

ABSTRACT:

Mutations in the KRAS gene have been shown to drive the proliferation of cancer. RNAi serves as a unique genetic tool that has the potential to selectively bind mutant KRAS mRNA while sparing its wildtype counterpart and mitigating cell toxicity. The objective of this project is to identify the most potent modifications for G13D mutant specific KRAS siRNAs at the transcriptional and translational levels. Endpoint readouts comparing mutant and wildtype mRNA levels after transfection of the four lead G13D specific siRNAs showed that the EFTX 7 and 10 sequences had the greatest specificity to the mutant mRNA over that for the functional KRAS and the highest knockdown efficiency. To assess oncogenic MAPK pathway activity, the western blot analysis conducted also demonstrated KRAS knockdown at the translational level. In vivo studies testing if knockdown of KRAS with siRNAs produces off-target effects of cell toxicity warrants further investigation. By elucidating the most potent modifications, novel siRNA drugs that preferentially silence mutant KRAS can be developed, revolutionizing cancer therapy.