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

Biological Sciences (Medicine, dentistry, and pharmacy Ⅰ)

Title of Project：Study on Innovative Molecular Target Nano-Medicines Using Nano Delivery System Encapsulating Smart Synthetic Oligodeoxynucleotides

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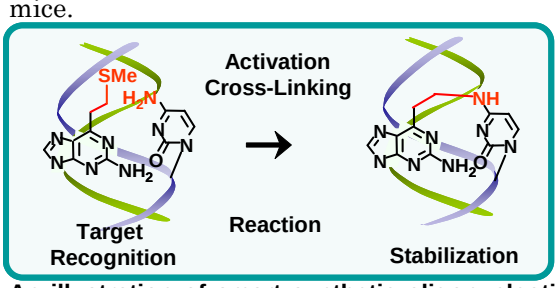
Research Area：Medicinal Chemistry

Keyword：Therapeutic Oligonucleotides, drug deliver system, nano-medicine, genetically engineered mouse, diabetes

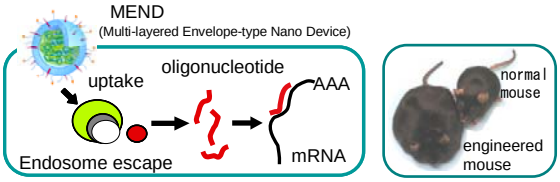
【Purpose and Background of the Research】

Therapeutic oligonucleotides such as antisense、siRNA affect the target RNA to inhibit its expression. In another interesting application, inhibitory roles of miRNA can be interrupted by oligonucleotides, resulting in enhancement of the expression of the target RNA. In spite of extensive investigations, only a few therapeutic oligonucleotides have been on market, and a number of problems have remained. In this project, chemical modification of the oligonucleotides for tolerance in living systems, new delivery systems for efficient and selective delivery to the target tissues, determination of the target gene for higher therapeutic efficacy will be investigated by collaborative studies of synthetic chemists, researchers of drug delivery, and research group of genetic engineering of mice.



An illustration of smart synthetic oligonucleotides that reacts with the target RNA to effect high specificity and enhancement of inhibition.

【Research Methods】



Delivery of oligonucleotide by delivery with MEND **Experimental model mouse**

(1) Therapeutic oligonucleotides (Sasaki Group, Nagatsugi Group, Shindo Group)
(2) Determination of the target gene for treatment of type II diabetes (Harashima group, Nomura group)
(3) Tissue specific delivery (Harashima Group)
(4) Evaluation of oligonucleotide-encapsulating nano device by using gene-engineered experimental mice (Nomura group)

The following groups will collaborate for accomplishment of this project; S. Sasaki (Kyushu University), F. Nagatsugi (Tohoku University), M. Shindo (Kyushu University), H. Harashima (Hokkaido University) and M Nomura (Kyushu University).

【Expected Research Achievements and Scientific Significance】

Molecular target nano-medicines for treatment of type II diabetes will be developed based on the multi-layered envelope type nano-device encapsulating the smart synthetic oligonucleotides. Candidate genes responsible of type II diabetes will be also explored by use of the newly developed nano- device.

【Publications Relevant to the Project】

・Ali M. M., Oishi M., Nagatsugi F., Mori K., Nagasaki Y., Kataoka K., Sasaki S., Intracellular Ability of an Inducible Alkylation System to Exhibit Antisense Effects with Greater Potency and Selectivity, *Angew. Chem. Int. Ed.*, **45**, 3136-3140 (2006).
・A. El-Sayed, IA. Khalil, K. Kogure, S. Futaki, H. Harashima, Octaarginine- and octalysine-modified nanoparticles have different modes of endosomal escape. *J Biol Chem.* **283**, 23450-61 (2008).
・Goto Y, Nomura M, Tanaka K, Kondo A, Morinaga H, Okabe T, Yanase T, Nawata H, Takayanagi R, Li E. Genetic interactions between activin type IIB receptor and Smad2 genes in asymmetrical patterning of the thoracic organs and the development of pancreas islets. *Dev Dyn* **236**, 2865-74 (2007).
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【Term of Project】 FY2009-2013

【Budget Allocation】 159,300 Thousand Yen

【Homepage Address and Other Contact Information】

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