

【Grant-in-Aid for Specially Promoted Research】

Science and Engineering (Chemistry)



Title of Project : Development of polymeric micelles for Brain-Targeted Delivery of Nucleic Acid Drugs to Treat Intractable Neurological Diseases

Kazunori Kataoka
(The University of Tokyo, Graduate School of Engineering,
Professor)

Research Area : Nanobiotechnology, Polymer chemistry

Keyword : Drug delivery systems, Nanobiomaterials, polymeric micelle, brain targeting

【Purpose and Background of the Research】

In the aging society of developed countries, strong demand is placed on the cure of neurological disorders, such as Alzheimer's disease, which now affects over 200,000 people in Japan. Recent progress in understanding the underlying molecular mechanisms of neurological disorders holds promise for development of nucleic acid-based therapies that modulate disease pathways through regulation of gene expression. To this end, novel drug delivery systems (DDS) are indispensable for the successful function of these nucleic acid drugs in brain cells, such as neurons, by penetrating the tight barrier of endothelial/ependymal cell layers that protect the brain from outer environments.

In this context, this research project aims to develop nano DDS that overcome the brain barrier for nucleic acid delivery to central nervous system, and further, demonstrate the efficacy of the nano DDS on the molecular therapy of neurological disorders. In particular, multifunctional block copolymers are elaborated to construct polymeric micelles featuring biocompatibility, target specificity, and stimuli responsivity for smart nucleic acid delivery (Figure 1).

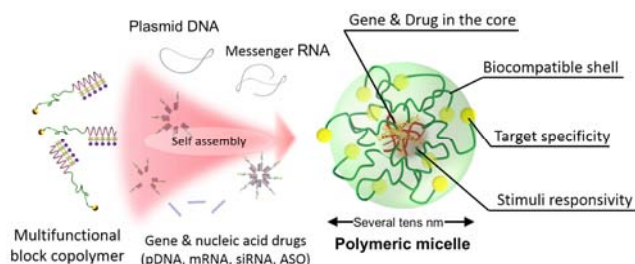


Figure 1 Polymeric micelle-based nanocarrier for smart nucleic acid delivery

【Research Methods】

This project is performed by three research groups on the molecular design, the functional assessment, and the therapeutic evaluation under the supervision of the principal investigator. The molecular design group develops multifunctional block copolymers and their self-assemblies with nucleic acids, i.e., polymeric micelles, for enhanced

blood circulation property and tissue penetrability (biocompatibility), brain cell-targeting ability (target specificity), and overcoming subcellular barriers in response to the intracellular stimuli (stimuli responsivity). The functional assessment group investigates the basic, biological functionalities of the obtained polymeric micelles using cultured brain-related cells and mice. Further, the therapeutic evaluation group optimizes the structure of therapeutic nucleic acids/targeting peptide ligands, and then, verifies the therapeutic efficacy of their polymeric micelles on murine disease models.

【Expected Research Achievements and Scientific Significance】

Accomplishment of this project will enable molecular therapy by nucleic acid drugs to cure neurological diseases, which lack established effective therapies. Furthermore, development of an approach to overcome the blood-brain barrier to deliver various bioactive compounds into the brain will certainly provide innovative contributions for the treatment of a broad scope of neurological disorders, such as brain tumors and amino acid metabolism disorders.

【Publications Relevant to the Project】

1. S. Uchida, K. Kataoka, et al. In vivo messenger RNA introduction into the central nervous system using polyplex nanomicelle. *PLoS One* 8, e56220 (2013)
2. R. J. Christie, K. Kataoka, et al. Targeted polymeric micelles for siRNA treatment of experimental cancer by intravenous injection. *ACS Nano* 6, 5174-5189 (2012)

【Term of Project】 FY2013-2017

【Budget Allocation】 427, 600 Thousand Yen

【Homepage Address and Other Contact Information】

<http://www.bmw.t.u-tokyo.ac.jp/>
kataoka@bmw.t.u-tokyo.ac.jp