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**IMPROVED ANTI-OVARIAN CANCER EFFECTIVENESS OF HER2-DIRECTING ADC VIA ENGINEERING WITH A SUPER-HYDROPHILIC PMPC POLYMER**

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**Background** Antibody-drug conjugates (ADC) are composed of a tumor-targeting antibody and a cytotoxic payload, enabling the specific elimination of targeted cells. Ado-trastuzumab emtansine (T-DM1) was approved in 2013 as an ADC directing human epidermal growth factor receptor 2 (HER2) and has been widely used for the treatment of HER2+ breast cancer. However, its potency was moderate against other cancers expressing HER2+, such as ovarian cancer having a refractory and metastatic nature due to the limited drug-to-antibody ratio (DAR) of 2–4. Using a higher DAR improves T-DM1's cytotoxicity, but results in poor pharmacokinetics and tumor targeting, increasing off-target toxicity and compromising tumor elimination. We hypothesize that site-specific conjugation of a super-hydrophilic polymer, poly (2-Methacryloyloxyethyl phosphorylcholine) (PMPC) allows a higher DAR without compromising its biological functions.

**Methods** PMPC was conjugated to trastuzumab (Tmab) thiol residues through a peptide crosslinker that is sensitive to the tumor-enriched matrix metalloproteinases (MMP-2 and 9). Emtansine (DM1) was subsequently conjugated to the lysine groups of Tmab with average DAR of 8.6 (T-DM1<sup>PMPC-MMP</sup>). The cellular binding, uptake, and HER2-specific cytotoxicity were tested in the SKOV3 human OC cell line. The pharmacokinetics, *in-vivo* tumor targeting, toxicity, and therapeutic outcome were validated in SKOV-3 xenograft NOD.Cg-Prkd<sup>scid\_112rg\_tm1Wjl/Szj</sup> (NSG) mice in comparison with T-DM1 carrying standard DAR (3.6) and high DAR (8.6).

**Results** PMPC conjugation endowed functional stability to T-DM1 with high DAR (~10). The cellular uptake and cytotoxicity were reduced by PMPC conjugation but retrieved after MMP-mediated PMPC detachment in the tumor microenvironment. T-DM1<sup>PMPC-MMP</sup> displayed prolonged body circulation, enhanced tumor-specific delivery, and reduced off-target toxicity compared with T-DM1(8.6) in xenograft mice. Two doses (8 mg/kg) of T-DM1<sup>PMPC-MMP</sup> achieved complete elimination of tumors with a size >200 mm<sup>3</sup> without relapse, whereas tumors rebounded 3 weeks after treatment with T-DM1(3.6).

**Conclusions** This novel methodology that addresses the current issue of T-DM1 with high DAR has great potential for the targeting therapy of refractory OC and may be used for other HER2+ aggressive cancers.

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