Structural Basis for Antigene and Antisense Duplexes with Mdified Nucleotides

Ella Czarina Magat Juan[a], Takeshi Kurihara[a], Jiro Kondo[a], Takanori Ito[b], Yoshihito Ueno[c], Akira Matsuda[b] and Akio Takénaka[a], [a]*Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, Yokohama, Japan.* [b]*Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.* [c]*Faculty of Engineering, Gifu University, Gifu, Japan.* E-mail: ella@bio.titech.ac.jp

Oligonucleotides containing polyamines are currently being evaluated as potential antigene and antisense compounds. Those with 5-(*N*-aminohexyl)carbamoyl-2'-deoxyuridine (^{N}U) and its 2'-*O*-methyl derivative ($^{N}U_m$) exhibit improved nuclease resistance. Furthermore, these nucleotides stabilize duplex formation of the modified DNA and its target DNA or RNA strand. X-ray structures of these duplexes have shown good correlation between the conformational changes and the observed chemotherapeutic properties.

The amide groups of the modified uracil bases form six-membered rings through the intramolecular NH---O4 hydrogen bonds, so that the aminohexyl chains protrude into the major grooves. Some of the terminal ammonium groups are involved in intra-duplex interactions with phosphate oxygen anions, whereas the others interact with those of the adjacent duplex. Such interactions contribute to the stability of duplex formation. The 2'-*O*-methyl modification in $^{N}U_m$ shifts the ribose ring toward the C3'-*endo* conformation and influences duplex stability. Observed changes in the dimensions of the minor grooves and in the hydration structures are well correlated to nuclease resistance.

Keywords: antigene, antisense, crystal structure