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Predictive Stability Modeling of mRNA Vaccines Based on Mechanisms of RNA Molecular Degradation

mRNA encapsulated in lipid nanoparticles (LNPs) is an important new platform for vaccines and therapeutics, with the demonstrated potential to be developed in record time to support public health emergencies. Characterizing drug properties during traditional long-term storage stability studies may be the slowest step in pharmaceutical development. Predictive stability models are essential to support rapid development while long-term stability studies proceed. Empirical models of stability are common and useful, but models based directly on scientific understanding of mRNA-LNP degradation mechanisms are required to enable the prediction of stability for new mRNA products with potential extrapolation of stability to longer storage times.

A key shelf life determining feature of mRNA-LNP systems is the proportion of mRNA remaining intact. In this work, two major molecular degradation mechanisms are elucidated and characterized using a mechanistic model. The model follows classical first-order kinetics, and connects to the fundamental understanding of the science of mRNA degradation. Modeling of degradation rates for mRNA-LNP products at different temperatures supports universal Arrhenius behavior independent of mRNA sequence. This allows for long-term shelf-life and storage prediction of mRNA products using accelerated stability studies. Degradation rates dependency on mRNA sequence is also investigated. Mechanistic models confirmed by data enable the prediction of shelf life for long-term storage of mRNA vaccines and therapeutics.