September 25, 2023

Summary of Dr. Sugo's review

"Propriety Nucleic Acid Delivery Technologies for Realizing a New Therapeutic Modality"

This article reviews the development of nucleic acid delivery technologies for emerging therapeutic modalities. It discusses the evolution of delivery systems, starting with lipid nanoparticles, N-Acetylgalactosamine (GalNAc) ligands, and antibody-ligand conjugates.

The introduction highlights the declining success rate of small-molecule drug development and the emergence of new modalities like siRNA therapeutics. The review focuses on the advancements in siRNA drug development, which rely on effective delivery systems.

The current state of development is described, with a focus on lipid nanoparticles (LNPs) as a prominent delivery method for siRNA drugs. LNPs encapsulate siRNA and use ionizable lipids to achieve endosomal escape, which is particularly effective for liver targeting.

Chemical modifications of nucleic acids have improved blood stability and reduced off-target effects. N-Acetylgalactosamine (GalNAc) ligands have been successfully used for liver-targeted delivery.

The review explores the challenges in ligand development for targeting organs beyond the liver. Antibodies are considered as ligands for specific targeting, but concerns about endosomal escape and formulation difficulties are noted.

The authors describe their research on anti-CD71 antibody-siRNA conjugates, demonstrating effective endosomal escape and in vivo knockdown activity in mouse muscle tissues. The potential therapeutic efficacy in muscle diseases, such as Peripheral Arterial Disease (PAD), is discussed.

Clinical development prospects include the need for anti-human CD71 antibodies and ongoing phase 1/2 trials. Avidity Biosciences' example of an antibody-nucleic acid conjugate is mentioned.

The article concludes by emphasizing the importance of cross-talk between delivery technologies and other fields like genome editing and RNA editing, highlighting the potential for further advancements in drug delivery systems.
