SARS-CoV-2 ゲノム RNA を標的とし COVID-19 治療薬を指向した新規触媒的標的 RNA 切断機能付与型キメラ人工核酸の開発Ⅰ：構造設計･合成と in vitro 機能評価

（東北大多元研[1]・名大院理[2]・東北大災害研[3]・長崎大院医歯薬[4]）○藤田 一寿[1]・石渡 望[1]・稲垣 雅仁[2]・西嶋 政樹[1]・林 宏典[3]・三瓶 悠[4]・荒木 保幸[1]・山本 剛史[4]・山吉 麻子[4]・児玉 栄一[3]・和田 健彦[1]

Construction of Catalytic Target RNA Cleavage Function Installed Chimeric Artificial Nucleic Acids (CANA) toward Development of COVID-19 Treatments-I: Design, Synthesis, and in vitro Properties ([1]*IMRAM, Tohoku Univ.*, [2]*Nagoya Univ.*, [3]*IRIDeS, Tohoku Univ.*, [4]*Grad. Sch. Biomed. Sci., Nagasaki Univ.*)○Kazutoshi Fujita[1], Nozomu Ishiwata[1], Masahito Inagaki[2], Masaki Nishijima[1], Hironori Hayashi[3], Yu Mikame[4], Yasuyuki Araki[1], Tsuyoshi Yamamoto[4], Asako Yamayoshi[4], Eiichi Kodama[3], Takehiko Wada[1]

To apply oligonucleotide therapeutics as promising pharmaceutics, the following three issues should be improved, I) Off-target effects, II) Low cellular uptake capability, and III) Low therapeutic potency mainly originating from extremely low intracellular concentrations. We have proposed and demonstrated a novel design strategy for resolving these issues by the enhancement of RNase H mediated target RNA cleavage efficiency by the Chimeric Artificial Nucleic Acids (CANAs). CANAs are consisting of 5'-terminus modified DNA moiety conjugated with non-ionic peptide backbone artificial nucleic acids moiety such as PNA. To enhance the nuclease resistance and turnover number of RNase H mediated target RNA catalytic cleavage cycle, we designed and synthesized the second generation of CANAs (Fig.1) incorporation of Locked Nucleic Acid (LNA) and phosphorothioate (PS-oligo) modification on DNA moiety. In this study, the genome RNA of SARS-CoV-2 was set as the target, and our group applied the CANA for COVID-19 treatments.

Keywords : Oligonucleotide therapeutics; RNase H; Catalytic cleavage; RNA cleavage; Chimeric Artificial Nucleic Acids

次世代分子標的薬モダリティーとして期待される核酸医薬の実用化には“オフターゲット効果”と“細胞内極低濃度に起因する低治療効果向上”が喫緊の解決課題である。我々は両課題解決を目指し、RNase H を活用した標的 RNA 触媒的切断戦略に焦点を当て、標的 RNA の位置選択的切断による触媒回転数の向上を実現し得る新規核酸医薬としてリン酸アニオン骨格 DNA/LNA（架橋型核酸）と PNA 等アミド骨格人工核酸を融合したキメラ人工核酸（CANA）を提案し、その有効性を報告してきた。本研究では SARS-CoV-2 ゲノム RNA を標的とし COVID-19 治療薬への展開に取り組んだ。

本発表では、PO 結合と PS 結合を導入した第 2 世代キメラ人工核酸（図 1）の構造設計・合成と in vitro における特性ならびに機能について検討した結果を報告する。

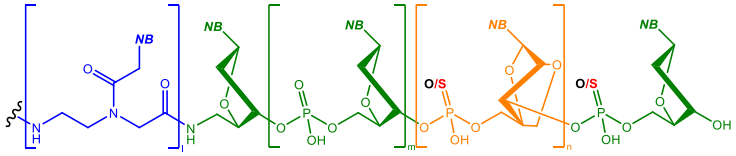

Fig.1 Structure of Chimeric Artificial Nucleic Acid (CANA).