Nanoparticle Loaded Granular Scaffolds for Local Gene Delivery to Enhance Wound Repair

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Statement of Purpose: Hydrogel-mediated nucleic acid delivery allows for localized transgene expression. This approach could serve as a pro-regenerative therapeutic for improving wound repair due to the potential for sustained release and expression. Conventional nanoporous scaffolds face loading challenges from electrostatics under higher nanoparticle concentrations, in addition to inhibiting rapid cell infiltration and delaying uptake.

To address loading, we had developed a stable, lyophilized nanoparticle formulation that allows for high amounts of loaded, active nucleic acids embedded within a hydrogel matrix. For tissue repair, microporous scaffolds can improve cell infiltration but have been limited to surface-coated or layered microgel building blocks. To address this, we developed “flowable linksir regular particle” or “FLIP” scaffolds, a nucleic acid loaded granular material for sustained gene delivery.

Here, we demonstrate how our technology serves as a tunable platform in vivo for localized gene expression from scaffolds loaded with viral and nonviral vectors across different animal models. Further, we explore how FLIP scaffolds can improve cell infiltration but have been limited to surface-coated or layered microgel building blocks.

Methods: FLIP scaffolds were prepared as previously described by embedding our stable, lyophilized DNA/polyethyleneimine (PEI) nanoparticle formulation within fragmented hyaluronic acid granular scaffolds. We compared conventional nanoparticle surfection methods by electrostatic decoration on the microgel surface prior to annealing, which is useful for less stable cationic lipid/mRNA nanoparticles. We have reported on how either type of loaded scaffold effectively delivers nucleic acids with a constant rate of expression, in addition to spatial control from combined or layered microgel building blocks.

We assessed the use of our FLIP scaffold platform across several mouse models, including subcutaneous (SubQ) and ischemic stroke, in immunocompetent and immune-compromised mice, for DNA, mRNA, and AAV delivery. In particular, we present here our progress on local DNA delivery for dermal wound healing. Briefly, using a skin biopsy hairless mouse model (SKH1e), we inject our particle loaded microgels at the wound site (10µL, 5mm wounds, four per mouse), annealed and tissue integrated using Factor XIII/Thrombin chemistry. Gene expression and immune response were tracked over two weeks with live reporter (luciferase) imaging and serum antibody or cytokine ELISAs. Endpoint analysis was performed with flow cytometry for immune cell populations and transfection, and histology for tissue ingrowth.

Results: FLIP scaffolds have been shown to promote adequate cell infiltration across various models, and this remains the case in dermal wounds. Previously, SubQ delivery of therapeutic genes for wound repair, such as those to promote angiogenesis or reduce inflammation. It is also important to continue exploring the co-delivery of immunomodulatory drugs to improve expression. Overall, we continue to advance our FLIP scaffold technology towards clinically translatable regenerative therapies.

Conclusions: FLIP scaffolds provide controlled, localized gene delivery of viral and nonviral vectors, particularly in dermal wounds. Further work is still needed to assess the delivery of therapeutic genes for wound repair, such as those to promote angiogenesis or reduce inflammation. It is also important to continue exploring the co-delivery of immunomodulatory drugs to improve expression. Overall, we continue to advance our FLIP scaffold technology towards clinically translatable regenerative therapies.

References:
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