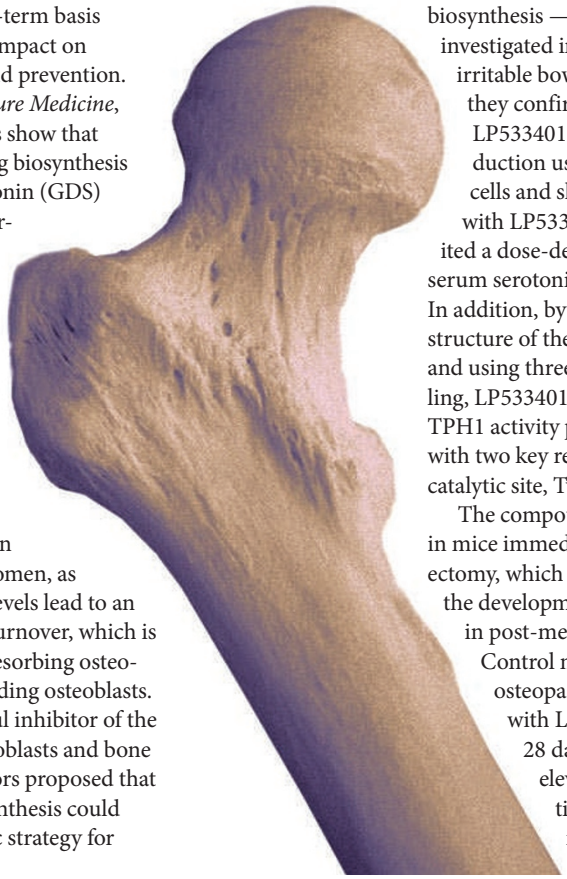
OSTEOPOROSIS

Serotonin biosynthesis block builds bone

Nearly all current drugs for osteoporosis act by inhibiting the resorption of bone, and novel agents that could safely increase bone formation on a long-term basis could have a major impact on disease treatment and prevention. Now, writing in *Nature Medicine*, Ducy and colleagues show that specifically inhibiting biosynthesis of gut-derived serotonin (GDS) can increase bone formation and prevent or reverse this disease in rodents.

Osteoporosis is characterized by decreased bone density and strength, leading to an increased risk of fracture. It is most prevalent in post-menopausal women, as reduced oestrogen levels lead to an imbalance in bone turnover, which is mediated by bone-resorbing osteoclasts and bone-building osteoblasts. As GDS is a powerful inhibitor of the proliferation of osteoblasts and bone formation, the authors proposed that blocking GDS biosynthesis could be a new therapeutic strategy for osteoporosis.



To test this hypothesis, they used LP533401, a small-molecule inhibitor of tryptophan hydroxylase 1 (TPH1) — the initial enzyme in GDS biosynthesis — that is currently being investigated in clinical trials for irritable bowel syndrome. First, they confirmed the capacity of LP533401 to inhibit GDS production using TPH1-expressing cells and showed that mice fed with LP533401 for 3 days exhibited a dose-dependent decrease in serum serotonin concentration. In addition, by analysing the crystal structure of the enzymatic domain and using three-dimensional modelling, LP533401 was found to inhibit TPH1 activity partly by interacting with two key residues near the catalytic site, Tyr235 and Phe241.

The compound was then assessed in mice immediately after ovariectomy, which provides a model for the development of osteoporosis in post-menopausal women. Control mice developed an osteopaenia, whereas mice fed with LP533401 once daily for 28 days exhibited a major elevation in bone formation parameters, resulting in a higher bone mass. Furthermore, the compound rescued established osteopaenia in mice that were left untreated for 2 or 6 weeks following ovariectomy.

The authors next compared LP533401 to parathyroid hormone (PTH), which is the only current treatment capable of stimulating bone synthesis and reversing osteoporosis. However, PTH must be injected daily and can only be used for 2 years. Ovariectomized rats were allowed to develop a severe osteopaenia over 3 or 12 weeks and then given either oral LP533401 or high-dose PTH injections for 4 weeks. Like PTH, LP533401 fully rescued the osteopaenia, increased osteoblast number and bone formation rate. LP533401 also increased the mass of load-bearing long bones, but not as efficiently as PTH, although bone integrity, architecture and quality were similarly restored.

Importantly, LP533401 did not affect brain serotonin content in these experiments — which is crucial as brain-derived serotonin and GDS oppositely influence bone formation — nor did it exert any adverse effects on the gastrointestinal tract or on haemostasis. It therefore seems that inhibitors of GDS synthesis could have the potential to become a new class of anabolic drugs for osteoporosis.

Sarah Crunkhorn

ORIGINAL RESEARCH PAPER Yadav, V. K. *et al.* Pharmacological inhibition of gut-derived serotonin synthesis is a potential bone anabolic treatment for osteoporosis. *Nature Med.* **16**, 308-312 (2010)
FURTHER READING Liu, Q. *et al.* Discovery and characterization of novel tryptophan hydroxylase inhibitors that selectively inhibit serotonin synthesis in the gastrointestinal tract. *J. Pharmacol. Exp. Ther.* **325**, 47–55 (2008)