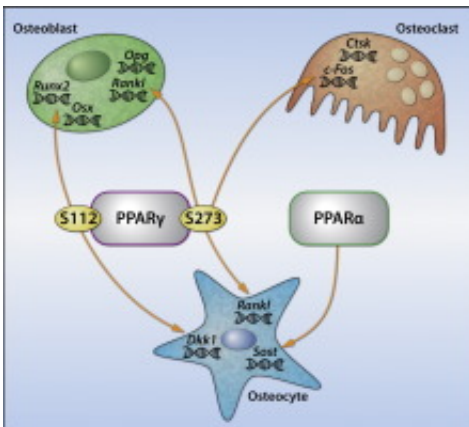


Study suggests new drug candidate could treat both type 2 diabetes and bone loss

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Credit: *EBioMedicine*

In addition to its more obvious ills, type 2 diabetes is a condition closely associated with bone fractures, increasing the risk of fractures twofold. To make matters worse, certain anti-diabetic drugs further increase this risk, particularly in postmenopausal women, severely limiting their treatment options.

A new study, co-led by Patrick R. Griffin, a professor on the Florida campus of The Scripps Research Institute (TSRI), and B. Lecka-Czernik, a professor at the University of Toledo, has shown that a new class of drug candidates developed at TSRI increases [bone](#) mass by expanding bone formation (deposition of new bone) and bone turnover (a normal process of replacement of old bone). A proper balance of

these two processes is critical to healthy bone maintenance), and this balance is frequently negatively affected in diabetic patients.

The result is a new dual-targeting drug candidate—or, as Griffin describes, "one drug addressing multiple therapeutic indications"—that could treat both diabetes and [bone disease](#). The compound has been referenced as "SR10171."

The study was published recently online ahead of print by the journal *EBioMedicine*.

Diabetes affects more than 29 million people in the United States, according to a 2012 report from the American Diabetes Association. Between 2010 and 2012, the incidence rate was about 1.7 to 1.9 million per year, and in 2013, estimated direct medical costs of the disease were \$176 billion.

Over the past decade, Griffin and his colleague, TSRI Associate Professor Theodore Kamenecka, have focused on the details of molecules that increase sensitivity to insulin (a hormone that regulates blood sugar). Using newly discovered information, the researchers made significant advances in developing a family of drug candidates that target a receptor known as peroxisome proliferator-activated receptors gamma (PPAR γ), a key regulator of stem cells controlling [bone formation](#) and [bone resorption](#) and a master regulator of fat.

Anti-diabetic drugs known as glitazones (TZDs) target the PPAR γ protein, but that interaction leads to severe bone loss and increased fractures. Stem cells in the [bone marrow](#) can differentiate either into [bone cells](#) or fat cells, and the glitazones drive them to fat at the expense of bone.

But SR10171 is designed to avoid this troubling outcome. In animal

models treated with the compound, fat formation in the bone marrow was successfully blocked independent of their metabolic state (healthy or diabetic).

"Using structural biology techniques and rational design synthetic chemistry, SR10171 was constructed to engage the PPAR γ protein in a unique way possessing an optimal balance with the receptor's other family member, PPAR α , to treat diabetes and, at the same time, improve [bone health](#)," Griffin said. "This targeted polypharmacological approach demonstrates that the target isn't the problem if you target it correctly."

The compound increases bone mass by protecting and increasing the activity of bone cells in various stages of normal bone maintenance, utilizing mechanisms that overlap those that regulate whole-body energy metabolism.

"SR10171 improves [bone mass](#) regardless of body mass index, normal to obese," Griffin added. "So you could use such a drug to treat osteoporosis whether patients are diabetic or not."

More information: L.A. Stechschulte et al. PPAR γ Post-translational Modifications Regulate Bone Formation and Bone Resorption, *EBioMedicine* (2016). [DOI: 10.1016/j.ebiom.2016.06.040](https://doi.org/10.1016/j.ebiom.2016.06.040)

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