Towards the development of safe and effective therapeutic antisense oligonucleotides

Laboratory of Bioorganic Chemistry, Graduate School of Pharmaceutical Sciences

Associate Professor Takao Yamaguchi Researchmap https://researchmap.jp/takao-yamaguchi?lang=en

Professor Satoshi Obika Researchmap https://researchmap.jp/read0014368?lang=en

Abstract

Antisense oligonucleotide is designed to form duplex with target RNA in a sequence-specific manner. It allows for various therapeutic approaches, such as reducing the expression levels of disease-causing mRNA or altering splicing to increase the expression of the targeted proteins. As of September 2023, this field has grown to the point where 10 products have received approvals. One of the significant features of antisense oligonucleotide is the ability to quickly develop drugs based on the sequence information of mRNA and pre-mRNA.

In our laboratory, we have been focusing on the development of artificial nucleic acids to enhance the safety and efficacy of antisense oligonucleotide. In recent years, we have successfully developed GuNA[t-Bu], AmNA, scpBNA, and 5′-cp. We are now advancing their applications by incorporating them into therapeutic antisense oligonucleotides.

Background & Results

Two crucial properties in antisense oligonucleotide are stability against nucleases and ability to form duplex with the target RNA. We have developed several artificial nucleic acids aimed at improving these two properties and have been advancing their applications in antisense oligonucleotide. For example, AmNA and scpBNA have been developed as artificial nucleic acids that significantly enhance both of these properties, leading to a remarkable enhancement of the therapeutic efficacy of antisense oligonucleotide. We have also developed 5′-cp that enhances stability against nucleases and improves the safety of antisense oligonucleotides. In recent studies, we have discovered that GuNA[t-Bu], which contains a bulky *tert*-butyl group, significantly enhances the duplex-forming ability of oligonucleotide toward the complementary single-stranded RNA. X-ray crystallography of the duplexes containing GuNA[t-Bu] revealed that the *tert*-butyl group fits into the minor groove of the duplexes. This result indicates that the *tert*-butyl group of GuNA[t-Bu] interacts with the minor groove and enhances duplex stability. Furthermore, incorporation of GuNA[t-Bu] into oligonucleotide significantly increased stability against nucleases. Therefore, GuNA[t-Bu] is a good candidate for use in therapeutic antisense oligonucleotides.

We are also working on establishing a supply system for these four artificial nucleic acids (GuNA[t-Bu], AmNA, scpBNA, and 5′-cp). We believe that these artificial nucleic acids are helpful for developing therapeutic antisense oligonucleotides.

Significance of the research and Future perspective

Development of therapeutic antisense oligonucleotides is becoming more active specially for genetic diseases that are difficult to treat with small molecule drugs or antibody-based drugs. We have developed several artificial nucleic acids that enhance the safety and efficacy of therapeutic antisense oligonucleotides. We are actively promoting the use of these artificial nucleic acids to therapeutic oligonucleotides, with the goal of expeditiously providing effective medications.

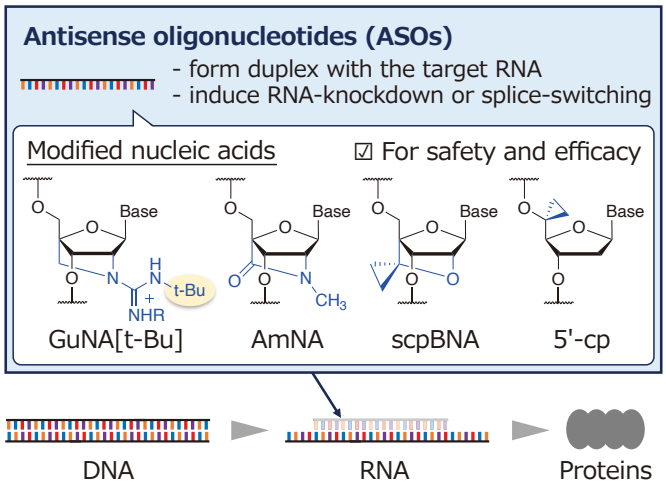

Figure 1 Development of modified nucleic acids for therapeutic antisense oligonucleotides.

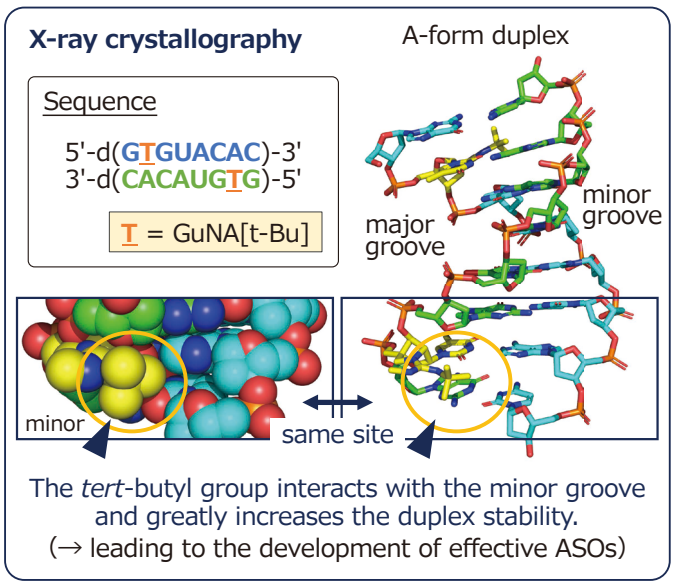

Figure 2 The structure of GuNA[t-Bu] in duplex.

Patent Japanese Unexamined Patent Publication No.WO2011052436, No.WO2014046212, No.WO2015125783, No.WO2020158910

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Keyword antisense, oligonucleotide therapeutics, drug discovery, RNA, DNA