is bone growth due to the inhibition of sclerostin [b]. Developing an OSM agonist that only interacts with LIFR and not OSMR could provide a potential therapeutic strategy for osteoporosis.

“The osteoporosis space has probably gone as far as it can with inhibiting osteoclasts—we need bone-formation targets,” said Sims. “It’s quite exciting that one molecule can affect resorption and formation separately—the whole principle of osteoclast and osteoblast activity being tied together has been a huge hurdle for bone-growing treatments.”

Sims’ group now needs to answer two main questions. The first, she said, is whether it’s possible to agonize OSM-LIFR signaling without a similar upregulation of OSM-OSMR signaling.

Brian MacDonald, CEO of bone disorder company **Zelos Therapeutics Inc.**, said generating such small molecules could be a major obstacle.

“The idea of developing a biased ligand—an agonist of oncostatin M that bound fully to one receptor and not at all to another—is going to be a tremendously challenging drug discovery approach,” he said. “You can configure the screens reasonably well but finding a compound that does one and not the other is going to be hard. And on top of that you have to consider bioavailability and safety.”

“A crystal structure of LIFR with oncostatin M hasn’t been resolved, and that needs to happen next” to see whether it’s possible to produce selective small molecule agonists of OSM-LIFR, Sims told *SciBX*. She added that her group is collaborating with **The Walter and Eliza Hall Institute of Medical Research** to generate and study the crystal structures.

The second question, Sims said, is whether agonizing OSM-LIFR signaling would have any benefit over direct antagonism of sclerostin.

MacDonald said that’s an important issue as well, given that there are

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sclerostin antagonists in the clinic.

“There might be interest in starting up a drug discovery effort around quickly getting a compound that” agonizes OSM-LIFR but not OSM-OSMR, he added.

“It sounds great at the beginning but at the end you’re faced with a 6,000-patient fracture outcome study—somebody has to pay for that,” said MacDonald, so there needs to be significant differentiation compared with compounds on the

market or in development.

Sims said the findings published in *JCI* are neither patented nor licensed.

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COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
St. Vincent’s Institute, Melbourne, Victoria, Australia
UCB Group (Euronext:UCB), Brussels, Belgium
The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia
Zelos Therapeutics Inc., West Conshohocken, Pa.