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NOVEL UBIQUITOUS CHROMATIN-OPENING ELEMENT FOR STABLE LONG-TERM TRANSGENE EXPRESSION

Researchers at Stanford and the Chan Zuckerberg Biohub have identified a novel chromatin remodeling element for stable long-term transgene expression.

Gene therapy applications and biomanufacturing of therapeutic proteins require stable long-term transgene expression. Unfortunately, heterologous expression of transgenes in mammalian cells is susceptible to time-dependent epigenetic silencing. Regulatory elements that resist transgene silencing, such as ubiquitous chromatin opening elements (UCOEs), can improve transgene expression both in vitro and in vivo. However, known UCOEs are relatively long in sequence length and can exhibit intrinsic bidirectional promoter activity, resulting in reduced cloning utility and non-specific transcriptional activation, respectively. Furthermore, their efficacy is highly dependent on cell type and promoter choice. Thus, there remains a need for a chromatin opening sequence under 1 kb that can predictably stabilize a broad diversity of gene expression constructs without off-target effects.

Stage of Research
The inventors designed a computational algorithm to search the human genome for putative UCOEs and have identified and characterized a novel UCOE, SRF-UCOE, which stabilized transgene expression across several different promoters. SRF-UCOE outperformed the well-characterized UCOE, A2UCOE, and its associated truncations in both stable transfection and lentiviral integration experiments. This work helps to elucidate the underlying mechanism of these chromatin opening elements and expands their utility.

Applications

- Improved UCOE for use in existing biotechnology applications
- Effective SRF-UCOE core sequence (761 bp) broadens utility in viral delivery systems for gene therapy

Advantages

- Versatile use in stable transfection and/or viral delivery systems
- Stabilizes transgene expression across several common promoters
- SRF-UCOE does not exhibit inherent transcriptional activity, limiting potential off-target effects

Publications

- Rudina SS and Smolke CD. A novel chromatin-opening element for stable long-term transgene expression. bioRxiv. 2019.

Patents

- Published Application: WO2020223160
- Published Application: 20220193266
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