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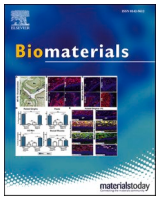

Preparation of an Ultrahigh-DAR PDL1 monoclonal antibody-polymeric-SN38 conjugate for precise colon cancer therapy

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ABSTRACT

Antibody-drug conjugates (ADCs) are the most potent active tumor-targeting agents used clinically. However, the preparation of ADCs with high drug-to-antibody ratios (DARs) remains a major challenge. Herein, a Fab-nondestructive SN38-loaded antibody-polymeric-drug conjugate (APDC), aPDL1-NPLG-SN38, was prepared that had a DAR as high as 72 for the first time, by increased numbers of payload binding sites via the carboxyl groups of poly (L-glutamic acid) (PLG). The bonding of Fc-III-4C peptide with PLG-*graft*-mPEG/SN38 (Fc-NPLG-SN38) was achieved using a click reaction between azide and DBCO groups. The aPDL1-NPLG-SN38 conjugate was then synthesized by the high-affinity interaction between the Fc-III-4C peptide in Fc-NPLG-SN38 and the crystallizable fragment (Fc) of PDL1 monoclonal antibody (aPDL1). This approach avoided the potential deleterious effects on the Fab structure of the monoclonal antibody. The aqueous environment used in its preparation helped maintain monoclonal antibody recognition capability. Through the specific recognition by aPDL1 of PDL1 that is highly expressed on MC38 tumors, the accumulation of aPDL1-NPLG-SN38 in the tumors was 2.8-fold greater than achieved with IgG-NPLG-SN38 that had no active tumor-targeting capability. aPDL1-NPLG-SN38 exhibited excellent therapeutic properties in both medium-sized and large MC38 tumor animal models. The present study provides the details of a novel preparation strategy for SN38-loaded ADCs having a high DAR.

1. Introduction

Antibody-drug conjugates (ADCs) are the most potent active agents used clinically to target tumors, consisting of a monoclonal antibody, linker and payload [1–3]. By accurately identifying monoclonal antibodies with the capability of targeting a specific tumor, a payload can be successfully delivered to the site of the tumor, achieving superior anti-tumor action and reducing the toxicity of the therapy due to its reduced distribution throughout normal tissue [4–6]. For example, T-DM1 [7,8], currently the best-selling ADC, widely used for the treatment of multiple HER2-positive cancers, consists of the anti-HER2 monoclonal antibody, trastuzumab, combined with the highly cytotoxic drug maytansine (DM1) at a drug-to-antibody ratio (DAR) of 3.5. Because trastuzumab specifically recognizes tumors with high expression of HER2 [9–11]. DM1 is delivered to the tumor and endocytosed, thus inhibiting tubulin polymerization and inducing apoptosis following G2/M cell cycle arrest [12,13]. Another common ADC, IMMU-132, consisting of an anti-Trop-2 monoclonal antibody and the moderately cytotoxic drug SN38, is used to treat tumors with high expression of Trop-2, such as gastric and pancreatic cancers [14,15]. The DAR of IMMU-132 is approximately 7.6, more than twice that of T-DM1. SN38 is an active metabolite of CPT-11 which creates a substantial bystander effect, acting on Topo1 in ribozymes and cleaving double-stranded DNA [16,17]. However, as the DAR of an ADC

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