Development of mRNA LNPs to elicit a non-classical T cell response against HIV

Zamora, ME; Gambale S; Coirada; F, Pardi, N; Hogan M.

University of Pennsylvania

HIV/AIDS remains a pressing global health emergency with no effective vaccine or cure despite decades of research. Currently, almost all human and non-human primate vaccine trials have failed to demonstrate protection. However, in the 2010s, a group used a cytomegalovirus vector to express simian immunodeficiency virus (SIV) antigens and showed 50% protection against SIV in monkeys, including eradication of viral reservoirs—a level of protection unseen in the HIV/SIV field. They subsequently discovered that this protective response is driven by CD8+ cytotoxic T cells that recognize SIV fragments presented by an unconventional molecule called MHC-E. Because MHC-E is functionally conserved across mammals, this form of protection might also be leveraged in humans. Given the significant safety and feasibility concerns associated with cytomegalovirus, we asked whether a safe, effective, FDA-approved mRNA-lipid nanoparticle (LNP) vaccine platform can stimulate MHC-E-restricted CD8 T cell responses against SIV and HIV antigens.

We and others have shown, however, that many SIV Gag-derived 9-mer peptides have poor affinity for MHC-E. To address this, we developed mRNA-LNP constructs that express mouse MHC-E, beta-2-microglobulin, and SIV Gag 9-mer peptides as a single-chain trimer (SCT). We then vaccinated C57BL/6 mice to assess the immunogenicity of our approach. When we collected blood and spleen cells from immunized mice and stimulated them with Gag peptide in vitro, we observed strong IFNγ, TNFα, and IL2 responses in CD8+ T cells, suggesting our construct was highly immunogenic. We next assessed whether this T cell response was indeed MHC-E-restricted. To do this, we transfected a cell line with our SIV Gag 9-mer SCT LNP, washed the cells, and used them to stimulate spleen cells from vaccinated mice. We found specific stimulation of IFNγ and TNFα in CD8+ T cells from Gag SCT-vaccinated but not control mice, suggesting an MHC-E-restricted T cell response.

Future studies will test this response in humanized mice and in non-human primates to determine whether this vaccine provides protection against HIV/SIV. To our knowledge, this is the first mRNA vaccine shown to elicit a non-classical MHC-E-restricted T cell response against lentiviral epitopes.