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

Development and Applications of Engineered Lipid Particles

Principal Investigator	Hokkaido University, Faculty of Engineering, Professor TOKESHI Manabu　Researcher Number : 60311437
Project Information	Project Number : 24H00038　Project Period (FY) : 2024-2028 Keywords : Lipid particles, Artificial exosome, Virus-like lipid nanoparticle

Purpose and Background of the Research

●Outline of the Research

In recent years, nucleic acid medicine (such as mRNA vaccines), exosomes (extracellular vesicles), and artificial cells have gained attention as lipid particles containing nucleic acids or cytoplasmic components. These entities are subjects of competitive research worldwide in drug discovery, clinical diagnostics, as well as fundamental research in cell biology and synthetic biology. Although various manufacturing techniques have been proposed for these lipid particles, their production heavily relies on empirical knowledge-based trial and error due to the difficulty in systematically altering conditions. In this study, we aim to establish a technique for reproducibly lipid particles (engineered lipid particles) of any composition, structure, and size using microfluidic devices (Figure 1). To uniformly consider nucleic acid medicine, exosomes, enveloped viruses, and artificial cells as engineered lipid particles, and to establish a technique for their engineering production.

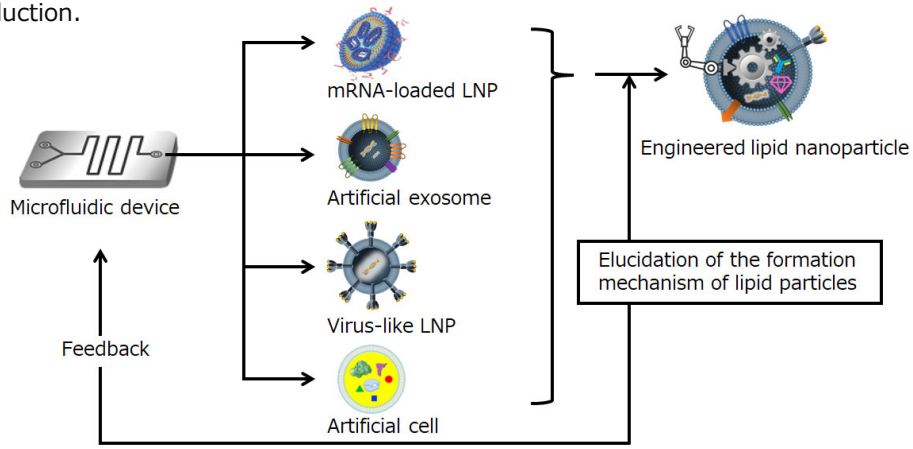

Figure 1. Research overview

●Background and Objectives

We have been working on the production of lipid nanoparticles using microfluidic devices. Based on the formation mechanism of lipid nanoparticles within microchannels, the microfluidic devices (Figure 2), which have been independently designed and developed, possess the world's highest performance in particle size control (Figure 3). By utilizing microfluidic devices, it has become possible to precisely control experimental conditions and obtain systematic data. By compiling a database of this information, we conceived the idea that in the near future, AI analysis could be used to produce lipid particles of any composition, structure, and size.

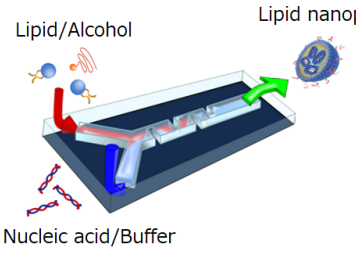

Figure 2. Microfluidic device

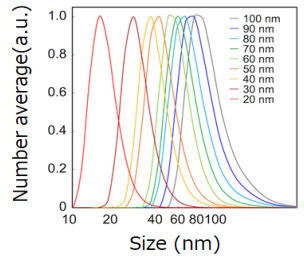

Figure 3. Particle size distribution

Specifically, we aim to create four types of engineered lipid particles (1) lipid nanoparticles loaded with mRNA, (2) artificial exosomes, (3) virus-like lipid nanoparticles, and (4) artificial cells, and demonstrate their utility. Furthermore, we will elucidate the formation process of lipid particles in microchannels through experiments (Figure 4) and molecular dynamics simulations (Figure 5), and use the obtained data to provide feedback for the production of engineered lipid particles.

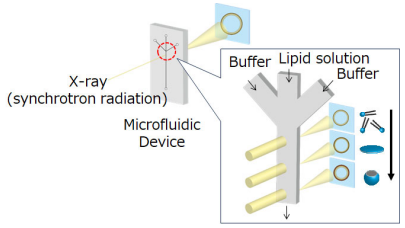

Figure 4. Real-time measurement by SAXS

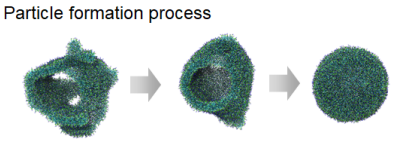

Figure 5. MD with coarse-grained model

Expected Research Achievements

●Development of mRNA-loaded LNPs and mass production technology

Development of lipid nanoparticles (LNPs) loaded with high-performance mRNA and the associated mass production technology.

●Preparation of artificial exosomes

Preparation and evaluation of lipid nanoparticles (artificial exosomes) incorporating membrane proteins specific to exosomes.

●Preparation of virus-like lipid nanoparticles

Preparation and evaluation of lipid nanoparticles (virus-like lipid nanoparticles) incorporating proteins present on the surface of viruses.

●Development of high-throughput artificial cell analysis system

Development of a microfluidic device system capable of high-throughput analysis of artificial cells containing genetic circuits.

●Elucidation of lipid particle formation mechanism

Elucidation of the formation mechanism of lipid particles in microchannels through large-scale coarse-grained molecular simulations and real-time measurements using SAXS. The obtained results will be fed back to each research topics.

Through this research, the research and development of lipid particles will significantly advance, bringing not only new insights to fundamental scientific fields such as medicine, biology, and pharmacy but also accelerating the societal implementation of lipid particles into various fields such as drug development and clinical diagnostics.

Homepage Address, etc.	https://microfluidic.chips.jp/jp/ http://theocomp.chem.okayama-u.ac.jp/index-j.html