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The MUC16 mucin is overexpressed and aberrantly glycosylated in ovarian carcinomas. Immunodetection of circulating MUC16 is one of the most used cancer biomarker assays, but existing antibodies to MUC16 fail to distinguish normal and aberrant cancer glycoforms. Although all antibodies react with the tandem-repeat region, their epitopes appear to be conformational dependent and not definable by a short peptide. Aberrant glycoforms of MUC16 may constitute promising targets for diagnostic and immunotherapeutic intervention, and it is important to develop well-defined immunogens for induction of potent MUC16 immunity. Here, we developed a MUC16 vaccine based on a 1.7TR (264 aa) expressed in Escherichia coli and in vitro enzymatically glycosylated to generate the aberrant cancer-associated glycoform Tn. This vaccine elicited a potent serum IgG response in mice and we identified two major immunodominant linear peptide epitopes within the tandem repeat. We developed one monoclonal antibody, 5E11, reactive with a minimum epitope with the sequence FNTTER. This sequence contains potential N- and O-glycosylation sites and, interestingly, glycosylation blocked binding of 5E11. In immunochemistry of ovarian benign and cancer lesions, 5E11 showed similar reactivity as traditional MUC16 antibodies, suggesting that the epitope is not efficiently glycosylated. The study provides a vaccine design and immunodominant MUC16 TR epitopes.