

IGF-1 ENHANCES THE OSTEOGENIC ACTIVITY OF BMP-6 *IN VITRO* AND *IN VIVO*, AND TOGETHER HAVE A STRONGER OSTEOGENIC EFFECT THAN WHEN IGF-1 IS COMBINED WITH BMP-2.

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Bone morphogenetic protein-2 (BMP-2) is widely used in orthopedic surgery and bone tissue engineering because of its strong osteogenic activity. However, BMP-2 treatments have several drawbacks and alternatives are being explored. Since BMP-6 has been demonstrated to be more osteoinductive, its use, either alone or together with other cytokines, might be an interesting option.

We have compared the effect of BMP-2, BMP-6, or insulin-like growth factor-1 (IGF-1), either alone or in combination. MC3T3-E1 cells were treated with IGF-1 and/or of BMP-2 or -6 and the expression of osteogenic genes, proliferation and alkaline phosphatase (ALP) activity *in vitro* were analyzed. The results showed that IGF-1 greatly enhanced the BMP-induced osteogenic differentiation of these cells and that the ALP activity in the cultures was higher when the combination was made with BMP-6 than with BMP-2. Other *in vitro* experiments showed that the osteogenic effect of these combinations can be modulated controlling the sequential administration of the growth factors.

Furthermore, we have tested the osteogenic potential of these treatments *in vivo* by loading them onto absorbable collagen sponges which were implanted into an ectopic bone formation model in rats. These experiments revealed that only BMP-6 was able to induce bone formation at the used dose and that the addition of IGF-1 contributed to an increase of the mineralization in the implants.

Hence, the combination of BMP-6 with IGF-1 might be a better alternative than BMP-2 for orthopedic surgery and bone tissue engineering approaches with potential application through using controlled delivery systems.