312 siRNA Delivery Using Hexameric Tetrahedral RNA Nanostructures

Asset Overview

Product Type	Others
Indication	Oncology
Current Stage	Target Identification
Target(MoA)	Increased functional capacity of RNA nanoparticles
Brief Description	• RNA interference (RNAi) is a biological response to double-stranded RNA that regulates expression of protein-coding genes and is a natural mechanism for gene silencing. Delivery of short, interfering RNA (siRNA) leads to RNAi of the targeted genes • A tetrahedral-shaped RNA nanoparticle comprised of four RNA nanorings for the delivery of siRNA to activate RNAi • Containing up to twelve Dicer substrate RNA duplexes, enabling the simultaneous targeting of multiple genes with several siRNA copies
Organization	National Institutes of Health

Differentiation

□ **Needs for the development of multifunctional non-viral cationic vectors (MNVCVs)**

- Inducing RNAi by small non-coding RNAs including siRNAs has become one of the critical assets for use in the treatment of cancer
- However, the therapeutic delivery of siRNAs is limited by; (i) exo and endo-nuclease degradation which in turn results in a shorter half-life and fast kidney filtration, (ii) physicochemical features such as high molecular weight (~13 kDa) and high negative charge hinders its binding and crossing the cell membranes in comparison to small molecule entities, (iii) rapid uptake by mononuclear phagocytic system (MPS), (iv) immunogenicity, and (v) off-target effects
- To circumvent these limitations, several approaches for siRNA delivery applied: (i) chemical modifications of siRNAs (ii) utilization of viral vectors and (iii) use of cationic nonviral vectors
- Chemical modifications of siRNAs can improve their stability in circulation; however, their efficacy is compromised due to off target effects and reduced therapeutic index
- Viral vectors are efficient delivery systems based on the use of genetically-modified viruses, exploiting their innate ability to introduce genetic material in eukaryotic cells, but these systems suffer from being immunogenic, having off-target effects and are expensive to produce
- Therefore, efforts have been made in recent years to develop NVCVs, since the cationic components have the inherent ability to electrostatically complex with the negatively charged siRNAs. Initial efforts to develop NVCVs such as cell penetrating peptides (CPPs), lipids, and polymers show promise for intracellular delivery of siRNAs; however, they encounter limitations including cytotoxicity of the carrier itself and undesirable side and off-target effects
- These limitations led to develop next-generation NVCVs (MNVCVs) that are functionalized with moieties that aid in cellular delivery, such as the cancer cell environment specific stimuli responsive moieties and tissue-specific targeting ligands for improving RNAi efficacy

□ **Competitive Advantages**

- Increased functional capacity of RNA nanoparticles
- Can contain up to 12 targeting siRNAs while maintaining thermodynamic stability
- Shown to have superior cell uptake capabilities and silencing capacity compared to some other RNA-based nanoconstructs

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Intellectual Property

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