Docket #: S20-174

Optimized Synthesis and Translation of RNA Therapeutics

Stanford researchers have developed improved methods for producing mRNAs. Efficient, robust and high fidelity production of mRNAs is critical for obtaining pharmaceutical quality vaccines, viruses and expression constructs, and for eliminating noise due to batch variation. The researchers optimized conditions for efficient mRNA synthesis, m^7G-capping, and poly(A)-tailing of in vitro transcribed RNA. Such mRNA synthesis can be performed for an individual mRNA but was optimized to be equally well performed for hundreds of different barcoded mRNAs in parallel in one reaction. They also developed a powerful new platform that uses barcoded synthetic mRNA libraries to measure translation efficiency (via polysome profiling) and stability (via time course RNA sequencing). Such synthetic mRNAs carry a unique nucleotide barcode in the 3' UTR that can be used for mRNA identification in large-scale parallel assays based on RNA-seq. This platform allows high-throughput testing of tens of thousands of rationally and/or computationally designed sequences to achieve optimal protein levels. The nucleotide sequence of mRNA is a primary determinant of efficient cellular gene expression; thus, the ability to perform a large-scale analysis of designed mRNA sequences for their ability to be translated efficiently and remain stable inside cells is essential to developing candidates. The new, massively parallel, powerful reporter assay platform is poised to evaluate existing and novel sequence designs as well as inform future rational designs of mRNA-based therapeutics in broader contexts.

Applications

- Discovery of the most efficient mRNA sequences for optimal gene expression
- RNA therapeutics, RNA-based vaccines, viral delivery vectors, reporter constructs, vectors for gene expression, and vectors for increased antigen production
- COVID-19 mRNA vaccine development

Advantages

- Supports efficient, robust and high fidelity production of mRNA
- High throughput
- Unique mRNA 3' UTR barcodes allow for analysis of hundreds of mRNAs in all-in-one assays
- Supports rapid and highly parallel library sequence design
- Allows repeated cycles of directed and unbiased selection of optimized mRNA sequences

Publications

- Leppek et al. bioRxiv (2021) Combinatorial optimization of mRNA structure, stability, and translation for RNA-based therapeutics

Patents

- Published Application: WO2022047427
- Published Application: 20220064631
- Published Application: 20230159915
- Issued: 11,492,611 (USA)

Innovators

- Maria Barna
- Kathrin Leppek
- Gun woo Byeon

Licensing Contact

Sam Rubin

Licensing Associate, Life Science

Email