Editorial

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Therapeutic oligonucleotides and delivery technologies: Research topics in Japan

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Summary **Oligonucleotides have been gaining considerable attention as promising and effective candidate therapeutics against various diseases. This special issue is aimed at providing a better understanding of the recent progress in the development of oligonucleotide-based therapeutics to encourage further research and innovation in this field to achieve these advancements. Several Japanese scientists have been invited to contribute to this issue by describing their recent findings, overviews, insights, or commentaries on rational designing of therapeutic oligonucleotide molecules and their novel delivery technologies, especially nanocarrier systems.**

Keywords: Oligonucleotide, drug delivery, chemical modification, conjugation

In new drug discovery, the inhibition of cellular mRNA relevant to diseases has become an attractive strategy, while the molecular biology of diseases has been revealed at gene levels (*1*). Functional oligonucleotides such as antisense and small interfering RNA oligonucleotides (ASO and siRNA, respectively) are currently recognized as promising therapeutic entities that are effective for not only intractable diseases and genetic disorders but also various illnesses that do not have adequate existing therapies. Although an oligonucleotide-based therapy is supposed to be specific for the sequence of its targeted gene, initial clinical trials have taught us safety and efficacy lessons (*2,3*). Oligonucleotides are polyanionic macromolecules and naturally instable against degradation by nucleolytic enzymes in the body. Therefore, their self-mediated transportation into targeted cells is limited, which may cause off-target effects, non-specific immune stimulation, or both. This is also partly due to the lack of safe and effective *in vivo* delivery techniques. Viral and non-viral artificial carriers have been reported as effective carrier systems for specific targets (*4,5*). However, the safety of these *in vivo* carriers including their materials or sources is another inevitable problem in the development of systemic delivery systems for oligonucleotides (*6*). Thus, the major challenge for the clinical application of ASO and siRNA is solving the oligonucleotide stability issues and their delivery to specific targets.

The remarkable progress in unraveling the medicinal chemistry of nucleic acids in the last decade has improved the *in vivo* stability and target affinity of synthetic oligonucleotides using chemical modifications or rational designs (*7*). These advances have also promoted the feasible use of synthetic oligonucleotides as therapeutics. After the successful introduction of phosphorothioate modifications into ASO (*8*), various chemical modifications improved its stability against different nucleases as well as the binding affinity for target mRNA. These modifications include the use of locked nucleic acids (LNAs), 2′-*O*-methoxyethyl, and a constrained ethyl bridge nucleic acid (BNA). Recently, Yokota and co-workers (*9,10*) reported a novel DNA/RNA heteroduplex oligonucleotide (HDO) and its α-tocopherol conjugate as a targeting ligand. This α-tocopherol HDO conjugate showed significantly high specificity for the target and exerted remarkably potent gene-silencing efficacy *in vivo*. Obika and co-workers (*11,12*) have greatly contributed to the development of synthetic oligonucleotides including LNAs and BNAs. In this special issue, they have provided their recent results of the synthesis of 5′-thio-modified

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2′-deoxy-5-methylcytidine ASO and the influence of this modification on the stability of ASO, which was demonstrated in *in vitro* and *in vivo* experiments. In contrast, the cost of manufacturing oligonucleotides appears to have increased with the advancement in chemical modifications and complicated molecular designs. Chemical modification should alter the physicochemical properties of oligonucleotides to affect their distribution in the body. Therefore, a significant increase in affinity and specificity for target genes is considered essential for such synthetic oligonucleotides. Nishikawa provides his insights on the issue while introducing a unique self-gelatinizable nucleic acid technology and DNA hydrogel.

The development of an effective and safe delivery system or technology is essential for the success of synthetic oligonucleotides. The laboratory of Kataoka (*13,14*) has developed polyplex nanomicelles composed of poly(ethyleneglycol)-polycation block copolymers as gene delivery systems that are leading the field of nanocarrier system development. Miyata reviews the recent discoveries of polymer-based carriers for systemic oligonucleotide delivery. Negishi and co-workers introduced a non-invasive gene delivery technology based on the combination of lipid bubbles and ultrasound, in addition to an overview of the research conducted in this area. Asami and co-workers reviewed the recent technologies of conjugating a functional ligand for effective targeting and introduced their novel HDO and α-tocopherol conjugate.

Oral drug delivery is the most popular and patient-friendly route of administration but developing an effective delivery system for oligonucleotides remains a major challenge. The bottleneck in developing nucleic acid-based oral therapeutics has been their low bioavailability, which leads to high costs because of drug loss in the alimental canal based on their instability and impermeability. We provide a commentary that describes the potential benefits of the colorectal route as another platform for the development of oral oligonucleotide therapeutics and introduce the liver-targeted enteral siRNA delivery technology we recently developed (*15*). The importance of targeting or the availability of oligonucleotides in targeted tissue is highlighted in contrast to systemic availability, which does not directly reflect the effects of oligonucleotide.

The editor hopes that this special issue will provide a better understanding of the recent progress in the development of oligonucleotide-based therapeutics and, thereby, encourage further research and innovation in this field for achieving advancements.

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