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# Small RNA zippers lock miRNA molecules and block miRNA function in mammalian cells

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Small non-coding RNA-based diagnostic and therapeutic applications for human cancer are expected soon. Knocking down the expression level or blocking the function of oncogenic miRNAs is believed to be a promising strategy for cancer treatment. miRNAs loss-of-function phenotypes are mainly induced by chemically modified antisense oligonucleotides. Here, we develop an alternative inhibitor for miRNAs, termed as small RNA zipper. It is designed to bind to the 5'-half sequences of one molecule and the 3'-half sequences of another molecule of the target miRNA through a complementary interaction. The small RNA zipper can connect the target miRNA molecules end to end forming a DNA–RNA duplex with high affinity, high specificity and high stability. To avoid self-complementarity and to enhance binding specificity, LNA nucleosides were applied to synthesize the small RNA zipper. Two miRNAs, miR-221 and miR-17, were tested in human breast cancer cell lines, demonstrating the 70%-90% knockdown of miRNA levels by 30–50 nM small RNA zippers at 24-48 h after transfection. The effect of the miRNA zipper was not limited to the target miRNA, but also to the expression of iso-miRNAs. Let-7 family members and point mutated sequence were applied to further validate the specificity of the miRNA zippers. The miR-221 zipper shows capability in rescuing the expression of target genes of miR-221 and reversing the oncogenic function of miR-221 in breast cancer cells. In addition, we demonstrate that the miR-221 zipper attenuates doxorubicin resistance with higher efficiency than anti-miR-221 in human breast cancer cells. Taken together, small RNA zippers are a novel type of miRNA inhibitors, which can be used to induce miRNA loss-of-function phenotypes and validate miRNA target genes.

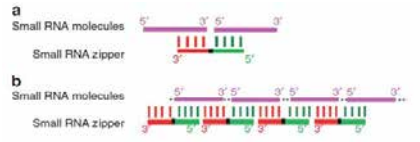


**Figure 1 | The construction of small RNA zipper.** (**a**) Schematic representation of the interaction between small RNA zipper and small RNAs. (**b**) Schematic representation of how the small RNA zippers connect the target small RNA molecules end to end, forming an RNA-DNA duplex.

## Biography

Zuoren Yu is currently a Professor at Tongji University School of Medicine, Research Center for Translational, Shanghai East Hospital. After obtaining PhD degree in 2003 from Chinese Academy of Medical Sciences, he started Post-doctoral training at University of Pennsylvania School of Medicine and Thomas Jefferson University Kimmel Cancer Center. In 2009, he was assigned for a Faculty position in the track of Research Assistant Professor at Thomas Jefferson University. After joining Tongji University in Shanghai in 2012, he has been focusing on non-coding RNA regulation of breast cancer stem cells related with drug sensitivity, tumour regeneration and cancer metastasis. His main research work includes: Finding cell cycle regulator CCND1 is involved in the regulation of miRNA biogenesis and histone H3K9 tri-methylation, finding a regulatory loop between CCND1 and miR-17/20 in breast cancer, and demonstrating a microenvironment-mediated heterotypic signalling through which miR-17/20 regulate cross talking between cancer cells and inhibit breast cancer cell migration and metastasis.

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