

Selective LNP-siRNA Targeting of ZNRF3/RNF43 for Regenerative MASH Therapy

Lilian Li¹, Dinglingge Cao², Lida Yang¹, Bruno Cogliati¹, Federico Di Tullio¹, Sue Bin Yang¹, Kaiyuan Guo, Emily Bramel¹, Anthony Lozano¹, Yizhou Dong², Tianliang Sun¹

¹Department of Stem Cell Biology and Regenerative Medicine, Division of Liver Diseases, Tisch Cancer Center, Icahn School of Medicine at Mount Sinai

²Icahn Genomics Institute, Precision Immunology Institute, Department of Immunology and Immunotherapy, Department of Oncological Sciences, Tisch Cancer Center, Friedman Brain Institute, Biomedical Engineering and Imaging Institute, Icahn School of Medicine at Mount Sinai

Metabolic dysfunction-associated steatohepatitis (MASH) is driven by intertwined metabolic dysfunction, inflammation, fibrosis, and impaired hepatocyte regeneration, yet most therapies target individual disease components rather than restoring the liver's intrinsic repair capacity. We identified the WNT/ β -catenin negative regulators ZNRF3 and RNF43 as actionable regenerative targets. Hepatocyte-specific ZNRF3/RNF43 deletion (ZRdKO) in established MASH reactivated endogenous β -catenin signaling and drove coordinated regression of steatosis, inflammation, and fibrosis. Importantly, LNP-siRNA-mediated ZNRF3/RNF43 silencing recapitulated key therapeutic benefits, establishing pharmacological proof-of-concept for transient pathway targeting.

A major challenge for β -catenin therapy is oncogenic risk. Our studies indicate that ZRdKO restored endogenous β -catenin activity without promoting tumor progression in MASH-HCC models and retained therapeutic activity in the surrounding diseased liver. Whereas oncogenic CTNNB1-N90 cooperated with MYC to induce extensive HCC, ZRdKO plus MYC failed to initiate tumors, supporting a therapeutic window for restoring regulated β -catenin signaling without recapitulating mutation-driven oncogenic activity.

We also established an RNA drug-development pipeline targeting ZNRF3/RNF43. LNP screening identified candidates with highly efficient delivery to hepatocytes in steatotic and fibrotic livers. Notably, these LNPs showed minimal delivery to HCC lesions, providing an additional layer of therapeutic selectivity. In parallel, systematic screening in primary mouse hepatocytes and human liver cancer cells identified potent mouse and human ZNRF3/RNF43 siRNA candidates. Lead siRNA-LNP combinations are now advancing through in vivo validation and PK/PD studies to define target engagement, durability, dosing, and therapeutic window.

Together, these studies support selective, transient restoration of endogenous regenerative signaling through ZNRF3/RNF43-targeted LNP-siRNA as a potential disease-modifying therapy for MASH.