【Grant-in-Aid for Transformative Research Areas（B）】

Cell Membrane Permeation of Oligonucleotides Controlled by Membrane Modulator Molecules

Principal Investigator	Osaka University, Graduate School of Pharmaceutical Sciences, Assistant Professor OSAWA Takashi　Researcher Number : 00783226
Project Information	Project Number : 24B206　Project Period (FY) : 2024-2026 Keywords : Membrane modulator, Cell membrane permeation, Molecular machine, Peptide, Oligonucleotide therapeutics

Purpose and Background of the Research

●Background

Oligonucleotide therapeutics are attracting attention as a new drug modality for diseases that have been difficult to treat with conventional drugs. Nowadays, rapid progress in chemical modification of nucleic acids (utilization of artificial nucleic acids, etc.) has made it possible to obtain highly active oligonucleotide therapeutics required for clinical research. On the other hand, oligonucleotides have low membrane permeability, which has been recognized as a problem to be solved in accelerating their practical application. Furthermore, through their development research to date, it has become clear that chemical modification of oligonucleotides alone does not lead to a drastic improvement in membrane permeability.

To overcome this issue, we try to develop general intracellular delivery technologies for oligonucleotide through interdisciplinary research. Through discussions within the field, a strategy to improve the membrane permeation efficiency of nucleic acid drugs was devised using membrane modulator molecules (MMs) designed based on the unprecedented concept of " inducing perturbation of cell membrane " (Figure 1).

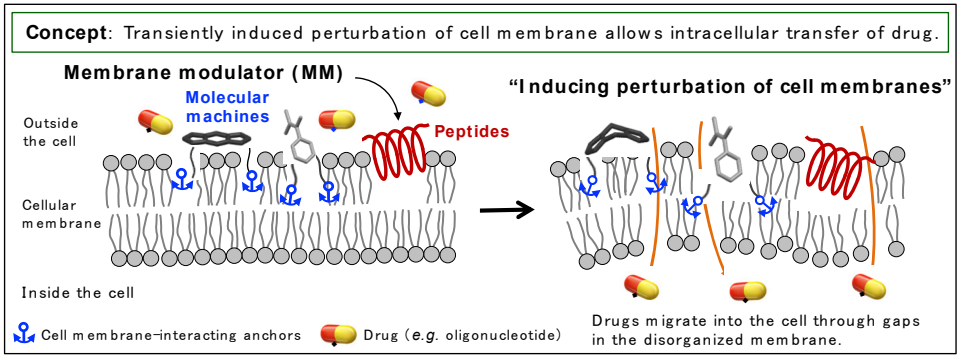

Figure 1. Cell membrane permeation of drugs by membrane modulator molecules (MMs) that induce perturbation of the membrane

● Outline of each group's research

This research area is a interdisciplinary research across nucleic acid science (Group A01), organic chemistry (Group B01), cell biology (Group C01), and computational science (Group D01). All group members will conduct joint research with shared objectives, making full use of cutting-edge technologies in their respective fields.

A01: Understanding the function of MMs

To examine and understand the function of MMs (molecular machines and peptides) and oligonucleotide therapeutics by acting on cells and using their drug efficacy as an indicator of cell-membrane modulating function.

● Outline of each group's research (continued)

B01: Development of MMs

Design and synthesize MMs (Figure 2), which have the property of interacting with the membrane and significantly change their molecular structure in response to external stimuli such as light irradiation.

C01: Observation of membrane permeation

Peptides and molecular machines are utilized as MMs, and their effects on membrane and membrane permeation efficiency of drugs are evaluated through microscopic observation and quantification.

D01: Theoretical elucidation of the mechanism

Computational molecular simulations to elucidate the membrane action of MMs, and then to approach the mechanism of membrane permeation of oligonucleotides.

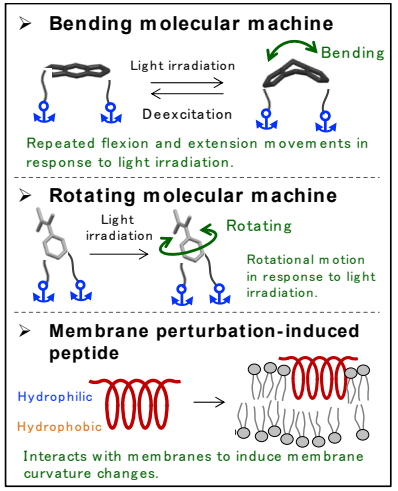

Figure 2. Membrane modulator (MM)

Expected Research Achievements

● Demonstration of an innovative membrane permeation mechanism

The goal of this research area is to propose and demonstrate innovative cell membrane permeation mechanisms that dramatically improve the membrane permeation efficiency of oligonucleotide therapeutics. Compared to conventional techniques, this method is expected to enable direct intracellular delivery of drugs independent of membrane surface properties (and independent of cell type).

●Creation of an interdisciplinary research field "Membrane Permeation Science"

The findings obtained from this research will clarify the essence of the phenomenon of cell membrane permeation, and create a "membrane permeation science" that encompasses chemistry, biology, pharmacology, and computational science (Figure 3).

"Membranes" are one of the three elements of cells in living organisms, and membrane permeabilization studies can be said to be fundamental research that approaches the roots of life. Therefore, in the future, it is expected to create an emerging field that integrates the science of "membranes" in a wide range of research areas, such as medicine, biotechnology, and energy.

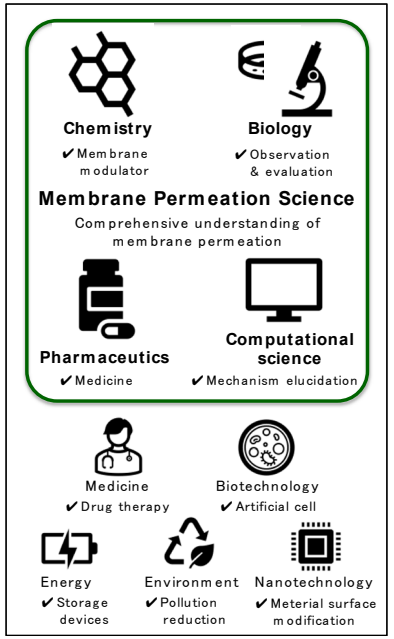

Figure 3. Membrane permeation science

Homepage Address, etc.	https://membrane-modulator.org