【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy I)

Title of Project：Road to Gene Therapy with MEND: from gene carrier to Nanomachine

Hideyoshi Harashima
(Hokkaido University, Faculty of Pharmaceutical Sciences, Professor)

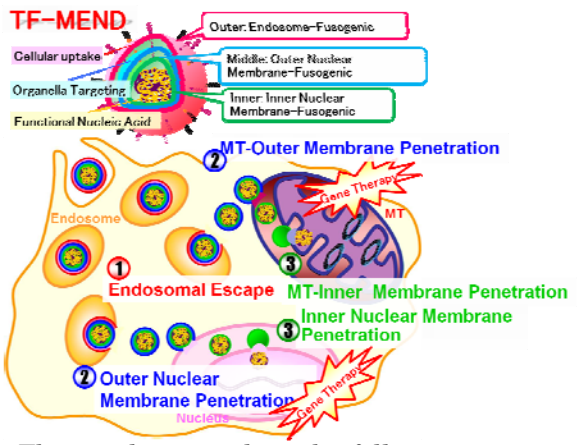
Research Area：Boundary medicine
Keyword：Drug delivery

【Purpose and Background of the Research】

The purpose of this study is to establish cutting edge technology that will permit gene therapy to be used successfully as the next generation nanomedicine. This novel technology allows for the control of, not only the biodistribution of nucleic acids but also intracellular trafficking as well as intra-organelle disposition (gene expression/gene correction), which means that these techniques achieve the level of nano-machine from a gene carrier.

In this study, we plan to construct a TF-MEND(Triple Fusion-Multifunctional Enve lope-type Nano Device) and functional nucleic acids as a core technology of nano-machine (as an intermediate goal), and then optimize these systems for nuclear targeting as well as mitochondrial targeting. In addition, a second goal is to extend their function to achieve the level of nano-machine, in the latter period. The ultimate goal of this project is to develop a system in which the TF-MEND selectively and efficiently delivers functional nucleic acids to nucleus/mitochondria and to perform gene expression/gene correction in each organelle.

【Research Methods】



This study is involves the following aspects:1) construction of the TF-MEND, 2) design/ evaluation of functional nucleic acids, 3) Nanomachine for controlled intranuclear disposition, 4) the development of a nanomachine for mitochondrial gene therapy. In the first year, we plan to develop a new packaging method for the TF-MEND, optimize nuclear and mitochondrial delivery. In 2011, we plan to design a series of functional nucleic acids and evaluate their functions. Our intermediate goal is to have a core technology of nano-machines by encapsulating functional nucleic acids into the TF-MEND. We then plan to optimize our system with respect to the nucleus and mitochondria to achieve our final goal.

【Expected Research Achievements and Scientific Significance】

The TF-MENHD is a new system created in our laboratory. It has the capability to overcome the rate-limiting steps associated with our preliminary systems such as the original MEND, the T-MEND and the MITO-Porter and is the top technology in the world by which not only biodistribution but also intracellular trafficking are controlled. In addition, functional nucleic acids encapsulated into the TF-MEND are endowed with abilities to perform gene expression/gene correction in the nucleus or mitochondria, which has never been achieved to date. Therefore, the new system proposed in this study could serve as both a “gene carrier” and a nanomachine, which has the potential to serve as a core technology for gene therapy originating from Japan.

【Publications Relevant to the Project】

1. H. Akita, et al. Multi-layered nano particles for penetrating the endosome and nuclear membrane via a step-wise membrane fusion process. ***Biomaterials*** 30(15): 2940-9 (2009).
2. Y. Yamada, et al. MITO-Porter: A liposome-based carrier system for delivery of macromolecules into mitochondria via membrane fusion. ***Biochim. Biophys. Acta*** 1778(2): 423-32 (2008).

【Term of Project】 FY2010-2014

【Budget Allocation】 166,700 Thousand Yen

【 Homepage Address and Other Contact Information】
http://www.pharm.hokudai.ac.jp/yakusetu/index.html