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Novel, multiphasic gene-activated matrices for gradient based multi-gene delivery

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Regeneration of tissue interfaces requires delivery modalities that can provide multiple instructive morphogenic cues in a spatially controlled manner. In order to provide a smart biomaterial that is capable of generating gradients of multiple morphogenic cues we aimed at designing hydrogel based gene-activated matrices (GAMs) for the nonviral delivery of multiple therapeutic genes in a spatially controlled manner. Hydrogels were loaded with multiple plasmid DNAs using a novel method for spatially controlled synthesis of DNA/nanoparticle co-precipitates in different areas of the gels. Nanoparticles were analyzed by scanning electron microscopy and composition confirmed by energy dispersive X-ray spectroscopy (EDX). Transfection efficacies and cell compatibility were analyzed in vitro using cell lines and subcutaneous in vivo implantation via bioluminescence imaging. Characterization of the agarose GAMs showed pDNA/nanoparticle (size ≤ 200nm) formation in the gel in distinct areas, confirming spatial control of loading. EDX confirmed these particles as nanocarrier/plasmid DNA coprecipitates. In vitro testing showed no substantial toxicity and confirmed enhanced transfection compared to naked DNA loaded matrices. In vivo results demonstrated gene delivery and persistent gene expression for more than 2 weeks and indicated improved gene expression using the complexation strategy. In conclusion this initial study demonstrated the generation of therapeutic gene/nanoparticle gradients within a hydrogel biomaterial for spatially controlled nonviral gene delivery in vitro and in vivo. The developed strategy will be applied in develop- mental engineering approaches in the future using gene encoded morphogenic gradients to induce the formation of complex tissue interfaces.