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Commentary

Therapeutic Gene Regulation in the Liver Using Lipid Nanoparticle Technology

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DESCRIPTION

Millions of individuals throughout the world suffer from hereditary genetic problems, cancer, and infectious illnesses of the liver, which are a huge public health concern. Because most modern treatments are aimed at alleviating disease symptoms they only provide limited alleviation. Targeting the fundamental cause of disorders originating in the liver by using nucleic acid based therapeutics to regulate gene holds a lot of potential as a therapeutic approach. However, because of their undesirable properties, using nucleic acid therapies is difficult [1]. The invention of Lipid Nanoparticle (LNP) delivery technology has enabled clinical translation of gene treatments. LNPs can carry siRNA, mRNA, DNA, or gene editing complexes allowing researchers to silence harmful genes, express therapeutic proteins, or rectify genetic abnormalities to cure hepatic disorders. The latest LNP technology for hepatic gene therapy is discussed here, covering formulation design parameters, production processes, preclinical research, and clinical translation.

Hepatitis, liver cancer, alcoholic liver disease, fatty liver disease, and genetic illnesses are the most common liver disorders [2]. These disorders can have a considerable impact on the liver's glucose, lipid, and protein metabolism in addition to their direct effects. Because of the rise in lifestyle-related incidence rates and the limited therapeutic efficacy of currently available treatments, drug developers are focusing their efforts on the liver [3]. Because of the development of nucleic acid-based medicines, our ability to treat liver illnesses by addressing their genetic is becoming a clinical reality. Nucleic acid treatments unlike small molecule medicines and biologics that target gene products (i.e. proteins) have the ability to therapeutically regulate virtually any gene of interest at the DNA or RNA level. Their capacity to produce efficient gene (inhibiting pathological/mutant protein production), gene expression (producing therapeutic proteins) or gene editing makes them versatile in treating hereditary or acquired liver ailments [4]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved several nucleic acid therapies, with many more in various stages of clinical study. As part of gene editing techniques, these treatments include Antisense Oligonucleotides (ASO) small interfering RNA (siRNA), plasmid DNA (pDNA) messenger RNA (mRNA) and complexes comprising guide RNA (gRNA).

Nucleic acids are difficult to use therapeutically due to their undesirable physicochemical properties such as negative charge and relatively large size, which limit efficient uptake into cells . Furthermore, nucleic acids are breakdown in the blood, have a fast renal clearance rate, and induce immune stimulatory effects [5]. As a result, chemical changes and sophisticated delivery technologies have been used to improve nucleic acid therapies' stability, stimulate target tissue accumulation, permit cellular internalization, and increase target affinity. Lipid Nanoparticle (LNP) systems are one of the most advanced non-viral gene delivery technologies currently available for gene treatments. Adapting LNP technology for nucleic acid delivery has been pushed by decades of creating lipid-based delivery systems for small molecule.

The term "liver gene therapy" is frequently used to refer to all gene therapy efforts for treating disorders that start in the hepatocytes. Although hepatocytes are the most common cell type in the liver, nanoparticles can interact with a variety of other cell types and alter their functioning. As a result, scientists should broaden their LNP research to encompass single cell measurement rather than the entire liver. Each lobule of the liver contains both parenchymal (hepatocytes) and non-parenchymal liver cells (i.e. Kupffer cells). The liver is made up of various cell populations in addition to these three major cell types. Stellate cells and cholangiocytes, as well as immune cells such B, T, and NK-like cells, were discovered in a recent study.

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