Development of Nucleic Acid Based Therapeutics Using 4'-Thionucleic Acids

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Chemical modifications of naturally occurring nucleosides are of particular interest not only for the development of antimetabolites against cancer and viral infection, but also for functional oligonucleotides (ONs), such as antisense, antigenes, ribozymes, aptamers, and decoys. The epoch-making scientific discovery of RNA interference (RNAi), especially short interfering RNA (siRNA), has opened the way for the development of functional ONs, which are expected to become future diagnostic probes and therapeutic agents for knockdown or regulation of gene expression. A number of nucleoside analogs already have been synthesized and incorporated into ONs by chemical and enzymatic approaches, and studies of their properties, including biological applications, are under way world wide.

A 4'-thionucleoside is a nucleoside derivative in which the furanose ring oxygen is replaced by a sulfur atom. We have currently succeeded the stereoselective synthesis, via the Pummerer reaction, of 4'-thioribonucleosides, and revealed the properties of oligonucleotide consisting of 4'-thioribonucleosides, 4'-thioRNA. Because the 4'-thioRNA showed high nuclease resistance and hybridization properties, we thought that the RNA molecule would be a promising candidate for functional RNAs including RNA aptamer and short interfering RNA.

In this talk, I would like to report 1) efficient RNAi induced by siRNA modified with 4'-thioribonucleosides and 2) selection of 4'-thioRNA aptamers using 4'-thioUTP and 4'-thioCTP.