Δ Targeted Delivery of GSK-3β Inhibitor-Loaded Nanoparticles for Fracture Healing in a Murine Nonunion Model

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Purpose: GSK-3β inhibitors, which activate the Wnt/β-catenin signaling pathway, are a promising option to accelerate fracture healing. However, poor biodistribution and off-target effects are a significant barrier. A novel bone-targeted nanoparticle (BT-NP) delivery system has been developed that enhances bone biodistribution of these drugs and limits off-target effects. While this system has demonstrated efficacy in expediting routine fracture healing, it has not been investigated in a nonunion setting. Our hypothesis is that BT-NP will increase fracture healing in a murine nonunion model.

Methods: An atrophic femur nonunion model was created in 14- to 16-week-old mice using a tapered plate and a 3.0-mm mid-diaphyseal osteotomy. Peptides with high affinity for tartrate-resistant acid phosphatase were conjugated to poly(styrene-alt-maleic anhydride)-b-poly(styrene) nanoparticles. The GSK-3β inhibitor (3-amino-6-(4-((4-methylpiperazin-1-yl)-sulfonyl)phenyl)-N-(pyridin-3-yl)pyrazine-2-carboxamide) was loaded into the nanoparticle cores, creating the fracture-targeting nanoparticle delivery system (BT-NP). Mice were randomized to 3 groups: early BT-NP (injected 3 days postoperatively), late BT-NP (injected 2 weeks postoperatively), and saline control. Femurs were harvested at 2, 4, 8, and 12 weeks postoperatively. Bone healing was determined using microCT.

Results: 107 mice underwent a femoral nonunion procedure. The early BT-NP group demonstrated increased trabecular thickness at 8 weeks compared to controls (0.294 mm vs 0.259 mm, $P = 0.020$). No other differences in bone volume, bone volume fraction, mineralization density, trabecular thickness, or trabecular number were identified between early BT-NP and controls or late BT-NP and controls at any time point. Within each treatment group, there was no significant increase in bone formation identified between time points ($P<0.05$ for all). Additional histologic analyses are ongoing.

Conclusion: These results demonstrate the successful establishment of a murine nonunion model that does not develop bony healing for at least 12 weeks. This has implications for future nonunion investigations as previous murine models have not been as reliable over this length of time. Treatment with BT-NP did not lead to the robust fracture healing in the nonunion model previously observed in a conventional fracture model. This highlights the differences in biology between a nonunion and conventional fracture site. Further investigation is needed to better understand and optimize BT-NP delivery in a nonunion model. Finally, our results suggest that therapies demonstrating success in routine fractures may not necessarily translate to a nonunion setting. This is an important consideration for other bone healing applications to focus efforts on clinically relevant scenarios.

Δ OTA Grant

The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or medical device they wish to use in clinical practice.