# Staple oligomer hijacks protein translation machinery based on the conformational changes of mRNA structure

([1]Faculty of Advanced Science and Technology, Kumamoto University, [2]Department of Medical Information Sciences and Administration Planning, Kumamoto University Hospital, [3]Department of Cardiovascular Medicine, Faculty of Life Sciences, Kumamoto University, [4]Faculty of Science and Technology, Hirosaki University, [5]Institute for Chemical Research, Kyoto University) ○ Takuto Kamura[1], Yousuke Katsuda[1], Taishi Nakamura[2,3], Kenichi Tsujita[3], Yusuke Kitamura[1], Masaki Hagihara[4], Shin-ichi Sato[5], Toshihiro Ihara[1]

**Keywords**: *RNA G-quadruplex; Staple oligomer; Suppression of gene expression; Off-target effect; Next generation nucleic acid medicine*

Nucleic acid-based technologies such as antisense oligonucleotide (ASO) and small interfering RNA (siRNA) are effective strategies to inhibit the expression of disease-causing genes with sequence complementarity. The technologies often exhibit off-target effects emerging from the mis-hybridization to unintended genes. This is one of the challenges in the development of nucleic acid medicines. Although various ASO and siRNA design platforms have been developed to address this problem, there are still some genes that are difficult to target due to the limited number of potential sequences for high suppression efficiency and low off target effects.

Here, we developed an alternative method to suppress gene expression through induction of G-quadruplex structure in the target mRNA using single strand DNA or RNA named staple oligomer (**Fig. 1**). RNA G-quadruplex structure is known to inhibit protein translation by blocking the progression of ribosomes. The staple induced G-quadruplex structure on 5'UTR of mRNA and its expression level was significantly decreased both in vitro and in vivo. Furthermore, we succeeded in inhibiting the progression of the disease by suppressing responsible gene expression using the staple in disease-model mouse (**Fig. 2**).

The staple system would be a promising technique as a research tool in life sciences and new class of nucleic acid medicines.

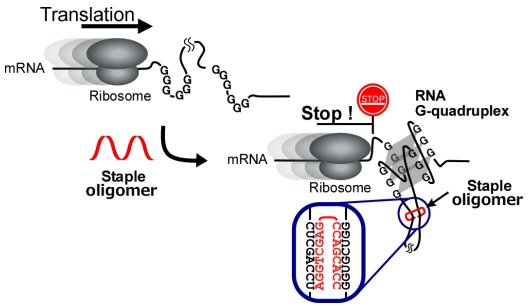


**Fig. 1** The suppression of target gene expression by staple-induced G-quadruplex

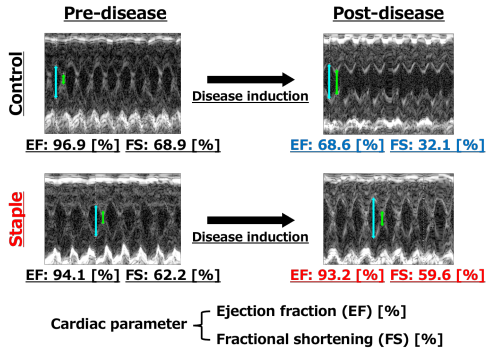


**Fig. 2** Evaluation of the effect of the staple on the disease progression.

© The Chemical Society of Japan