Engineering Biology – *an mRNA Vaccine Design Challenge*

Faced with a global COVID-19 pandemic in 2019, researchers created an effective mRNA vaccine directed against the CoV-2 virus – in less than one year. This remarkable achievement required a knowledge of both *science* and e*ngineering*. The science developed over the last seven decades as we discovered molecular biology's central dogma (i.e., DNA/RNA/Proteins) and how our immune system works. The engineering involved is a new branch of biological engineering in which traditional materials of engineers – lumber, steel, and plastics – are replaced with nucleic acids, proteins, and cells.

In this activity, your students will be challenged to apply what they know about DNA/RNA/Proteins to design an mRNA vaccine that can activate our immune systems to protect us from virus infection.

Your students will explore:

- The nucleotide sequence encoding the CoV-2 spike protein.
- A Genetic Codon Chart and some fascinating consequences of codon degeneracy.
- The value of persistence by researchers who refuse to take *No* for an answer.
- The unexpected importance of a modified nucleotide discovered in tRNA in the 1960s.
- The clever mechanism whereby our immune systems distinguish between our endogenous mRNA and incoming viral RNA.

What your students need to know before they start:

- The sequence of amino acids in a protein is encoded by the sequence of nucleotides in messenger RNA.
- Codons consisting of 3 nucleotides can be translated into one of the 20 amino acids that make up proteins.

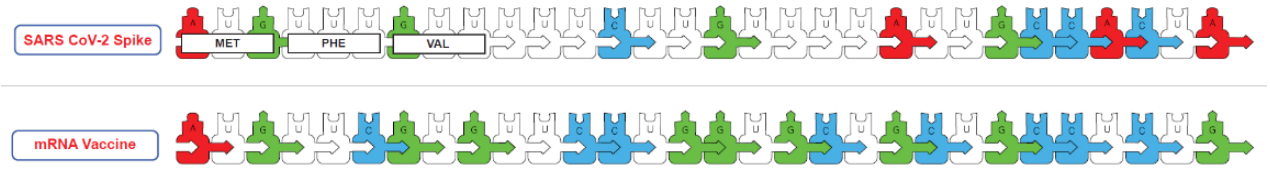
- Our genetic code is degenerate, meaning that more than one codon can encode the same amino acid. (We have four nucleotides (A-T & G-C) that can make 64 triplet codons.)

Provide your students with a model of the nucleotide sequence of the first ten amino acids of the mRNA encoding the CoV-2 Spike protein. The first three amino acids of the spike protein have been translated into the first three amino acids of the protein. (The RNA nucleotides shown are found in several 3D Molecular Designs' kits or can be purchased separately, as the Replacement DNA & RNA Nucleotide Set, or you can use whatever RNA nucleotides you have on hand.) [Flow of Genetic Information Kit© – 3D Molecular Designs].

1. Use the Table of Genetic Codons to translate the following seven codons into amino acids. (Pin the amino acid names on their corresponding codons.)

2. Provide your students with the printed copy of the CoV-2 mRNA vaccine sequence and ask them to compare it with the nucleotide sequence of the CoV-2 Spike mRNA. *Why are these two sequences different?*

3. Next, position the model of the beginning of the mRNA vaccine on top of the printed sequence. Complete the model of the mRNA vaccine by adding nucleotides to the mRNA vaccine following the published sequence.

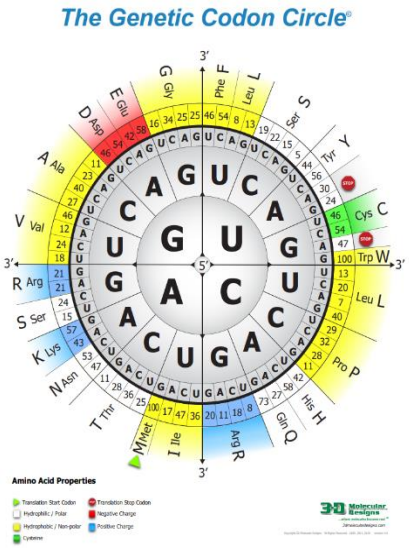


4. Using the Table of Genetic Codons – translate the nucleotide sequence of the mRNA into protein. What did you notice?

DISCUSSION: The reason the two different sequences encode the same amino acid sequence is a result of ***codon degeneracy*** (i.e., more than one codon can encode the same amino acid). The nucleotide sequence of the mRNA has been codon *optimized* so the mRNA vaccine will be more efficiently translated into the spike protein once it is taken up by the dendritic cells at the vaccination site.

To understand how codon optimization works, your students need to understand that humans (and all other species) prefer to use a subset of the 64 codons. For example, Leucine is encoded by 6 six different codons. But while CUG is used 40% of the time, UUA is only used 8% of the time.

5. Examine the circular Genetic Codon Circle (right) which includes the human codon preference for our 64 codons. Compare the codon preferences of the first ten codons of the SARS CoV-2 mRNA with the codon preferences of the engineered sequence of the mRNA vaccine.



EXTENSION: Remove the printed sequence of the mRNA vaccine and ask your students to use the codon preference numbers to design a new mRNA sequence that will be more efficiently translated than the SARS-CoV-2 mRNA.

Codon Optimization was one of several ways the COVID-19 mRNA vaccine was engineered to be more effective. Another important modification of the mRNA was the substitution of ***pseudouridine*** for uridine. To learn more, see our 2021 *Biotechnology & Coronavirus Webinar* @ about 47 minutes, or watch this video here.