Design of a Multivalent mRNA Vaccine to Protect Against Multiple Variants

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Overview

The constant emergence of new variants threatens the success of the mRNA vaccines developed against SARS-CoV-2. Therefore, there is an urgent need to develop a vaccine that will provide immunity against multiple variants â€“ both existing and potential. Prof. Yitzhak Pilpel and his collaborators created an algorithm to redesign the nucleotide sequence of mRNA vaccines such that a single sequence can give rise to multiple antigen variants, thus providing cross-immunity against multiple strains at once with broader immune protection.Â Â Â

Background and Unmet Need

Vaccines can elicit an efficient immune response against existing pathogens, such as viruses, bacteria, and fungi. However, the rapid evolution of pathogens can result in the emergence of strains/variants that can evade such immunity. Due to the obvious selective advantage of such evading strains, they might take over the pathogen population and ultimately lead to the collapse of herd immunity. This phenomenon raises great concerns these days as the efficiency of the successful mRNA vaccines developed against SARS-CoV-2 is jeopardized by the constant emergence of new variants. This reality compels constant redesigning of vaccines against newly formed variants and repeated vaccination of the population. Therefore, there is an urgent unmet need to develop a multivalent vaccine that will provide immunity against multiple variants, including ones that are only predicted to evolve, thus providing a broader and more durable immune response.

The Solution

Profs. Yitzhak Pilpel and his collaborators from the Weizmann institute created a computational platform for optimizing the nucleotide sequence of mRNA vaccines so a single or a few mRNA sequences may give rise to more than one variant in the body, thus eliciting broader immune protection.

Technology Essence

Prof. Pilpel and his team have recently exposed a code that governs translation errors in live cells (Ref. 1). The code rests on differential tendencies of synonymous codons to be translated with errors and to give rise to other amino acids. They also used immunopeptidomics to detect and quantify the presentation of aberrant peptides on MHC molecules for immune presentation (Refs. 2-3). Based on their findings, the team devised an algorithm that optimized the Moderna and Pfizer mRNA vaccine for SARS CoV-2. The algorithm consists of three ingredients: (i) the original nucleotide sequence of the vaccines; (ii) the ribosomal â€œconfusion matrixâ€ (Ref. 1) that depicts the errors that the ribosome is prone to make upon translation of each codon in the genetic code, and (iii) a collection of Variants of Concern (VoC) of SARS CoV-2. In short, the algorithm scans the original vaccine sequences, and in each position in which the original encoded amino acid differs from that of any VoC, it replaces the codon used in the vaccine with another codon of that same amino acid, which has a higher chance to

be translated to the VoCâ€™s amino acid due to a translation error, based on the â€œconfusion matrix.â€ The VoC collection includes two subsets: a retrospective set based on data collected from infected human individuals and a prospective set constructed from experimental molecular screens of mutated versions of the Spike protein. Specifically, mutations of the Receptor Binding Domain that were measured for increased expression, increased affinity to the ACE2 receptor or for reduced affinity to neutralizing antibodies (e.g. Ref. 4) . With the algorithm, the team detected several codon positions that upon synonymous replacements might translate the amino acid sequence of several variants of concern such as delta, D614G, etc., as well as variants that are anticipated to emerge based on data from molecular evolution screens.

Applications and Advantages

- Optimized, next-generation mRNA vaccine for SARS-CoV-2, covering multiple variants (both existing and those predicted to emerge), and for optimization of vaccines against new strains such as Omicron, for backward compatibility against old strains that may relapse
- A new platform for the engineering of multivalent mRNA vaccine capable of targeting multiple variants with a single nucleotide sequence
- A multivalent vaccine based on a single mRNA should confer superior immune protection without the technical challenges associated with introducing multiple mRNA sequences into a vaccine formulation

Development Status

The team created the algorithm described above and applied it to Moderna and Pfizer mRNA vaccine for SARS CoV-2, yielding a list of codon substitutions that would be synonymous yet increase the chance of translation within cells into amino acid mutations that represent VoC. New versions of the SARS CoV-2 mRNA vaccine designed by the algorithm will be tested and validated in several experimental systems.

References

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Patent Status

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