Towards novel therapeutics against SARS-CoV-2

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus that caused the pandemic in 2019, which resulted in >776 million infected cases and >7.1 million deaths as of September 2024. Although 13.6 billion vaccine doses have been administered globally so far, outbreaks are still occurring in several countries due to the emergence of new variants with increased transmissibility and immune evasive ability.

Recently, we have reported a high-resolution atlas of the translatome and transcriptome of SARS-CoV-2 for various time points after infecting human cells and have identified a potential translational regulatory element of SARS-CoV-2, termed the translation initiation site located in the leader sequence (TIS-L). Since TIS-L is included in all the genomic and subgenomic RNAs of SARS-CoV-2, we postulate that blocking this region may reduce the viral infectivity of SARS-CoV-2.

To evaluate this hypothesis, our group has designed antisense oligonucleotides (ASOs) that target TIS-L and assessed their antiviral abilities *in vitro* and *in vivo*. Some of our designed ASOs showed significant viral repression against the >95% original, delta, and omicron variant strains of SARS-CoV-2. Furthermore, when we assess the antiviral ability of our ASO *in vivo*, it is shown to be significantly effective against omicron BA.1 and original strains BALB/c and k18-hACE2 mouse models.

Overall, our results suggest that our designed ASO shows great potential as an effective antiviral therapeutic agent against SARS-CoV-2. For future studies, we are planning on identifying the exact mechanism of how TIS-L affects the viral translatome and the extent of its role in viral propagation.