LB214

A first-in-class bispecific antibody-drug conjugate (DM002) targeting HER3 and the juxtamembrane domain of MUC1

Yifu Zhang[1], Chengzhang Shang[1], Nannan Wang[2], Gao An[1], Ellen Zhang[1], Qingcong Lin[1], Yi Yang[1]

[1]Biocytogen Pharmaceuticals (Beijing) Co., Ltd., Beijing, China; [2]Doma Pharmaceutical (Suzhou) Co., Ltd., Suzhou, China

biocytogen.com | info@biocytogen.com

ABSTRACT

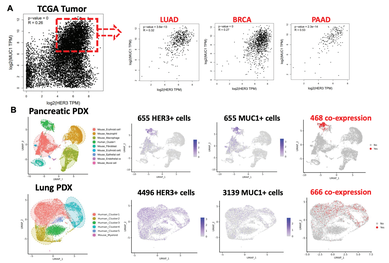
Despite the entry of new anti-cancer drugs into the market, there were more than 10 million deaths from cancer globally in 2021[1], with cancers of the lung, stomach, breast, and pancreas contributing to the most cancer-related deaths in China and the USA[2,3]. Accordingly, there is an urgent need for improved therapeutic interventions. Antibody-drug conjugates (ADC) are novel drugs that exploit the specificity of a monoclonal antibody for target antigens expressed on cancer cells in order to achieve targeted delivery of a potent cytotoxic payload. More recently, bispecific ADCs (BsADC) targeting two tumor-associated antigens (TAA) have been developed to further amplify tumor c with other currently available HER3 mAb. These bsAbs were subsequently conjugated with monomethyl auristatin E (MMAE) via a protease-cleavable linker to obtain first-in-class BsADC candidates, DM002. DM002 candidates showed robust anti-tumor activity in multiple CDX and PDX models of lung, breast, gastric and pancreatic cancer; most notably, DM002 candidates outperformed benchmark ADCs in BP0508 lung PDX models. Together, these data indicate that DM002 will be a promising therapeutic drug for patients with HER3 and MUC1 co-expressing tumors.

[1] World Health Organization: "Cancer."
[2] Siegel, RL, Miller, KD, Fuchs, HE, Jemal, A. Cancer statistics, 2022. CA Cancer J Clin. 2022.
[3]Xia C, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N, Chen W. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chin Med J (Engl). 2022 Feb 9;135(5):584-590.

Co-expression of HER3 and MUC1 in tumors

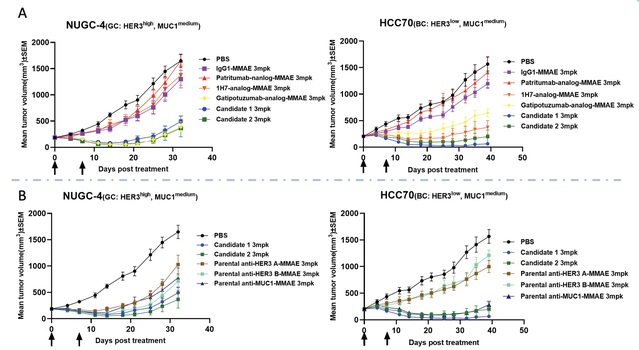
A) Correlation analysis indicates that HER3 and MUC1 are commonly co-expressed in multiple tumors, especially in LUAD (lung), BRCA (breast), and PAAD (pancreas), according to the GEPIA 2 database[1]. TCGA, Cancer Genome Atlas.
B) Single-cell RNA sequencing results demonstrate HER3 co-expression with MUC1 in some PDX sample cell populations.

[1]Reference: Tang Z, Kang B, Li C, Chen T, Zhang Z. GEPIA2: an enhanced web server for large-scale expression profiling and interactive analysis. Nucleic Acids Res. 2019 Jul 2;47(W1):W556-W560. doi: 10.1093/nar/gkz430.

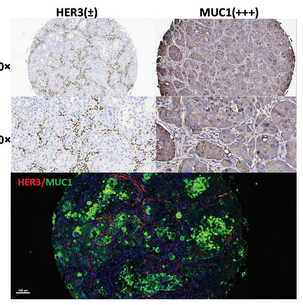


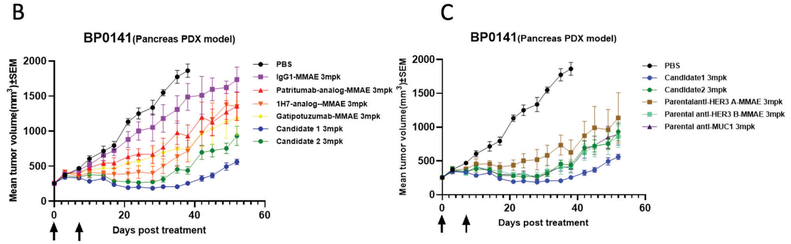
DM002 candidates demonstrate robust anti-tumor activity in CDX models

Efficacy of DM002 *in vivo*. Treatment with test articles indicated by arrows. Each CDX experiment in A and B was parsed into two graphs to compare the potency of each dose and test article. **A)** Both DM002 candidates demonstrate robust anti-tumor activity in cell line-derived xenografts with different levels of HER3 expression, especially HCC70 (HER3^{low}MUC-1^{med}); efficacy was stronger or comparable to their benchmark ADCs. **B)** DM002 candidates showed superior or comparable anti-tumor activity compared with the parental Ab-ADCs. GC: gastric cancer, BC: breast cancer.



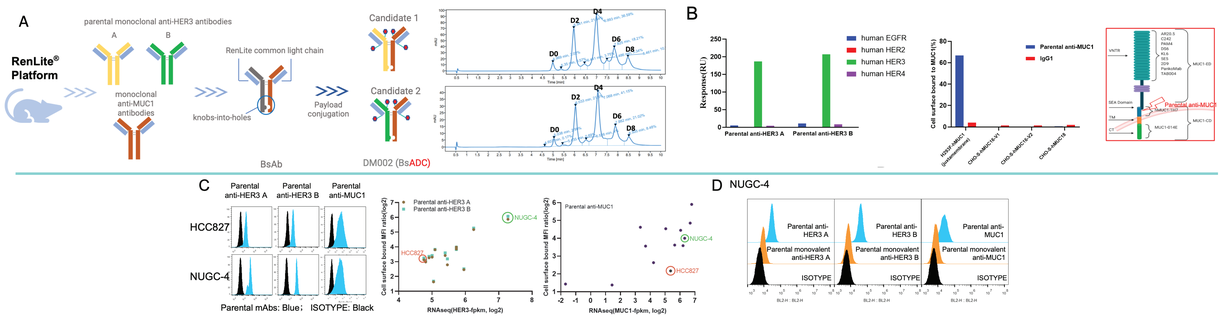
DM002 exhibits robust anti-tumor activity in the BP0141 pancreas PDX model





Efficacy of DM002 in PDX models. A) HER3 (low) and MUC1 (+++) expression in the BP0141 pancreas PDX model, as confirmed by immunohistochemical methods. **B)** DM002 candidates showed robust anti-tumor efficacy in patient-derived pancreatic cancer xenografts, with stronger activity compared to benchmarks. Treatments indicated by arrows. **C)** Treatment with DM002 candidates led to sustained growth inhibition. Candidate 1 efficacy was more pronounced than the parental Ab-ADCs, while candidate 2 performed similarly to parental Ab-ADCs. Graphs B and C are representative of a single experiment parsed into two graphs to compare the potency of each dose and test article.

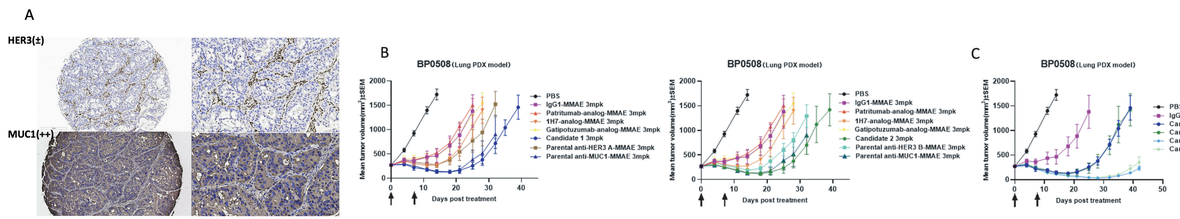
DM002 discovery workflow and characterization



A) Two parental anti-HER3 antibodies (A&B) and one parental anti-MUC1 antibody were screened from RenLite® mice, which contain the full human heavy chain variable domain with a common human light chain. Antibodies were then assembled into two DM002 candidates. Both DM002 candidates carry a MMAE payload (DAR ~4) via a cleavable VC-PAB linker. **B)** Parental anti-HER3 antibodies A and B, and parental anti-MUC1 antibody do not recognize other EGFR family members as assessed by SPR. Binding assessments (flow cytometry) indicate that parental anti-MUC1 targets the juxtamembrane domain of MUC1 and prevents antibody neutralization induced by shedding of MUC1-N. Image from Bose et al., 2020. **C)** Parental antibodies can bind to multiple tumor cell lines with different HER3 and MUC1 expression levels as measured by RNA sequencing. **D)** Parental antibodies showed high endocytic activity compared with the parental monovalent antibodies.

Bose, M.; Mukherjee, P. Potential of Anti-MUC1 Antibodies as a Targeted Therapy for Gastrointestinal Cancers. Vaccines 2020, 8, 659. https://doi.org/10.3390/vaccines8040659

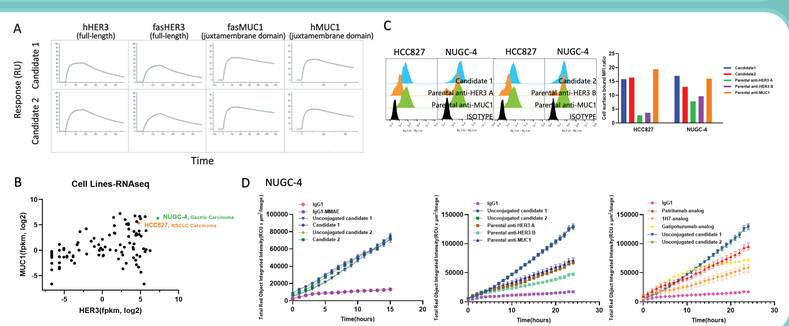
DM002 demonstrates robust anti-tumor activity in the BP0508 lung PDX model



DM002 efficacy in patient-derived lung cancer xenografts (BP0508) with (A) low expression of HER3 indicated by IHC. B) Both DM002 candidates showed robust anti-tumor activity stronger than benchmarks and parental HER3 Ab-ADCs. **C)** The anti-tumor activity of DM002 candidates is dose-dependent. Graphs are representative of a single experiment parsed into three graphs to compare the potency of each dose and test article.

Unconjugated DM002 candidates exhibit cross-species reactivity and induce endocytosis

A. The affinity of unconjugated DM002 to both HER3 and the juxtamembrane domain of MUC1 (human and cynomolgus monkey) are about 10^{-8} M (KD), measured by SPR. **B, C.** Unconjugated DM002 candidates can bind to cells with different levels of HER3 and showed stronger binding than their parental HER3 antibodies in HER3^{low} tumor cells (HCC827). **D.** The endocytosis activity of DM002 candidates was not altered after conjugation. Internalization of unconjugated DM002 was better than its parental monoclonal antibodies, reflecting a synergistic effect, and was also stronger than the benchmark antibodies.



SUMMARY

- HER3 and MUC1 are co-expressed in a variety of solid tumors, especially those with the highest mortality.
- DM002 is a novel fully human bispecific antibody-drug conjugate generated by the RenLite® common light chain mouse platform. DM002 cross-reacts with human and monkey HER3 and the MUC1 juxtamembrane domain.
- DM002 displayed higher endocytosis activity and more potent tumor growth inhibition of HER3 and MUC1 co-expressing tumors (especially HER3^{low} tumors) compared to HER3 and MUC-1 benchmarks.
- DM002 is a promising first-in-class ADC with potential to treat a variety of HER3 and MUC-1-expressing cancers.