INTRODUCTION

MUC16 is a well-validated cell surface antigen expressed by ovarian cancer cells; the extracellular domain (ECD) is known as CA125. Drug-conjugated antibodies (“antibody-drug conjugates” or “ADC”) directed against MUC16 might therefore have therapeutic value against this disease (1).

OBJECTIVES

1) Develop and characterize MAbs against the ECD of MUC16.
2) Evaluate drug-conjugated MAbs in vitro and in vivo efficacy against MUC16-expressing cell lines. Select lead ADC based on efficacy.
3) Assess toxicity of ADC in rodent and primate models. Determine impact of binding to circulating CA125 on toxicity.

11D10 Binds to a Unique Epitope of MUC16 and 3A5 Binds to a Repeating Epitope

Figure 2: Characterization of anti-MUC16 MAbs. MAbs 11D10 was generated by immunizing BALB/c mice with MUC16ECD. MAb 3A5 was generated by immunization with commercial CA125 (Genentech, Inc., South San Francisco, CA, USA) in Freund’s complete adjuvant and boosted monthly for 10 months. MAbs were purified by protein A affinity chromatography. MAb 3A5 was generated by immunization with commercial CA125 (Genentech, Inc., South San Francisco, CA, USA) in Freund’s complete adjuvant and boosted monthly for 10 months. MAbs were purified by protein A affinity chromatography.

1. MUC16 can be effectively targeted with ADC to inhibit tumor growth.
2. ADC of a MAb (3A5) that binds to multiple epitopes is much more potent than MAB ADC binding to a unique epitope (11D10).
3. Major toxicity in rats and monkeys is transient, MUC16-independent neutropenia. Circulating MUC16 ECD (CA125) does not increase ADC toxicity.

CONCLUSIONS

References

The authors thank the staffs of Seattle Genetics (ADC) and OncoDesign (mK Kits) for assistance with these studies. We also thank our Genentech colleagues in Cancer Pathways, Antibody Engineering, Translational Oncology, and Protein Chemistry for advice and support.