

## Modified siRNA Structure With a Single Nucleotide Bulge Overcomes Conventional siRNA-mediated Off-target Silencing

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### Abstract:

Off-target gene silencing is a major concern when using RNA interference. Imperfect pairing of the antisense strand with unintended mRNA targets is one of the main causes of small interfering RNA (siRNA) off-target silencing. To overcome this, we have developed “bulge-siRNA,” a modified siRNA backbone structure with a single nucleotide (nt) bulge placed in the antisense strand. We found that siRNAs with a bulge at position 2 of the antisense strand were able to discriminate better between perfectly matched and mismatched targets, with no loss in silencing of the intended target. Genome-wide analysis also revealed that the bulge-siRNAs significantly reduced off-target silencing of transcripts with complementarity to the seed region of the siRNA antisense strand. When compared to 2'-methoxy ribosyl (2'-OMe) modified siRNAs previously developed to alleviate antisense off-target silencing; the bulge modification could better discriminate between on- versus off-targets. Our results suggest that the bulge-siRNA structure is a simple, yet superior alternative to chemical modifications for minimizing off-target silencing triggered by conventional siRNA structures.

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