CORRESPONDENCE

'Smart' biomaterials and osteoinductivity

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In their recent paper in *Nature Reviews Rheumatology*, Boyan and Schwartz discussed the use of synthetic biomaterials in repair strategies of large bone defects (Are calcium phosphate ceramics 'smart' biomaterials? *Nat. Rev. Rheumatol.* **7**, 8–9; 2011).[1] This News & Views commentary, which is largely based on our publication in the *Proceedings of the National Academy of Sciences*,[2] justly emphasizes the importance of the search for alternatives to autologous bone grafts, which are limited in availability, for treatment of large bone defects. Boyan and Schwartz question if calcium phosphate ceramics are indeed 'smart' biomaterials, in the sense of being truly osteoinductive. Referring to our work they state: "…unfortunately, however, it is not clear whether the intramuscular implants used in the dog and sheep models were only the porous ceramics or if they were the composite grafts with human mesenchymal stem cells (hMSCs) that had been pre-differentiated in osteogenic medium".[1] We would like to explicitly emphasize and clarify that the referred data were obtained by using ceramics alone, without the addition of any cells and/or growth factors.

This is not a trivial matter, as the value of our work lies in the unequivocal proof that a class of ceramics can induce substantial bone formation ectopically without the addition of growth factors and/or cells. Furthermore, we have proven that, in a large bone defect in sheep, the microstructured tricalcium phosphate ceramic (which had the highest osteoinductive potential of the intramuscularly implanted ceramics tested) was at least equally as efficient in bone repair—without the addition of cells and/or growth factors-—as autologous bone grafts and recombinant human BMP-2 delivered on an absorbable collagen sponge.[2]

We certainly agree with the authors that an increased expression of osteogenic markers upon culture of hMSCs on a ceramic in osteogenic medium is not proof of osteoinductivity, and neither is bone formation that results from subcutaneous implantation of ceramic–hMSC constructs into immunodeficient mice. The rationale behind the experiments with ceramic–cell constructs was to explain the mechanism of osteoinduction by synthetic biomaterials, and to develop an assay that is predictive of *in vivo* osteoinductivity. As such, these experiments provided insight into the effect of physicochemical and structural material properties on protein adsorption, as well as on the osteogenic differentiation of hMSCs. As correctly mentioned by Boyan and Schwartz,[1] a more complete appreciation of the biology of bone regeneration is required for further improvement of the existing synthetic biomaterials. The fact that small laboratory animals such as mice only seldom show synthetic material-induced bone formation will force us to develop more suitable *in vitro* models that enable understanding of the biological processes, since large animals like sheep and dogs, which do support osteoinduction, are expensive and impractical for such endeavors .

We realize that a paradigm shift is needed before this specific class of microstructured synthetic biomaterials will be generally accepted as a valid alternative to natural bone grafts, a process that requires time. Nevertheless, there can be no doubt that fully synthetic ceramics, with specific physicochemical and structural properties, do possess intrinsic osteoinductivity.

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Competing interests
H. Yuan, C. A. van Blitterswijk and J. D. de Bruijn are stockholders and/or directors of Progentix Orthobiology and Revisios. The other authors declare no competing interests.

1. Boyan, B. D. & Schwartz, Z. Regenerative medicine: Are calcium phosphate ceramics 'smart' biomaterials? *Nat. Rev. Rheumatol.* **7**, 8–9 (2011).
2. Yuan, H. *et al.* Osteoinductive ceramics as a synthetic alternative to autologous bone grafting. *Proc. Natl Acad. Sci. USA* **107**, 13614–13619 (2010).