MUC1 Targeted Immunotherapy with an Oncolytic Adenovirus Coding for a Bispecific T cell Engager

Saru Basnet (saru.basnet@helsinki.fi), Joao M. Santos1,2, Dafne C.A.Quixabeira1, James H.A. Clubb1,2, Susanna AM Grönberg–Väähö–Koskela1,2,3, Victor Arias1, Santeri Pakola1,2, Tatiana V. Kudling1, Camilla Heinilä1, Riiikka Havunen1,2, Victor Cervera–Carrascon1,2, SuviSorsa1,2, Marijukka Anttila1, Anna Kanerva1,2 and Aksei Hemminki1,2,4

1. Cancer Gene Therapy Group, Translational Immunology Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland 2. TILT Biotechnologies Ltd, Helsinki, Finland 3. Helsinki University Hospital (HUS), Helsinki, Finland 4. Department of Pathology, Finnish Food Authority, Helsinki, Finland 5. Department of Gynecology and Obstetrics, Helsinki University Hospital, Helsinki, Finland 6. Department of Oncology, Comprehensive Cancer Centre, Helsinki, Finland.

Abstract

Bispecific T cell engager (BsTe) is a fusion recombinant protein comprised of two single-chain variable fragments with dual specificity for a tumor-associated antigen and T cell receptor (usually CD3e). Immunotherapy with BsTe has shown efficacy in patients with hematologic malignancies and uveal melanoma. However, antitumor efficacy of BsTe in most solid tumors has been limited due to their short serum half-life and insufficient tumor concentration. We designed a novel serotype 5/3 oncolytic adenovirus encoding for a BsTe cross-linking Mucin1 (MUC1) to CD3, Ads5/3-EEF-d24-MUC1aCD3/ TILT-321. The BsTe (aMUC1aCD3) is designed for the treatment of human solid tumors, where the BsTe links CD3 molecules on the surface of T cells and MUC1 on the target cancer cells.

Introduction

Methods

• Infection and cell viability assays were performed to determine the oncolytic potential of the novel construct.

• The functionality of the virus-derived aMUC1aCD3 was evaluated in vitro.

• TILT-321 was characterized in vivo using MUC1 expressing A549 lung cancer and patient derived xenograft (PDX) of ovarian cancer (OvCa) with autologous PBMC in humanized mouse models.

Result- I: In vitro characterization of TILT-321

1. TILT-321 virus, which is armed with human aMUC1, kills cancer cells and exhibits synergy when combined with T cells.

2. TILT-321 secreted aMUC1aCD3 is functional: binds to target MUC1 antigen and enhances T cell function.

Result- II: In vivo monitoring

3. TILT-321 virus improves tumor growth control in a human xenograft models of A549 (A) and PDX-OvCa (B) by increasing the intratumoral cytotoxic tumor microenvironment

Figure 1. Schematic representation of the genetic structure of TILT-321.

Figure 2. TILT-321 mediated tumor cell killing.

Figure 3. Functionality of virus-derived aMUC1aCD3 in co-cultures of T cell with MUC1+ tumor cells.

Figure 4. TILT-321 derived supernatants aggregate T cells around cancer cells.

Figure 5. In vivo characteristics of TILT-321.

Conclusion

• TILT-321 is a novel approach and it kills solid tumors preferentially expressing MUC1 in vitro and in vivo.

• TILT-321 derived aMUC1aCD3 is functional; binds to its target antigens and causes higher T cell activation at the tumor site.

• In vivo, TILT-321 showed better tumor control in MUC1+ A549 lung cancer and PDX-OvCa in humanized mouse models.

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