

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

Integrated Disciplines (Complex Systems)



Title of Project : Development of heteroduplex oligonucleotide crossing the blood-brain barrier

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Research Area : Complex Systems

Keyword : Oligonucleotide, Biotechnology, Glucose transporter, Recycling

【Purpose and Background of the Research】

We developed heteroduplex oligonucleotide having a new molecular structure and mechanism of action, which is a breakthrough platform technology from Japan showing 10 to 1000 times the effectiveness of existing oligonucleotides (Nat Commun 2015). Moreover, we also developed a delivery system for polymeric drugs efficiently crossing the blood brain barrier (BBB) to reach the central nervous system by manipulating the blood glucose level of animals (Nat Commun [in revision]).

In this study, we aim to develop an innovative heteroduplex oligonucleotide that conjugates to the glucose transporter (Glut), crosses the BBB, and enables the regulation of arbitrary genes in the central nervous system.

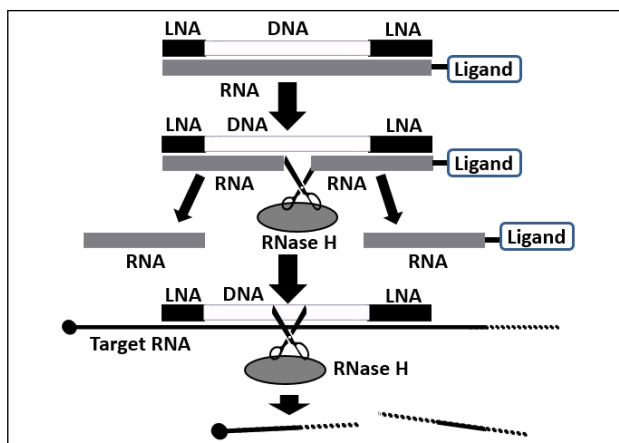


Figure 1 Gene silencing mechanism of heteroduplex oligonucleotide

【Research Methods】

We perform the screening of antibody clones that bind to Glut and create a linker that increases cell transduction efficiency and blood retention. We also elucidate the biological mechanism of and optimize the efficiency of BBB-crossing. In addition, we control the blood kinetics of heteroduplex oligonucleotide and to create technologies that increase RNase resistance. Furthermore, we optimize the oligonucleotide sequence and structure

for the treatment of neurodegenerative diseases, and examine the therapeutic effect and safety in model mouse.

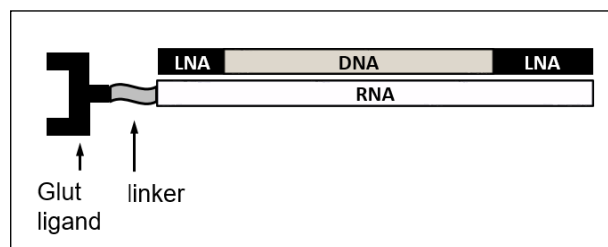


Figure 2 Structure of heteroduplex oligonucleotide crossing the blood-brain barrier

【Expected Research Achievements and Scientific Significance】

Our heteroduplex oligonucleotide is expected to become useful to achieve gene regulation in the central nervous system by systemic administration. We expect that this innovative platform technology opens a new field of drug development to treat many intractable neurological and psychiatric disorders, such as Alzheimer's disease, in the future super aging society.

【Publications Relevant to the Project】

Nishina K, Piao W, Yoshida-Tanaka K, Sujino Y, Nishina T, *et al.* DNA/RNA heteroduplex oligonucleotide for highly efficient gene silencing. Nat Commun 6: 7969, 2015.

Anraku Y, Kuwahara H, Fukusato Y, Mizoguchi A, Ishii T, *et al.* Crossing the BBB: Glycaemic control boosts glucosylated nanocarrier transport into the brain. Nat Commun (in revision).

【Term of Project】 FY2017-2021

【Budget Allocation】 133,100 Thousand Yen

【Homepage Address and Other Contact Information】

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