

Biomimetism, *Smart* Biomimetic Matrices and the Induction of Bone Formation

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The novel concept of tissue engineering of bone is the induction of bone formation by the implantation of *smart* self-inducing biomimetic matrices endowed with shape memory geometries that *per se* initiate the ripple-like cascade of bone differentiation without the addition of exogenously applied osteogenic proteins of the transforming growth factor- β (TGF- β) superfamily, the bone morphogenetic/osteogenic proteins (BMPs/OPs) and, uniquely in the non-human primate *Papio ursinus*, the three mammalian TGF- β isoforms^{1,2}. There is no bone formation by induction without the osteogenic soluble molecular signals of the TGF- β super gene family. The basic tissue engineering paradigm is tissue induction and morphogenesis by combinatorial molecular protocols whereby soluble molecular signals are combined with insoluble signals or substrata acting as three-dimensional scaffolds for the initiation of *de novo* tissue induction and morphogenesis². The induction of bone formation, by combining soluble osteogenic molecular signals with different insoluble signals or substrata, is the essence of the tissue engineering paradigm. Can we engineer biomimetic matrices that differentiate invading myoblastic myoendothelial stem cells into osteoblastic cell lines? Can we design biomimetic matrices in which differentiating osteoblast-like cells express and secrete mRNA species of the TGF- β superfamily later embedded into the biomimetic matrix initiating bone formation as a secondary response? The molecular scaffolding lies at the hearth of all tissue engineering strategies and in particular '*bone: formation by auto induction*'³. The insoluble signal, the carrier substratum that when combined with the osteogenic proteins triggers the bone induction cascade¹, provides an exciting and novel concept of bone tissue engineering, i.e. the development of biomimetic matrices that *per se* initiate the induction of bone formation even without the addition of exogenously applied osteogenic proteins of the TGF- β superfamily, i.e. a bioactive biomimetic matrix that differentiates resident myoblastic myoendothelial cells into osteoblastic-like cell lines expressing and secreting osteogenic gene products of the TGF- β superfamily initiating bone formation as a secondary response^{2,4}. A solid state regulatory biomimetic matrix in which concavities *per se* differentiate myoendothelial

stem cells into osteoblastic-like cells immobilizing osteogenic gene products of the TGF- β super gene family as secreted directly onto the matrix and embedded within the regulatory inductive micro-environment of the concavities. Our systematic studies in *Papio ursinus* have shown that the driving force of the intrinsic induction of bone formation by bioactive biomimetic matrices is the shape of the implanted scaffold; the language of shape is the language of geometry; the language of geometry is the language of a sequence of repetitive concavities that biomimetizes the remodelling cycle of the primate osteonic bone⁵. The remodelling cycle entails a *resting* phase with quiescent resting cells over trabeculae of bone, *activation* phase, whereby osteoclastic cells are activated to resorb mineralized bone and the *formation* phase, whereby differentiating osteoblasts appear in the lacunae and pits cut by osteoclastogenesis inducing bone formation within the concavities cut by osteoclastogenesis. The lacunae and concavities cut by osteoclastogenesis within the biomimetic matrices are the driving morphogenetic cues to induce bone formation in a *continuum* of sequential phases of resorption/dissolution and induction of bone formation which biomimetize the remodelling cycle of the primate cortico-cancellous bone^{4,5}. The concavities assembled in highly crystalline¹ and/or hydroxyapatite/ β -tricalcium phosphate biomimetic bioceramics⁴ are endowed with multifunctional pleiotropic self-assembly capacities initiating and promoting angiogenesis and bone formation by induction by differentiating resident myoendothelial stem cells into secreting osteoblasts initiating the induction of bone formation.

REFERENCES:

¹Ripamonti U (2006). *Biomaterials* **27**:807-22

²Ripamonti U, Crooks J, Khoali L, Roden L (2009). *Biomaterials* **30**:1428-39

³Urist MR (1965) *Bone: formation by autoinduction*. *Science* **150**: 893-99

⁴Ripamonti U, Richter PW, Nilen RWN, Renton L (2008). *J Cell Mol Med* **12** **6B**:2609-21.

⁵Ripamonti U (2009). *J Cell Mol Med* doi: 10/1111/j.1582.2008.00562.x