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VEGFA mRNA-LNP promotes biliary epithelial cell-to-hepatocyte conversion in acute and chronic liver diseases and reverses steatosis and fibrosis

Abstract: The liver is known for its remarkable regenerative ability through proliferation of hepatocytes. Yet, during chronic injury or severe hepatocyte death, proliferation of hepatocytes is exhausted. To overcome this hurdle, we propose vascular-endothelial-growth-factor A (VEGFA) as a therapeutic means to accelerate biliary epithelial cell (BEC)-to-hepatocyte conversion. Investigation in zebrafish establishes that blocking VEGF receptors abrogates BEC-driven liver repair, while VEGFA overexpression promotes it. Delivery of VEGFA via non-integrative and safe nucleoside-modified mRNA encapsulated into lipid-nanoparticles (mRNA-LNP) in acutely or chronically injured mouse livers induces robust BEC-to-hepatocyte conversion and elimination of steatosis and fibrosis. In human and murine diseased livers, we further identified VEGFA-receptor KDR-expressing BECs associated with KDR-expressing cell-derived hepatocytes. This defines KDR-expressing cells, most likely being BECs, as facultative progenitors. This study reveals unexpected therapeutic benefits of VEGFA delivered via nucleoside-modified mRNA-LNP, whose safety is widely validated with COVID-19 vaccines, for harnessing BEC-driven repair to potentially treat liver diseases.

Biography: Dr. Valerie Gouon-Evans is Associate Professor in the Center for Regenerative Medicine at Boston University, Boston Medical Center, Director of the Boston University Liver Biologist program, and Co-director of the Molecular and Translational Medicine PhD program. She has greatly contributed to the efficient generation of hepatocytes from mouse, human and macaque pluripotent stem cells by pioneering the use of BMP4 to induce hepatic specification. Currently, her research interests aim to harness liver regeneration using nucleoside-modified mRNA complexed to lipid nanoparticles, a technology that her lab has validated to induce transient expression of proteins in the liver to accelerate liver regeneration.

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