

Apatite-Polymer Composites for the Controlled Dual Delivery of BMP-2 and BMP-6 for Bone Tissue Engineering

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Abstract – The release of growth factors from tissue engineering scaffolds provides signals that influence the migration, differentiation, and proliferation of cells. The incorporation of a drug delivery platform that is capable of tunable release will give tissue engineers greater versatility in the direction of tissue regeneration. We have prepared a novel composite of two biomaterials with proven track records - apatite and poly(lactic-co-glycolic acid) (PLGA) – as a drug delivery platform with promising controlled release properties. These composites have been tested in the delivery of a model protein, bovine serum albumin (BSA), as well as therapeutic proteins, recombinant human bone morphogenetic protein-2 (rhBMP-2) and rhBMP-6. The controlled release strategy is based on the use of a polymer with acidic degradation products to control the dissolution of the basic apatitic component, resulting in protein release. Therefore, any parameter that affects either polymer degradation or apatite dissolution can be used to control protein release. We have modified the protein release profile systematically by varying the polymer molecular weight, polymer hydrophobicity, apatite loading, apatite particle size, and other material and processing parameters. Biologically active rhBMP-2 was released from these composite microparticles over 100 days, in contrast to conventional collagen sponge carriers, which were depleted in approximately 2 weeks. The released rhBMP-2 was able to induce elevated alkaline phosphatase and osteocalcin expression in pluripotent murine embryonic fibroblasts.

To augment tissue engineering scaffolds with tunable and sustained protein release capabilities, these composite microparticles can be dispersed in the scaffolds in different combinations to obtain a superposition of the release profiles. We have loaded rhBMP-2 into composite microparticles with a fast release profile, and rhBMP-6 into slow-releasing composite microparticles. An equimixture of these two sets of composite particles was

then injected into a collagen sponge, allowing for dual release of the proteins from the collagenous scaffold. The ability of these BMP-loaded scaffolds to induce osteoblastic differentiation *in vitro* and ectopic bone formation in a rat model is being investigated.

We anticipate that these apatite-polymer composite microparticles can be extended to the delivery of other signalling molecules, and can be incorporated into other types of tissue engineering scaffolds.