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Use of a proteasome inhibitor to improve bone properties

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Classical Osteogenesis Imperfecta (OI) is a dominant brittle bone disease caused by mutations in the type I collagen genes. No definitive treatment is so far available for OI and the pharmacological therapy of choice is based on the use of biphosphonates, that, inhibiting osteoclasts activity, cause a delay in bone turnover and an increase in bone density. Similar effect should be obtained acting in increasing the number of bone producing cells, with the advantage that bone turnover will not be compromised. The osteoblasts derive from bone marrow pluripotent mesenchymal stem cells (MSCs), thus it seems feasible to ameliorate bone density by increasing specifically the number of MSCs differentiating in bone cells.
Recently, the proteosomal inhibitor bortezomib (Bzb) has been shown to induce mesenchymal stem cells to preferentially undergo osteoblastic differentiation[1]. In order to evaluate the effect of Bzb as a therapy for OI patients, we treated by intraperitoneal injection WT and BrtlIV mice (an OI murine model[2]) with the drug or with placebo. We evaluate the effect of this therapy by *in vitro* differentiation of MSCs extracted from bone marrow of treated and untreated mice. Our preliminary data show a difference in the response between treated wild type and BrtlIV MSCs, with an increase in osteoblastic differentiation in OI derived stem cells ($P<0,005$).
RT-qPCR, to evaluate osteoblast-specific genes expression level, quantitative analysis of serum osteocalcin and evaluation of the structural bone properties by pQCT are ongoing.
This work will be complementary to the *in utero* cell therapy approach developed by another member of the project. The treatment with this drug acting on MSCs differentiation could represent a valid tool to increase the donor cells engraftment in recipient bone following transplantation in OI as well as in other bone diseases.

References

1. Pharmacologic targeting of a stem/progenitor population in vivo is associated with enhanced bone regeneration in mice. Mukherjee S. et al. The Journal of Clinical investigation 2008.

2. Use of the Cre/lox recombination system to develop a non-lethal knock-in murine model for osteogenesis imperfecta with an alpha1(I) G349C substitution. Variability in phenotype in BrtlIV mice. Forlino et al. J Biol Chem. 1999