Cleveland Clinic Innovations

Improved mRNA Vaccine Design via Alteration of Codon Usage

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PRODUCT
Codon optimization strategy

INDICATION
mRNA Vaccines, Infectious Disease

VALUE PROPOSITION
- HSV codon optimization paired with ICP27 viral regulatory protein increases mRNA vaccine antigen expression
- Approach can be applied to other mRNA vaccines and viruses

DEVELOPMENT STAGE
- *In vivo* validation of codon optimization strategy

INTELLECTUAL PROPERTY
Patent application submitted

RELATED PUBLICATIONS
Lai, Chih-Jen et al. "Viral codon optimization on SARS-CoV-2 Spike boosts immunity in the development of COVID-19 mRNA vaccines." Journal of medical virology vol. 95,10 (2023): e29183.

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UNMET NEED

Codon optimization plays a crucial role in antigen design of mRNA therapeutics and vaccines through multiple aspects of the target protein expression: mRNA abundance, mRNA stability, translational efficiency, and correct protein folding. Synonymous codons and their cognate tRNAs occur at different frequencies across proteins, their domains, and the organisms they originate from. Regions of proteins mostly comprised of abundant codons and tRNAs in the organism tend to have high translational elongation rates and, therefore, efficient translation. Thus, codon-optimizing a target protein into the corresponding expression system or host significantly increases the protein expression. Over the last few years, mRNA vaccines have recently emerged as a promising alternative to traditional protein-based vaccines due to their capacity for rapid development, low-cost manufacture, and safe administration but there is still a need to reliably increase antigen expression and vaccine potency primarily as viruses do not carry their own translational machinery and need the host's translation system to express viral proteins. Therefore, to improve vaccine efficacy and host response, a novel codon-optimization platform utilizing viral codon usage may pave the way for the development of broadly protective mRNA therapeutics with lower dosages and fewer adverse effects.

SOLUTION

Cleveland Clinic researchers have developed a matched pair system where utilizing codon-optimization-based approaches results in higher antigen expression, increased immunogenicity, and enhanced protection. The methodology was tested for SARS-CoV-2 where the inventors packaged the mRNA construct containing ICP27 and HSV codon optimized SARS-CoV-2 spike protein (S-6P) in a lipid nanoparticle and demonstrated increased S-6P expression compared to delivery of S-6P mRNA in human cell lines. In addition, in vivo experiments for mice immunized with the codon optimized vaccine (mRNA-S-6P-ICP27) exhibited higher S-6P expression and IgG antibody titers against S-6P after a priming and booster dose compared to a non-codon optimized mRNA-S-6P vaccine. The codon optimized vaccine also demonstrated more durable neutralizing antibody titers 4 weeks following booster dose.

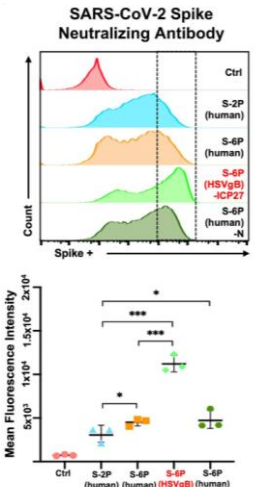

Fig 1. Codon Optimization to (HSVgB)-ICP27 increases S protein expression, folding and stability

While SARS-Cov-2 is used as a proof of principle, this platform can be adapted to a wide range of mRNA vaccine formulations.