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Losartan reduces circulating TGFb and CTX and increases vertebral bone mass in the OIM mouse

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Background
Losartan is an angiotensin II receptor type 1 (AT1) antagonist. Losartan reduces circulating TGFb concentrations in a variety of myopathic models. We hypothesised that losartan administration to the murine osteogenesis imperfecta model OIM would result in lower circulating TGFb and CTX (bone resorption marker) and increase bone mass.

Methods
All procedures were approved by the UConn Health Institutional Animal Care and Use Committee and performed in an AAALACi accredited facility. OIM mice were obtained from Jackson Labs (Bar Harbor, ME) on a mixed background (B6C3Fe *a*/*a*-*Col1a2*^{oim}/J) for Study 1 and then rederived onto a pure C57BL6 background for Study 2.
In study 1 OIM mice were exposed to 0g/l, 0.6g/l and 1.2g/l in drinking water. At sacrifice, blood was taken to measure TGFb and CTX. In Study 2, OIM mice were exposed to either 0g/l or 0.6g/l losartan for 8 weeks; blood and vertebral bodies were taken at sacrifice.

Results
In Study 1, 4 weeks' losartan at 0.6g/l, but not 1.2g/l, was associated with a significant reduction in TGFb (ng/ml): losartan 0g/l, 79.2 (14.6); 0.6g/l, 60.0 (18.6) p=0.0440 vs 0g/l; 1.2g/l, 82.1 (18.7); and in CTX (ng/ml): Losartan 0g/l, 275.9 (100.2); 0.6g/l, 157.2 (128.2) p=0.0205 vs 0g/l; 1.2g/l, 263.1 (80.7).
In Study 2, 8 weeks' losartan treatment at 0.6g/l vs 0g/l was associated with significant differences in L3 vertebral body BV/TV%; 63.7 (40.0) vs 10.0 (2.0) p=0.0215; Tb. N. 0.019 (0.003) vs 0.014 (0.003) p = 0.0158; Tb. Sp. 17.6 (17.4) vs 46.4 (5.3) p=0.0085; and Tb. Th 33.1 (20.8) vs 6.9 (0.2) p=0.0278. CTX and TGFb measured at 8 weeks were not significantly different between treated and control mice.

Discussion
Losartan 0.6g/l reduced bone turnover and TGFb at 4 weeks and increased vertebral trabecular bone mass at 8 weeks. The lack of difference in CTX and TGFb at 8 weeks suggests earlier reductions in bone turnover, resulting in increased retention of trabecular bone, are carried through to 8 weeks of age when turnover is intrinsically lower in both treated and untreated animals. Further studies are needed to clarify the biological mechanisms and pathways involved.