

 BONE DISEASES

Dual sclerostin–DKK1 antibody outperforms monotherapy

The Wnt antagonist Dickkopf-1 (DKK1) is part of a negative feedback mechanism that limits the effect of sclerostin inhibition on bone mass accrual, according to new research published in *Nature Communications*. The findings could explain the declining bone-forming activity of sclerostin antibodies observed during chronic monotherapy.

DKK1 expression was measured in whole-bone lysates from sclerostin-deficient mice and mature ovariectomized rats treated with a sclerostin antibody. In both models, DKK1 mRNA and protein levels were increased compared with controls. To test if simultaneous inhibition of sclerostin and DKK1 could increase bone formation and mass beyond that

of either monotherapy alone, ovariectomized rats were subcutaneously administered DKK1 and sclerostin antibodies, alone and in combination, twice weekly for 5 weeks. Combination therapy resulted in greater increases in BMD in the leg and at the lumbar spine than either monotherapy alone. Moreover, co-inhibition of both Wnt antagonists improved fracture healing in rats with a femoral closed fracture.

The team next engineered a bispecific antibody that targets both sclerostin and DKK1. Compared with either monotherapy alone, this bispecific antibody increased bone mass and strength in mice, improved fracture repair in rats and increased levels of bone formation markers in

non-human primates. Importantly, the new antibody had a similar pharmacokinetic profile to the parental sclerostin antibody that is in late-stage clinical trials.

Commentating on the study, lead investigator Monica Florio says “a bone anabolic agent (such as the bispecific antibody) that can also promote healing of fractures could have far-reaching consequences for patients with osteoporosis who have or are at risk of fractures, and for patients who have fractures that fail to heal.”

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ORIGINAL ARTICLE Florio, M. *et al.* A bispecific antibody targeting sclerostin and DKK-1 promotes bone mass accrual and fracture repair. *Nat. Commun.* 7, 11505 (2016)