【Grant-in-Aid for Scientific Research (S)】

Activated mRNA delivery system based on core-shell structured LNP with smart polymers

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Project Information	Project Number : 23H05451 Project Period (FY) : 2023-2027 Keywords : mRNA, Polymer, Lipid nanoparticles, nucleic acid medicine

Purpose and Background of the Research

●Outline of the Research

Nucleic acid therapeutics, including mRNA vaccines, have revolutionized drug development, wherein lipid nanoparticles (LNPs) based on ionizable cationic lipid (iCL) have played a central role. While LNPs have shown extremely high efficiency in nucleic acid delivery in vivo, various technological challenges remain, such as targeting extrahepatic tissues. Although current LNP development relies on screening a large number of iCLs, further improvement is unlikely in this strategy. We believe that the rational designing of a novel drug delivery system (DDS), rather than the screening of iCL, is the key to solving current issues of LNPs and realizing next-generation nucleic acid delivery systems. Herein, we will tackle the current issues of mRNA DDS through an interdisciplinary approach by integrating lipid and polymer-based systems and mRNA engineering.

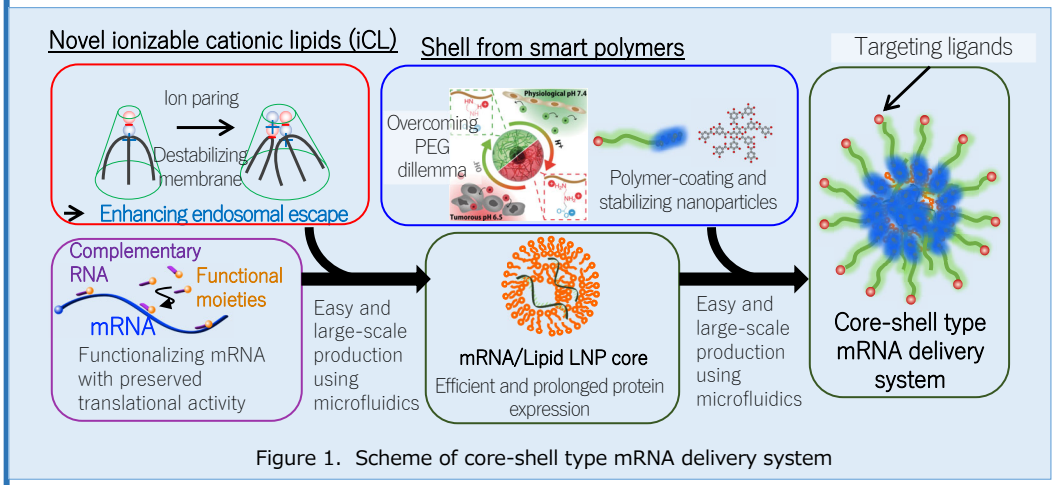

Figure 1. Scheme of core-shell type mRNA delivery system

Prof. Harashima, Prof. Sato, and Prof. Nishiyama have been conducting cutting-edge research on lipid- and polymer-based DDS. This project will integrate these two systems to develop next generation-DDS outperforming current LNPs. Regarding lipid DDS, Prof. Harashima and Prof. Sato have identified iCLs, including CL4H6, from their own iCL library, which outperformed MC3, a global standard iCL. CL4H6 showed practical utility in mRNA delivery and genome editing. Regarding polymer DDS, Prof. Nishiyama has developed a pH-responsive betaine polymer for use as a nanoparticle shell to solve the PEG dilemma. His system demonstrated the world's highest level of cancer accumulation (32% dose/g tissue) with deep penetration into the tumor tissue and is now under R&D for commercialization by NOF Co. Ltd. The integration of this polymer and iCLs will lead to the development of innovative mRNA carriers.

● **mRNA functionalization :** Prof. Uchida will stabilize the core consisting of iCL and mRNA by introducing hydrophobic groups into mRNA. Furthermore, by controlling core stability, he will achieve sustained release of mRNA for prolonged protein expression from mRNA. Furthermore, this study includes introducing factors into mRNA for efficient endosomal escape as well as cell type-specific translation.

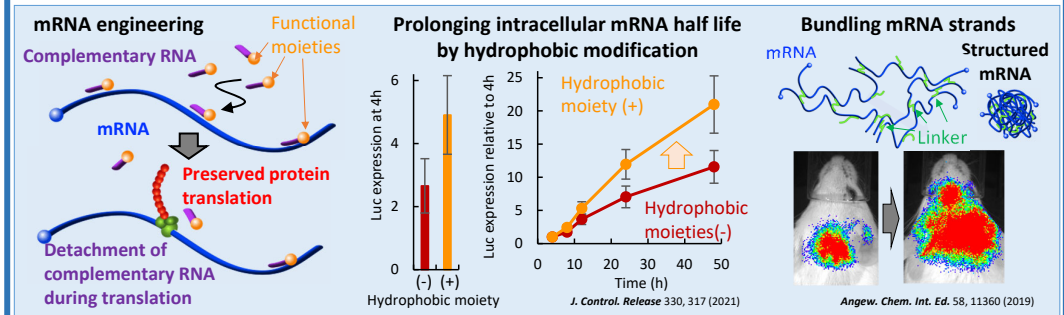

Figure 2. mRNA engineering

Expected Research Achievements

● **Technology integration through close collaboration between medicine, pharmaceutics, and engineering**: This project will realize an innovative nucleic acid delivery system by combining three elements: lipid- and polymer-based DDS and RNA engineering. Especially a "simple yet highly functional" system is essential for clinically-translatable nanomedicine. To outperform current LNPs, we will develop a core-shell-type innovative mRNA delivery system comprised of LNP core from mRNA functionalized by Uchida's RNA engineering and Harashima and Sato's iCLs coated with Nishiyama's functional polymer shell. This system will achieve efficient mRNA delivery, prolonged protein expression, and selective mRNA delivery to cancerous and inflammatory tissues to demonstrate its therapeutic utility.

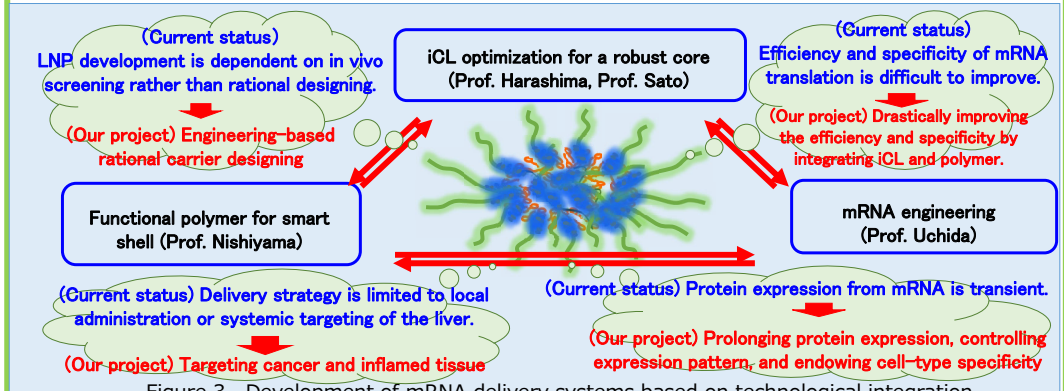

Figure 3. Development of mRNA delivery systems based on technological integration and close collaboration between medicine, pharmaceutics, and engineering

●Related Grants (KAKENHI) :

2019-2022 : Grant-in-Aid for Scientific Research (A) "Innovative gene/nucleic acid delivery system based on optimized intracellular trafficking steps" Hideyoshi Harashima, Yusuke Sato, et al.
2022-2025 : Grant-in-Aid for Scientific Research (A) "Development of polymeric micelles based on innovative core-shell design for various therapeutic modalities" Nobuhiro Nishiyama, et al.
2021-2024 : Grant-in-Aid for Scientific Research (A) "Development and therapeutic application of short mRNA therapeutics based on mRNA engineering" Satoshi Uchida, et al.

Homepage Address, etc.	Harashima・Sato: https://www.pharm.hokudai.ac.jp/nano/english Nishiyama: http://www.bmw.res.titech.ac.jp/index-e.html Uchida: https://www.tmd.ac.jp/mri/anme/index.html