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

Molecular Transport Revolution by Intracellular Shuttles

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Project Information	Project Number : 26B307 Keywords : Molecular transport system, Peptide, *In silico* molecular design	Project Period (FY) : 2026-2028

Purpose and Background of the Research

●Outline of the Research

Inside every cell, countless molecules — proteins, nucleic acids, lipids, and metabolites — are constantly in motion, carrying out essential functions at precisely the right place and time. Protein synthesis, energy production, molecular degradation, and drug action all depend on this finely orchestrated intracellular transport. In short, intracellular molecular transport is the fundamental mechanism by which cells live, respond, and function.

Drug delivery systems (DDS) have been developed to carry therapeutic molecules to target tissues and cells. Yet conventional DDS largely stops at the cell boundary: once a molecule enters the cell, where it goes, what it interacts with, and how it functions remain beyond our control. This critical gap is what our research aims to close.

We are building the foundation for "Intracellular Shuttles" — molecular tools that control the destination, binding partners, and spatial organization of molecules inside the cell. By uniting expertise in DDS, generative AI, and peptide science, we will create a new platform for life science and drug discovery.

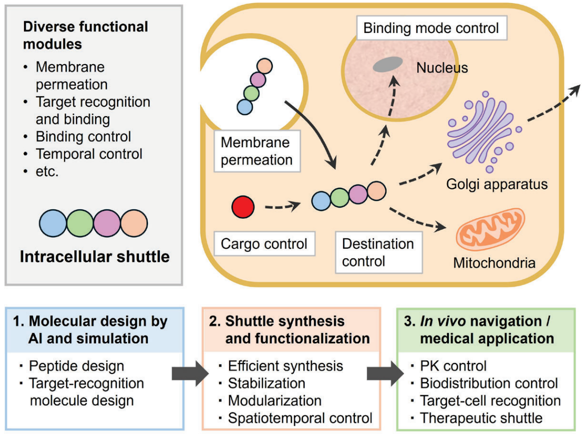

Figure 1. Our approach to intracellular shuttles

● Background to the Concept

This vision grew from the drug delivery research of project leader Mochida, who has worked on controlling the pharmacokinetics and targeted delivery of small molecules, proteins, and nucleic acids. It became clear that delivering drugs to target cells was not enough — controlling what happens to molecules once inside the cell was the next frontier.

Current technologies cannot guide molecules to specific intracellular destinations or manipulate the interactions of molecules already inside the cell. Furthermore, only 1–4% of intracellular proteins are addressable by known binders, leaving the vast majority out of reach.

To overcome these barriers, Mochida joined forces with AI researcher Hayashi and peptide scientist Yokoo. Generative AI enables rapid design of peptides that recognize target cells and intracellular molecules with high precision, while peptide science enables control over when, where, and how molecular recognition occurs. The convergence of these three disciplines gave rise to the Intracellular Shuttle concept.

Expected Research Achievements

●Vision of the Research Area

"By achieving precise control of intracellular molecular transport, we seek to understand, manipulate, treat, and advance life."

●What This Area Will Elucidate

We will establish the molecular foundation of Intracellular Shuttles and develop a platform for controlling intracellular molecular transport. In parallel, we will develop *in vivo* delivery systems for directing Shuttles to specific target cells following systemic administration. These efforts aim to transform intracellular molecular transport from a phenomenon we observe into one we can design, control, and apply.

●Plan and Implementation Strategy

X00 — Coordinating Group (Mochida, Hayashi, Yokoo):
The group fosters autonomous yet tightly coordinated research across all teams, driving integrated advancement of Shuttle design, synthesis, evaluation, and *in vivo* implementation.

A01 — Shuttle Implementation Group (Mochida):
Intracellular Shuttles are designed as combinations of interchangeable modules, enabling flexible adaptation to different target cells, molecules, and functions. The group develops *in vivo* delivery technology for systemic administration and pursues drug discovery based on new mechanisms of action.

A02 — Shuttle Design AI Group (Hayashi):
Using generative AI, the group designs peptides that drive Intracellular Shuttle function. AI models for cell-penetrating peptides (CPPs) are combined with molecular dynamics simulations to achieve cell-type-selective CPPs, alongside peptides that bind specifically to intracellular targets.

A03 — Shuttle Function Pioneering Group (Yokoo):
A parallel synthesis and high-throughput evaluation system enables rapid peptide screening in feedback with AI design. The group develops organelle-targeting peptides for spatiotemporal control, and pursues novel therapeutics that eliminate disease-causing proteins by transporting them out of the cell.

●Anticipated Ripple Effects

As the Intracellular Shuttle platform matures, intracellular molecular transport — once only observable — will become something we can design, manipulate, and apply. Applications are anticipated in medicine, pharmacy, agriculture, food science, and environmental science. This research aims to open a new frontier in life science, driving transformation in both academia and society.

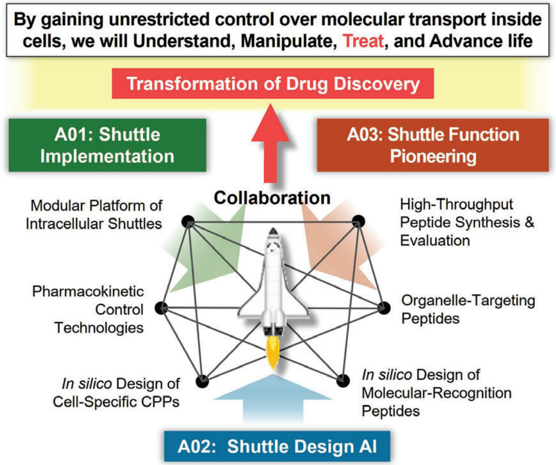

Figure 2. Collaboration Scheme

Website(s)	Website: in preparation X: @InCellShuttle