Group #24

Development of Novel Circularizable Self-Amplifying RNAs for Prolonged and Potent Therapeutic Gene Expression

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Abstract

Next-generation RNA therapeutics such as self-amplifying RNAs (saRNAs) and circular RNAs (circRNAs) have been developed to confront two major challenges in conventional mRNA therapeutics: rapid intracellular degradation by exonucleases and the high dosage requirements of mRNA lipid complexes. saRNAs, which encode a replicase enzyme that makes copies of the delivered RNA, show promise for increasing absolute transgene expression but fail to significantly increase expression duration. This project sought to synthesize circRNA and saRNA platforms into a single next-generation RNA that captures the strengths of both. The resulting RACER RNAs display efficient replication and circularization in cells, demonstrating their promise as multifunctional RNA therapeutics. Throughout this project, multiple constructs testing this concept were cloned and tested to confirm mechanisms, compare expression levels with previous designs, and analyze dynamics of amplification.