Focused Ultrasound Mediated Release of Bone Morphogenetic Protein 2 for Bone Regeneration

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Abstract:

Segmental bone defects impact human health at the global scale, causing disabilities in populations suffering from aging, osteomyelitis, traumatic injuries, and cancer. With the elderly population expected to multiply threefold, this translates to over 570 million individuals globally who will experience a significant loss of bone mass by 2050. The lack of success with current methods of vascularized bone transport, bone grafting, distraction osteogenesis, cytokine therapeutics, and stem cell-based therapies present major challenges to segmental bone reconstruction. Current methods deliver bone morphogenetic protein 2 (BMP-2) by injection or device. One key limitation to these delivery techniques is the lack of precise spatiotemporal control. Due to uncontrolled diffusion into surrounding tissues, the current cytokine delivery methods often lead to adverse effects. Furthermore, the uncontrolled diffusion presents the need for repetitive treatments or counter treatments, decreasing overall effectiveness and increasing cost. As a novel solution to this challenge, we can use focused ultrasound (fUS) to release growth factors from stimuli-responsive hydrogel systems. With fUS as an image-guided external stimulus, release from hydrogel systems can be precisely and spatiotemporally controlled. Through careful design of the hydrogel systems and crosslinking groups, a controlled release delivery system can be engineered to provide independent control of BMP-2 delivery at the site of defect.

Hydrogel systems crosslinked with stimuli-responsive Diels-Alder linkages were successfully restructured at a higher rate than the control crosslinking group. Protein quantification data and ultrasound imaging show highest levels of release and restructuring in PEG FDA-4. Ultrasound-mediated protein release from hydrogels is a promising approach for the future of bone regeneration. Current studies on the ultrasound-responsive PEG hydrogel constructs include BMP-2 release kinetics and differentiation of BMSC's from hydrogel release. With promising *in vitro* data, future studies would include an *in vivo* femoral defect model.