≪NEW INHIBITORS OF miRNA – Stable expression of efficient decoy RNA that inhibits specific microRNA≫

＜Summary of the inven＞

¦ Background

In order to understand the function of miRNA, it is essential to have means to inhibit the activity of individual miRNA selectively and persistently to facilitate the functional analysis. The existing methods to inhibit miRNA, such as “Locked Nucleic Acids (LNA)” and “Antagomirs” (Orom, U.A. et al. (2006) Gene, 372, 137-141; Krutzfeldt, J. et al. (2005) Nature, 438, 685-689) are designed to be directly introduced into cells and are effective only transiently. Recently, plasmid vectors that express competitive inhibitors of miRNA, “microRNA Sponge” have been reported (Ebert, M.S. et al. (2007) Nature Methods, 4, 721-726). MicroRNA Sponge inhibits miRNA to some extent but its inhibitory effects do not last long. It is desirable to have new potent miRNA inhibitors, which achieve long-term suppression to allow more accurate analysis in broad biological processes.

¦ Current Invention

The inventors have succeeded in designing inhibitory RNA decoys that inhibit miRNA much more effectively for longer periods (more than three months). These RNA decoys have a unique secondary structure with two complementary sequences to the specific miRNAs and can be expressed by lentiviral vectors. These decoys are transported into the cytoplasm after transcription by RNA polymerase III. Because these RNA decoys resist hydrolysis in the cell, they are named **“Tough Decoy RNAs (TuD RNAs)”.** Each TuD RNA molecule form stable structure that has high accessibility to a specific miRNA species and can strongly inhibit its function.

TuD RNAs can be used as a research tool to analyze the function of each miRNA. It is possible to prepare a library containing mixture of TuD RNAs to identify miRNAs that are involved in specific biological processes. By accumulating the experiences to design the most efficient TuD RNA molecules, synthetic version of TuD (designated **Synthetic TuD, S-TuD**) has been developed very recently, which is composed of two 2’-0 methylated RNA strands and has a similar structure to TuD. S-TuD have so potent inhibitory activity at nano-mol order that a single transfection of S-TuD can retain inhibitory effects even after several round of cell division. It is also anticipated that this approach will open doors for development of new RNA-based therapeutics through inhibiting specific target miRNAs.

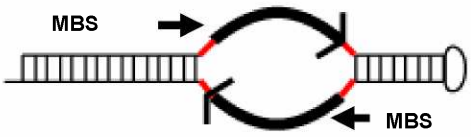

Fig ：Structure of Tough Decoy RNA

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＜Notes＞

■ Patent pending

■ Takeshi Haraguchi, et.al. (2009) “Vectors expressing efficient RNA decoys achieve the long-term suppression of specific microRNA activity in mammalian cells” Nucleic Acids Research, 2009, Vol. 37, No. 6 e43

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