A CRISPR-based system for modifying the length of 3’ untranslated regions (3’UTR) of an mRNA transcript that offers novel treatment strategies for prostate cancer and other diseases

Unmet Need

Abnormal length changes in the 3’ untranslated region (3’UTR) of mRNAs are associated with many diseases such as systemic lupus erythematosus, α-thalassemia, facioscapulohumeral muscular dystrophy, and cancer. While existing technologies can manipulate expression of polyadenylation machinery factors to globally increase or decrease 3’UTR length in a non-specific fashion, current methods cannot directly manipulate the length of a desired 3’UTR in a targeted manner. Prostate cancer, a disease associated with abnormal lengths in the 3’UTR, is the second most common cancer among men in the United States and androgen-deprivation therapies have been the mainstay of treatment for over 70 years. Advanced androgen-dependent prostate cancer ultimately progresses to lethal castration-resistant prostate cancer (CPRC) within five years of diagnosis for 10-20% of prostate cancers. The median survival rate of these patients is between 15 and 36 months. Neuroendocrine prostate cancer is an important aggressive subtype of prostate cancer that rarely arises de novo, but it is present in up to 20% of the CRPC patients who have failed androgen receptor-targeted therapies. There is a need for alternative treatment options to improve the outcome for patients diagnosed with CRPC.

Technology

Inventors at Duke and UC Irvine have reported a CRISPR-based system for modifying the length of 3’ untranslated regions intended to offer a novel treatment strategy for diseases with abnormal 3’UTR

Duke File (IDF) Number

IDF #:T-006713

Meet the Inventors

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Publication(s)

External Link(s)

- From the lab of Dr. Qianben Wang
- From the lab of Dr. Wei Li
- Alternative polyadenylation of mRNA and its role in cancer (Genes Dis, 2019)
- An atlas of alternative polyadenylation quantitative trait loci contributing to complex trait and disease heritability (Nat Genet, 2021)
- 3' UTR shortening represses tumor-suppressor genes in trans by disrupting ceRNA crosstalk (Nat Genet, 2018)
- CFIm25 links alternative polyadenylation to glioblastoma tumour suppression. (Nature, 2014)

length including prostate cancer. Specifically, this is a 3’UTR CRISPR-dCas13d Engineering System (3’ UTRCES) that manipulates the length of 3’UTR of an mRNA transcript by using gRNA to guide catalytically dead Cas13d (dCas13) to *cis* elements upstream and/or downstream of desired polyadenylation sites (PAS), thus preventing binding of trans factors involved in cleavage and polyadenylation and redirecting these processes to the alternative PAS. This technology has been demonstrated with *in vitro* studies and *in vivo* studies are ongoing.

Advantages

- Offers an alternative treatment strategy for castration-resistant prostate cancer patients
- Could be expanded to other applications and cancers as the length of 3’ untranslated regions of mRNA transcripts can have tremendous impact on processes vital to cell growth and development