Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Blood 138 (2021) 738–740

63rd ASH Annual Meeting Abstracts

ORAL ABSTRACTS

703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

Loss of an Immunodominant HLA-A *01:01 Restricted Epitope for CD8+ Cytotoxic T Lymphocytes (CTLs) in the Delta Variant of COVID-19: An Example of Immunologic Escape and Implications for Immunologic Treatment

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Abstract SARS-COV-2 (COVID-19) has resulted in over 4 million deaths worldwide. While vaccination has decreased mortality, there remains a need for curative therapies for active infections. Uncertainties regarding the duration of post-vaccination immunity and the rapidity of mutational evolution by this virus suggest that it is unwise to rely on preventative measures alone.

Humoral and cellular immunity provide selective pressure for the emergence of variant strains which have eliminated target epitopes. Elimination of immunodominant epitopes provides the strongest advantage to newly emerging strains and, consequently, immunodominant epitopes would be expected to be preferentially eliminated compared to subdominant epitopes in emerging variants. Immunologic treatments for SARS-COV-2 need to be continuously reassessed as new sequence information becomes available.

TVGN-489 is a clinical grade product consisting of highly enriched, highly potent CD8+ CTLs recognizing peptides derived from COVID-19 gene/ORF products in an HLA restricted manner. CTLs are generated from apheresis products from individuals who have recovered from COVID-19 infections. Lymphocytes are serially primed and selected using APCs from these donors pulsed with small numbers of peptides encoded by the COVID-19 genome predicted or demonstrated to bind to specific HLA class I alleles. The resulting products are typically >95% CD3+/CD8+, >60% positive by tetramer staining and demonstrate strong cytolytic activity with >60% lysis of peptide pulsed targets typically at an effector to target ratio of 3:1 (See Figure).

Given the immunologic pressure to lose dominant target epitopes, we assessed whether the peptides derived from genomic sequences from early SARS-COV-2 strains (and successfully used to generate CTLs from donors infected with these early strains) were still present in the more recently evolved Delta variant.

Seven peptides were used to generate CTL products restricted by HLA-A*02:01, the most common allele worldwide. These peptides are derived from the spike (S) and nucleocapsid (N) proteins as well as ORF3a and ORF1ab. The contributions of these peptides to the overall cytotoxicity and tetramer staining range from 2% to 18% without clear immunodominance by one of these peptides. Though identified in early viral strains, these sequences persist in 97.5%-100% of the more than 120 Delta variant sequences present in the NIH database.

For HLA-A*01:01, eight peptides derived from the matrix (M) protein as well as ORF1ab and ORF3a were utilized to generate CTLs. Seven of the eight peptides showed binding similar to what was seen with the HLA-A*02:01 peptides (1% to 18%). However, in contrast to HLA-A*02:01, an immunodominant peptide (TTDPSFLGRY, ORF1ab 1637-1646) was noted which was responsible for over half of the observed tetramer binding. This region of ORF1ab was mutated in the Delta variant resulting in loss of this immunodominant epitope from nearly 93% of the Delta genomic sequences in the NIH database. The remaining subdominant peptides were all preserved in 100% of the sequences. Given the growing number of Delta cases, it will be essential to remove this peptide from the HLA-A*01:01 peptide pool used to stimulate SARS-COV-2-specific CD8+ CTLs to avoid encouraging the expansion of cells which would recognize early strains of the virus, but not Delta variants. The remaining CTLs, generated in the absence of TTDPSFLGRY, should be capable of eradicating Delta as well as the earlier prototypic strains of COVID-19.

The loss of immunodominant epitopes is not surprising in a virus such as SARS-COV-2, with a high frequency of mutation. This provides an example of immunologic escape similar to what has been described for the Delta variant in the case of HLA-A24.

These data are consistent with the hypothesis that immunodominant epitopes will be preferentially eliminated as the virus continues to evolve. They further illustrate the need to monitor viral sequences and to tune the production of CTLs in order to ensure that they can continue to recognize and effectively treat newly emerging variants of COVID-19.

Disclosures No relevant conflicts of interest to declare.

OffLabel Disclosure: The drug is Cytotoxic T lymphocytes that are specific to COVID-19. Preclinical data.

https://doi.org/10.1182/blood-2021-147487

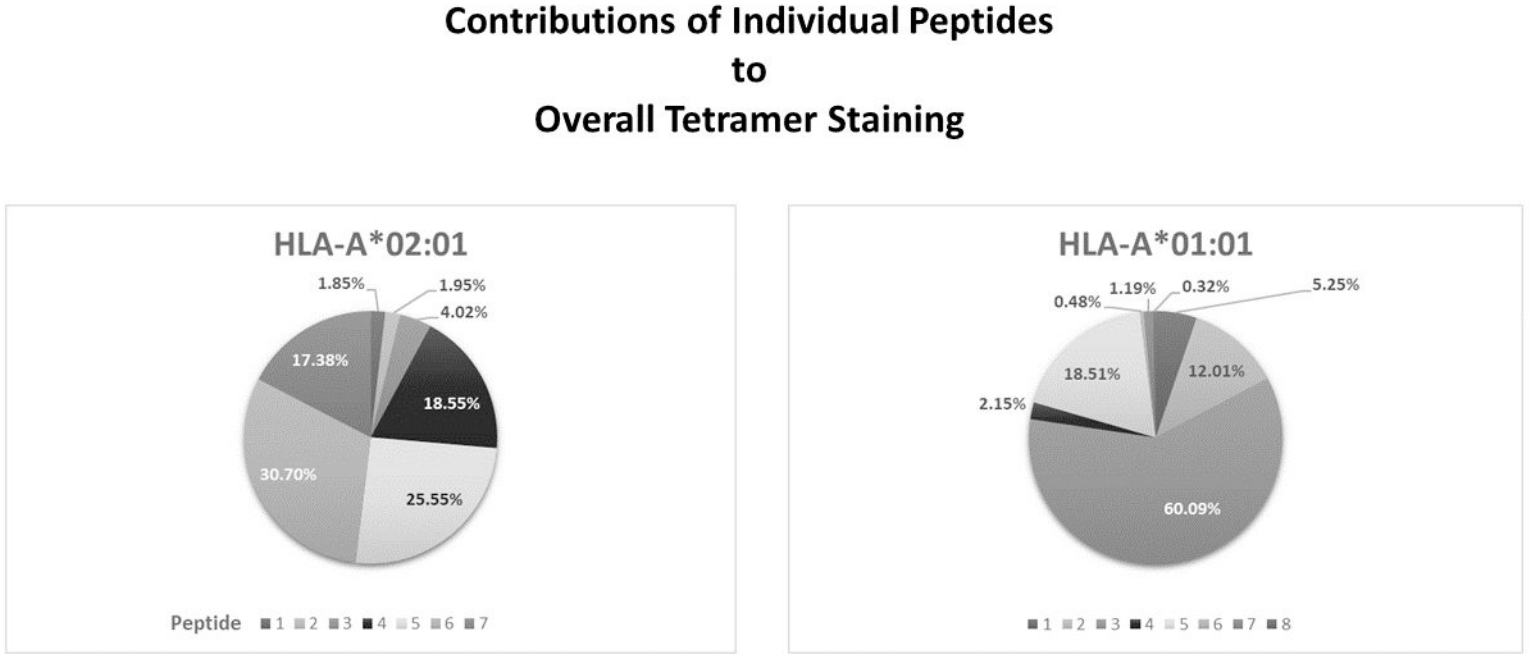
Contributions of Individual Peptides
to
Overall Tetramer Staining
HLA-A*02:01
1.85%
1.95%
4.02%
17.38%
18.55%
30.70%
25.55%
Peptide 1 2 3 4 5 6 7
HLA-A*01:01
0.48%
1.19%
0.32%
5.25%
18.51%
12.01%
2.15%
60.09%
1 2 3 4 5 6 7 8

Figure 1