

# Engineered Therapeutic Viruses can Target Abnormal RNA Splicing in Cancer

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**Abstract:** Cancer is notoriously difficult to cure. While many modern therapies – like cytotoxic chemotherapies and radiation therapies – are highly effective at killing cancerous cells, most of them are not selective. Instead, they have off-target effects that harm healthy tissues and result in prototypical cancer treatment side-effects: anemia, infection, nausea, hair loss, and more. Even breakthrough treatments like CAR T-cell therapy have harmful side effects resultant from nonspecific targets. Here, we explore a novel approach to exploit mutations in RNA splicing machinery present in some cancers as a method for highly specific cancer cell elimination. SF3B1 is one of the most commonly mutated spliceosome associated proteins in cancer, where mutant SF3B1 results in aberrant splicing and abnormal protein expression or nonsense mediated mRNA decay. By creating engineered gene constructs that capitalizes on mutant-SF3B1's cryptic exon selection, we have created a gene therapy that allows for a suicide gene or toxic protein to selectively express in, and eliminate, SF3B1 mutant cancer cells. Initial transfections with naked plasmid have validated the ability of our gene constructs to selectively express apoptotic and fluorescent proteins in SF3B1-mutant cancer cells. Currently, we are working on utilizing adeno-associated virus vectors to deliver the gene therapy *in-vitro* in cultured cancer cell lines and primary patient-derived cells.

## Incidence and Need

**Globally:** 19 million cancer cases, 100,000 SF3B1 cases

	Cancer cases	Spending on healthcare	Productivity loss and premature mortality
<b>U.S. (2017)</b>	1.7 million	\$161.2 billion	\$190 billion
<b>U.S. (SF3B1)</b>	0.5%	\$850 million	\$1 billion

- 1 Selective activity in mutant cells
- 2 Vehicle for efficient intracellular delivery
- 3 Effective toxic protein or immune stimulant
- 4 Compatibility with other cancer treatments/chemotherapies

## Construct Design and Selective Expression

