Novel Peptide Camptothecin Drug-linkers for Potent ADCs—Letter

David M. Goldenberg[1], Robert M. Sharkey[1], Serengulam V. Govindan[2], and Thomas M. Cardillo[2]

We respond to the article by Lyski and colleagues (1) in the December 3 online edition of the journal because of the comparison between the article's antibody–drug conjugates (ADC) and a complementary ADC incorporating our linker payload, CL2A-SN-38, which the authors refer to as "GT." While we have shown specificity for our ADCs versus non-specific ADC controls in several tumor xenograft models (2–5), which the authors overlooked, specificity *in vitro* was not observed. We reported previously that this is likely due to the hydrolysable nature of the linker and the 96-hour assay timeframe which would result in the release of the coupled SN-38, the active principle of camptothecin, thereby making specificity impossible to show under these conditions. However, specificity was reported initially using a different assay with shorter incubation periods (5), and later in studies that also documented bystander killing of antigen-negative tumor cells due to extracellular release of SN-38 [e.g., Lopez and colleagues (6)].

Regarding the activity of SN-38 conjugates *in vivo*, it should be noted that SN-38 conjugates are well tolerated, and therefore amenable administration in repeated cycles of therapy, which is conducive for the cell cycle–dependent activity of SN-38. This repeated cycle approach has been successful in multiple clinical trials and indications (7).

Therefore, we submit that the head-to-head comparison of conventional ADCs, which follow the paradigm of using ultrapotent cytotoxic payloads and strictly intracellularly cleavable linkers, with our ADCs, whose design is different, is not useful in the preclinical setting, because the dose and dose schedule are distinctly different. Ultimately, the therapeutic index is key, and any comparison is meaningful when made in the clinical setting for the same disease indication.

We are gratified to note that the article's ADC design utilizes a short PEG and lysine combination as part of the linker, which we introduced in our early studies to enable high drug substitution with a high monomeric ADC profile [low dimer or aggregation (8)], and which we believe defines a third-generation platform for ADCs (7).

We congratulate the authors for exploring a topoisomerase I inhibitor as an ADC payload. Such advances auger well for patients by providing more potential options for advancing the ADC field.

Authors' Disclosures

R.M. Sharkey reports personal fees and other from Immunomedics, Inc during the conduct of the study; personal fees and other from Immunomedics, Inc outside the submitted work. S.V. Govindan reports other from Immunomedics, Inc. outside the submitted work; in addition, S.V. Govindan has a patent for US 7999083B2 issued. T.M. Cardillo reports other from Gilead Sciences outside the submitted work. D.M. Goldenberg reports other from Immunomedics, Inc. outside the submitted work; in addition, D.M. Goldenberg has a patent for RS7 Antibodies pending, issued, licensed, and with royalties paid from Immunomedics, Inc.; D.M. Goldenberg and his spouse, Cynthia Goldenberg (former CEO of Immunomedics, Inc.) owned stock in Immunomedics until November 2020. No other disclosures were reported.

Received March 7, 2021; revised March 22, 2021; accepted April 7, 2021; published first January 7, 2022.

[1]Center for Molecular Medicine and Immunology, Mendham, New Jersey. [2]Immunomedics, Inc., a subsidiary of Gilead Sciences, Inc., Morris Plains, New Jersey.

Corresponding Author: Robert M Sharkey, (retired), Center for Molecular Medicine and Immunology, Mendham, NJ, 07945, United States. E-mail: robmshark@gmail.com

Mol Cancer Ther 2022;21:237

doi: 10.1158/1535-7163.MCT-21-0212

References

1. Lyski RD, Bou LB, Lau UY, Meyer DW, Cochran JH, Okeley NM, et al. Development of novel antibody-camptothecin conjugates. Mol Cancer Ther 2021;20:329–39.
2. Cardillo TM, Govindan SV, Sharkey RM, Trisal P, Goldenberg DM. Humanized anti-Trop-2 IgG-SN-38 conjugate for effective treatment of diverse epithelial cancers: preclinical studies in human cancer xenograft models and monkeys. Clin Cancer Res 2011;17:3157–69.
3. Cardillo TM, Govindan SV, Sharkey RM, Trisal P, Arrojo R, Liu D, et al. Sacituzumab Govitecan (IMMU-132), an anti-Trop-2/SN-38 antibody-drug conjugate: characterization and efficacy in pancreatic, gastric, and other cancers. Bioconjug Chem 2015;26:919–31.
4. Goldenberg DM, Sharkey RM. Antibody-drug conjugates targeting TROP-2 and incorporating SN-38: a case study of anti-TROP-2 sacituzumab govitecan. MAbs 2019;11:987–95.
5. Goldenberg DM, Cardillo TM, Govindan SV, Rossi EA, Sharkey RM. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). Oncotarget 2015;6:22496–512.
6. Lopez S, Perrone E, Bellone S, Bonazzoli E, Zeybek B, Han C, et al. Preclinical activity of sacituzumab govitecan (IMMU-132) in uterine and ovarian carcinosarcomas. Oncotarget 2020;11:560–70.
7. Goldenberg DM, Sharkey RM. Sacituzumab govitecan, a novel, third-generation, antibody-drug conjugate (ADC) for cancer therapy. Expert Opin Biol Ther 2020;20:871–85.
8. Moon SJ, Govindan SV, Cardillo TM, D'Souza CA, Hansen HJ, Goldenberg DM. Antibody conjugates of 7-ethyl-10-hydroxycamptothecin (SN-38) for targeted cancer chemotherapy. J Med Chem 2008;51:6916–26.