(SD2022-275) Methods and compositions governing the use of proteins and protein domains that enhance exon inclusion

Tech ID: 33400 / UC Case 2021-Z08-1

ABSTRACT

The strategy employed by the invention is inspired by splicing factors, a category of RNA-binding protein that influence alternative splicing outcomes. These splicing factors are trans-acting, and act to enhance or silence exon inclusion by binding near or on the target exon and promoting or repressing the activity of splicing machinery. Scientifically, a highly programmable, minimally disruptive system to increase exon inclusion could allow for higher-throughput identification of functional roles of specific exons than have been previously shown.

TECHNOLOGY DESCRIPTION

Alternative splicing is a co- and post-transcriptional processing step in which certain regions of transcribed pre-mRNA are included or skipped from the final mRNA product depending on the regulatory environment at the time of processing. Alternative splicing is a major source of expanded protein diversity over the raw number of genes in the genome, with virtually all human protein coding genes expressing multiple alternatively spliced isoforms. Mis-regulation of this process has been implicated in many diseases.

Targeted modulation of alternative splicing presents an opportunity for therapeutics, by correcting mis-splicing of specific RNA targets, and for scientific inquiry, by functionally probing individual splicing events.

Approaches have been taken to induce the skipping of alternative exons. Targeted inclusion, however, is less common since the blunt approaches of inhibiting splicing mechanisms by targeted destruction or steric inhibition of splicing signals at the target is not a viable strategy.

Researchers from UC San Diego have developed a scalable approach to identify known and novel proteins that enhance inclusion of alternatively spliced exons when placed in proximity to the target exon. Engineering is informed by a large-scale assay of naturally occurring/expressed human RNA-binding proteins to determine the strongest splicing factors that when tethered close to a target exon causes inclusion. The resulting list of natural candidates is utilized for the optimization of the synthetic, targeted systems for tunable strength and minimal size. This invention consists of the list of RNA binding proteins identified through the large-scale assay, engineered effector protein domains optimized using these results, and the use of these with RNA-targeting modalities to induce the inclusion of targeted exons.

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OTHER INFORMATION

CATEGORIZED AS

- **Biotechnology**
  - Genomics
- **Medical**
  - Gene Therapy
  - Research Tools

RELATED CASES

2021-Z08-1

APPLICATIONS

This invention can be used for many applications depending on the specifics of the target exons, including but not limited to modulation of gene expression and correction of aberrant splicing. Therapeutically, genetically encoded exon inclusion is of relevance to many diseases, including cancer and spinal muscular atrophy, where the concept is currently applied therapeutically.

ADVANTAGES

STATE OF DEVELOPMENT

INTELLECTUAL PROPERTY INFO

RELATED MATERIALS

▶ Schmok JC, Jain M, Street LA, Tankka AT, Schafer D, Her HL, Elmsaouri S, Gosztyla ML, Boyle EA, Jagannatha P, Luo EC, Kwon EJ, Jovanovic M, Yeo GW. Large-scale evaluation of the ability of RNA-binding proteins to activate exon inclusion. Nat Biotechnol. 2024 Jan 2 - 01/02/2024

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