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In Utero transplantation of stem cells as treatment for the brittle bone disease Osteogenesis Imperfecta

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Classical Osteogenesis Imperfecta (OI) is an autosomal dominant skeletal disorder characterized by bone deformity and fragility caused by mutations in the COL1A1 and COL1A2 genes encoding type I collagen. To develop a cellular treatment for this disease we decided to perform an *in utero* stem cells transplantation in *Brittle IV* mouse, the murine model for Type IV OI, mainly because OI is an inborn disorder and prenatal administration may prevent organ injury before irreversible damage without immunologic rejection or conditioning therapy. We isolated adult bone marrow from long bones of EGFP transgenic mice and injected the cells into the liver of *Brtl IV* and *wild-type* E14.5 embryos. Transplanted mice were analyzed at 2 months, the age corresponding to the severest bone *Brtl IV* phenotype with respect to *WT*, and compared to *Brtl IV* and wild-type untreated mice. Engraftment of EGFP+ donor cells with a characteristic patchy distribution was detected in tissues of haematopoietic and non-haematopoietic origin and in particular in the bone where we could appreciate an improvement in the trabeculae compartment of treated versus non treated mutant mice. The femur length was significantly increased in transplanted mutant mice.
The preliminary phenotypic evaluation of treated mice suggested that cell therapy using *in utero* transplantation is a promising treatment for classical OI in spite of a relatively low engraftment.
In order to increase the donor chimerism and improve our results we plan to test two other donor cell types such as enriched marrow mesenchymal stem cells to increase the number of osteogenic precursors and fetal liver stem cells that seems to have a greater differentiative potential and plasticity than adult BM cells. In addition, if tolerance is induced to the transplanted cells, postnatal booster injections may contribute to ameliorate the level of engraftment and therefore the phenotype of the disease.