Alpha-1 Antitrypsin Inhibits Cathepsin k and Osteoclastic Bone Mineral Resorption In Vitro

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Purpose
Osteoporosis is a disease of imbalance bone remodeling where bone resorption is higher than bone formation resulting in poor bone mass and fragility fracture. Cathepsin K (CatK), a cysteine protease produced by osteoclasts, is the primary enzyme mediating the degradation of the mineralized bone matrix. CatK is an attractive target for the treatment of osteoporosis since its inhibition results in the reduction of bone resorption allowing the bone formation to continue and ensuring the balanced bone remodeling. We tested the effect of human alpha-1 antitrypsin (hAAT), a serine protease inhibitor, on the inhibition of CatK.

Methods
We used cathepsin K drug discovery kit in order to evaluate hAAT’s activity as a modulator of CatK. In order to test the effect of hAAT on osteoclastic bone mineral resorption, we generated osteoclasts from mouse bone marrow macrophage cells of C57BL/6 mouse and from murine macrophage cell line, RAW264.7 cells. We tested the mineral resorption activity using Osteo Assay Surface plates in the presence or absence of hAAT.

Results
Our results showed that hAAT significantly inhibits CatK activity. We observed that hAAT dose dependently reduced osteoclast associated resorption pit area indicating its inhibitory effect on osteoclast associated mineral resorption. Together, these results demonstrated that hAAT inhibited CatK activity and osteoclast function.

Conclusion
We for the first time demonstrated that hAAT has therapeutic potential against osteoclast function.