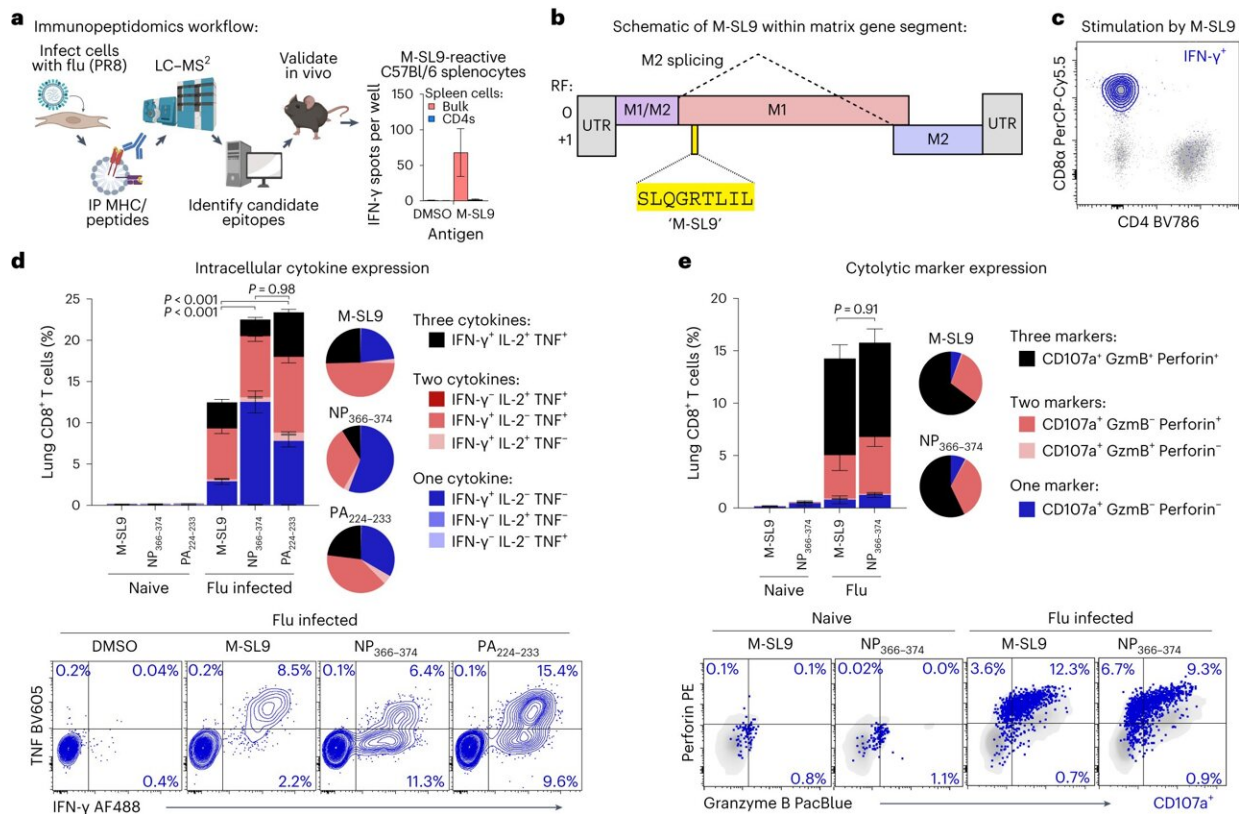


# Researchers show 'cryptic' viral peptide drives large part of immune response in influenza A virus infection

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Discovery of co-immunodominant CTL response directed against M-SL9, an epitope encoded by a noncanonical IAV matrix ORF. Credit: *Nature Immunology* (2023). DOI: 10.1038/s41590-023-01644-5

Conventional wisdom lays out two major roles for the major histocompatibility complex (MHC): Class I MHC (MHC-I) displays peptide fragments of proteins from within the cell on the cell surface and elicits a response from cytotoxic T cells (CD8 T cells), and class II MHC (MHC-II) does the same for helper T cells (CD4 T cells). Together, these two classes of MHC molecules are known as "classical" MHC molecules and have been understood to drive most of the immune response when a host is infected by a pathogen.

However, [a new study](#) by researchers at Children's Hospital of Philadelphia (CHOP) and the Perelman School of Medicine at the University of Pennsylvania has identified an important role for a non-classical MHC molecule that engages with a cryptic viral peptide derived from influenza A virus and drives large proportion of the CD8 T cell response after infection.

The findings, published in *Nature Immunology*, could have implications for the development of future vaccines and antiviral therapies.

"This discovery was somewhat serendipitous because we initially set out to investigate the possibility that MHC-II may display 'cryptic' peptides from parts of the viral genome that aren't usually translated and that these peptides would drive a CD4 T cell response," said first author Michael Hogan, a postdoctoral fellow in the Eisenlohr Lab at Children's Hospital of Philadelphia. "Instead, we found a cryptic peptide displayed on a non-classical MHC molecule, and importantly, it drives a major fraction of the CD8 T cell response, exhibiting potent effector functions after infection or mRNA vaccination."

Using [mass spectrometry](#) to scan the immunopeptidome in mouse cells infected with influenza A virus, the researchers searched for unconventional epitopes that might be involved in T cell responses. They identified a nine amino acid epitope that drives a potent CD8 T cell

response and found the peptide was unconventional in two ways: It was presented by Qa-1, a non-classical MHC molecule that is also known as MHC-E (or HLA-E in humans); and the peptide had a cryptic origin, as it maps to a portion of the influenza virus that isn't typically thought to be translated into proteins.

The researchers then showed that CD8 T cells specific to this cryptic peptide and Qa-1 can be strongly induced by mRNA vaccination and demonstrate cytotoxic activity in mice, raising hopes that this type of [immune response](#) could contribute to vaccine protection.

"These results show that non-canonical translation products can account for an important fraction of the T cell repertoire and add to a growing body of evidence that MHC-E-restricted T cells could have significant therapeutic value," said senior author Laurence Eisenlohr, VMD, Ph.D., professor of Pathology and Laboratory Medicine at Children's Hospital of Philadelphia. "Future studies should examine the roles for non-classical MHC molecules and cryptic epitopes in other [viral infections](#), like coronavirus and HIV, and also investigate the implications for diseases like cancer and autoimmunity."

**More information:** Michael J. Hogan et al, Cryptic MHC-E epitope from influenza elicits a potent cytolytic T cell response, *Nature Immunology* (2023). [DOI: 10.1038/s41590-023-01644-5](https://doi.org/10.1038/s41590-023-01644-5)

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