Docket #: S18-318

TUNABLE RNA INTERFERENCE VIA NUCLEOTIDE MISMATCH DESIGN

Researchers at Stanford, the University of Massachusetts and the Chan Zuckerberg Biohub have developed methods to increase or decrease RNA interference target cleavage rates.

Harnessing the power of RNA interference (RNAi), the biological process of RNA-guided and sequence-specific gene expression downregulation, has revolutionized biomedicine by providing means for treating various diseases, especially diseases caused by mutated or aberrant gene expression. However, predicting the specificity and efficiency of RNAi reagents, such as microRNAs (miRNAs) and small interfering RNAs (siRNAs), has been constrained by an incomplete understanding of the sequence determinants of RNAi.

Stage of Research
The inventors have developed methods for the design and generation of guide RNAi reagents that can increase or decrease rates of RNA-induced silencing complex (RISC)-mediated target gene cleavage. The inventors introduce RISC Cleave-'n-Seq (RISC-CNS), a method for high-throughput screening of favorable guide:target mismatches. Analysis of RISC-CNS data (e.g., binding energies, association and cleavage rates) led to a generalizable model to predict the cleavage rate of any RISC complex. The inventors validate their model by assessing gene knockdown in a cellular system.

Applications

- Tunable RNA interference by introducing nucleotide mismatches

Advantages

- Nucleotide mismatches can be designed to increase or decrease target cleavage rate
- *In vitro* measured biochemical parameters explain knockdown in cells

Publications

- Becker et al., 2019, Molecular Cell 75, 1-15 (doi: https://doi.org/10.1016/j.molcel.2019.06.012)
- PCT publication WO2020251973

Patents

- Published Application: WO2020251973

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