ABSTRACT SUBMISSION

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An innovative injectable human bone graft for cranio-facial skeletal regenerative medicine

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In the cranio-maxillofacial area, bone grafts are extensively used for skeletal regeneration in several forms (blocks, powders…). To improve their use in irregular or hardly accessible sites [1,2], we have developed an easy handling bone paste, injectable in a cohesive form, made of partially demineralized and heated bone powder from decellularized human femoral heads. The purposes of this work was to investigate the *in vivo* bone regenerative capacity of this bone paste, its *in vitro* ability to stimulate human mesenchymal stromal cells from bone marrow (hBM-MSC) osteogenic properties as well as its potential to polarize macrophages towards a pro-regenerative phenotype.

In vivo, critical-size defects (5mm, full thickness) were performed in syngeneic Lewis1A rat calvaria (2 defects/rat, n=6/condition). The defects were filled with bone paste, bone powder (0.5-1mm) or left empty as a control. After 7 weeks, the mineral volume (MV) among the total volume (TV) of the defects (MV/TV ratio) was measured by micro-CT and bone tissues were histologically analyzed. Undecalcified histological sections showed new-formed bone only in the defects filled with the bone paste. The MV/TV ratio was significantly higher in defects filled with the paste than the powder (fig. 1A), and the fold increase of MV/TV ratio after 7 week compared to MV/TV ratio at the implantation was also significantly higher in defects filled with the paste than the powder (fig. 1B) indicating more mineral formation induced by the paste.
In vitro, hBM-MSC grown in proliferative or osteogenic medium for 14 and 21 days, showed both ALP mRNA expression and enzymatic activity higher when cultured in contact with the bone paste compared to the bone powder after 14 and 21 days. Moreover, human monocytes isolated from circulating blood cultured in presence of 20ng/mL of GM-CSF (inflammatory environment) or its vehicle, in contact with powder or paste for 3 days showed an increase of pro-regenerative factors mRNA expression (IL-10 and VEGF) in comparison with the bone powder.

Our data demonstrated the substantial *in vivo* bone regenerative capacity of the bone paste. We also demonstrated that bone paste is able to support the *in vitro* osteogenic differentiation of hBM-MSC and promote the switch of inflammatory macrophages to pro-regenerative ones. Taken together, these data highlight the potential of this innovative bone paste as an injectable allogeneic bone substitute, and further experiments are under consideration to assess whether this bone paste may be a relevant clinical alternative to the "gold standard", the autologous bone graft.

References: [1] Wang, W. et al. *Bioactive Materials* 2, 224–247 (2017). [2] Gaihre, B., et al *Journal of Functional Biomaterials* 8, 49 (2017).

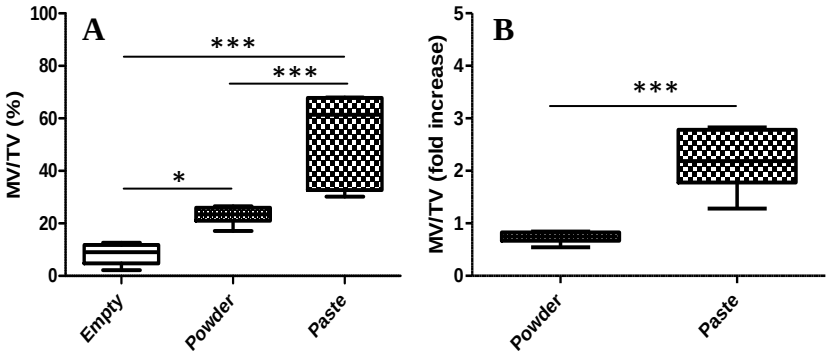

Figure 1: µCT quantitative analyses of the MV/TV ratio in the defects after 7 weeks. A: MV/TV ratio, B: MV/TV ratio fold increase. ANOVA with Newman-Keuls post-hoc test, *:p<0.05; ***:p<0.001.