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Base Editing of the *PCSK9* Gene in Human Hepatocytes via Lipid Nanoparticle-Delivered Adenine Base Editors: A Non-Viral Approach for Familial Hypercholesterolemia

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Abstract

Familial hypercholesterolemia (FH) is characterized by loss-of-function mutations in the LDL receptor pathway. Current therapies require lifelong administration. We report a non-viral gene editing strategy employing adenine base editors (ABE8e) packaged in liver-targeted lipid nanoparticles (LNPs) to precisely disrupt the *PCSK9* translational start site in human hepatocytes. In humanized *PCSK9* mouse models and primary human hepatocyte spheroids, a single intravenous administration achieved 65% editing efficiency at the target locus, resulting in 80% reduction of plasma PCSK9 protein and 50% lowering of LDL-cholesterol levels sustained for 20 weeks. Off-target analysis via GUIDE-seq detected no significant unintended mutations. Deep sequencing confirmed permanent hepatocyte DNA modification without episomal persistence. This direct base editing platform offers a potential one-time curative intervention for autosomal dominant hypercholesterolemia.

Keywords: base editing, PCSK9, familial hypercholesterolemia, lipid nanoparticles, adenine base editor, non-viral gene therapy