Osteochondral Tissue Engineering Using Macroscopic Gradients of Bioactive Signals

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The objective of this study was to evaluate the performance of stem cell-seeded 3D gradient scaffolds *in vitro* (Phase I) and *in vivo* (Phase II). The scaffolds were prepared using our unique gradient technology, which uses protein-loaded microspheres to achieve spatially and temporally controlled delivery of bioactive signals in 3D, which we hypothesized would lead to a seamless transition from bone-like to cartilage-like tissue formation in a single construct. In Phase I, scaffolds were fabricated with opposing gradients of microspheres containing either bone morphogenetic protein-2 or transforming growth factor-β_1, then seeded with either hBMSCs or hUCMSCs. Constructs were analyzed for matrix production using biochemical assays, immunohistochemistry, and mechanical testing at 3 and 6 weeks. Matrix analysis at wk 6 demonstrated that the gradient scaffolds outperformed blank scaffolds in cell number, GAG production, and ALP activity, while mechanical properties were similar for the two groups. Histological staining for GAGs, calcium, and collagen I and II confirmed temporal control of stem cell differentiation and spatial control of the interface location. In Phase II of this study, we induced osteochondral defects in the knees of New Zealand White rabbits, and implanted either blank, gradient (acellular), or gradient scaffolds seeded with rabbit UCMSCs. Histologically, after 12 weeks, gradient scaffolds were superior in interface regeneration compared to blank, and constructs seeded with rUCMSCs had even higher calcium deposition than acellular gradient scaffolds.