Identification and elimination of helper and cytotoxic T cell epitopes in AAV9

Technology Summary

Adeno associated viruses (AAV) are one of the most common vectors used in gene therapy products due to their potency. However, immunogenicity of AAV vectors is a great safety and efficacy problem. Immune responses against the AAV capsid can cause neutralization and accelerated clearance that often limits gene therapy to a single use without switching to an alternative vector. Cytotoxic immune responses against transfected cells can occur, reversing the gene therapy effect and causing liver toxicities. Researchers have found CD4 and CD8 T cells play a critical role in most of these responses. A simultaneous CD4 and CD8 T cell epitope identification approach has been developed to find immunogenic epitopes in AAV, so they can be eliminated to lessen or eliminate these issues.

In this approach, PBMCs have been stimulated with diverse human HLAs with aggregated AAV9 particles and expanded the AAV9-specific T cells. Isolated CD4, CD8 or whole PBMC are then restimulated the with AAV9-derived peptides to identify the specific CD4 and CD8 T cell epitopes in. The specific type of T cells (CD4 and CD8) that were activated and the HLA class I or class II molecule that presents the peptide to the T cell are also identified. Rational design is used to eliminate these CD4 and CD8 T cell epitopes in AAV9 by amino acid insertion, deletion, or replacement. These amino acid substitutions are determined using in silico HLA binding predictions and followed by experimental validation of the eliminated epitopes.

As proof of principal, this technique has been performed on the AAV9 vector as it is utilized in many products currently in clinical development as well as in one FDA approved gene therapy. This same approach is applicable to other viral vectors used in gene therapy.

Potential Commercial Applications

- Lower immunogenic AAV vectors for gene therapy
- Identified immunogenic epitopes (peptides) can be used in assays
- Generation of T cell lines targeting a specific epitope for use in assay and research

Competitive Advantages

- There are others attempting to mitigate AAV immunogenicity from antibodies, but reduction of the CD4 and CD8 T cell response will likely be superior as they have been shown to be the main source of liver toxicities and loss of efficacy

Development Stage: In vitro data

Inventors: Ronit Mazor, Sojin Bing, Luis Santana-Quintero, Arya Eskandarian

Publication(s): Bing SJ, Justesen S, Wu WW, Sajib AM, Warrington S, Baer A, Thorgrimsen S, Shen RF, Mazor R. Differential T cell immune responses to deamidated adeno-associated virus vector. Mol Ther Methods Clin Dev. 2022 Mar 10;24:255-267.

Intellectual Property: U.S. provisional application 63/486,299 was filed February 22, 2023

Product Area: Gene Therapy, Immunology Research, Assay Development

FDA Reference: E-2022-010

Licensing Contact:
FDA Technology Transfer Program
Email: FDAInventionLicensing@fda.hhs.gov