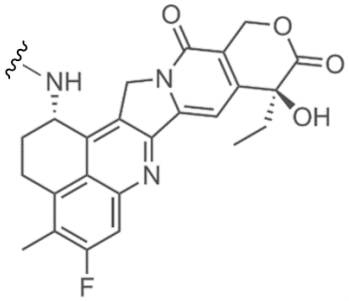
Claims:

1. An antigen-binding molecule that binds to HER3, comprising (i) a HER3-binding moiety, and (ii) a linker-payload moiety comprising exatecan or a derivative thereof.

2. The antigen-binding molecule according to claim 1, wherein the linker-payload moiety comprises structure (A):

(A)

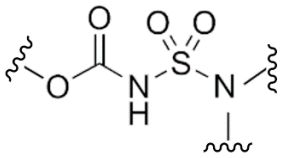


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3. The antigen-binding molecule according to claim 1 or claim 2, wherein the linker-payload moiety and the HER3-binding moiety are connected via a cleavable linker moiety.

4. The antigen-binding molecule according to any one of claims 1 to 3, wherein the antigen-binding molecule comprises a cleavable linker moiety comprising structure (B):

(B)

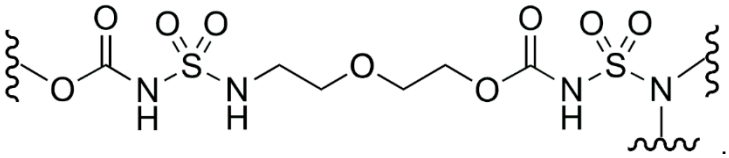


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5. The antigen-binding molecule according to any one of claims 1 to 4, wherein the antigen-binding molecule comprises a cleavable linker moiety comprising a polyethylene glycol (PEG) moiety.

6. The antigen-binding molecule according to any one of claims 1 to 5, wherein the antigen-binding molecule comprises a cleavable linker moiety comprising structure (E):

(E)

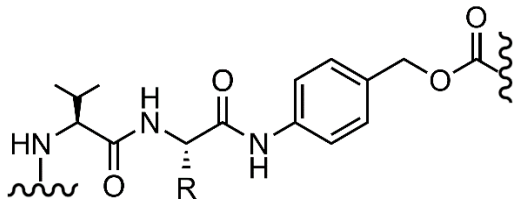


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7. The antigen-binding molecule according to any one of claims 1 to 6, wherein antigen-binding molecule comprises a cleavable linker moiety comprising a *p*-aminobenzyl carbamate (PABC) group.

8. The antigen-binding molecule according to any one of claims 1 to 7, wherein the antigen-binding molecule comprises a cleavable linker moiety comprising structure (D):

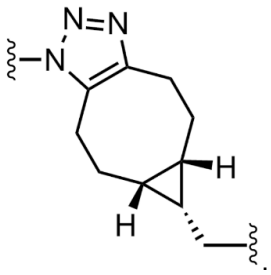
(D)



wherein R is selected from CH_3 and $(CH_2)_3NHCOCNH_2$.

9. The antigen-binding molecule according to any one of claims 1 to 8, wherein the antigen-binding molecule comprises structure (E):

(E)



10. The antigen-binding molecule according to any one of claims 1 to 9, wherein the antigen-binding molecule comprises SYNtecan E.

11. The antigen-binding molecule according to any one of claims 1 to 10, wherein the HER3-binding moiety comprises an Fc region, and wherein the linker-payload moiety is conjugated to the HER3-binding moiety at an azido group provided in an 6-azido-6-deoxy-*N*-acetylgalactosamine residue of an *N*-glycan linked to N297 of a CH2 domain of the Fc region (EU numbering).

12. The antigen-binding molecule according to any one of claims 1 to 11, wherein the HER3-binding moiety binds to HER3 in the region shown in SEQ ID NO:77.

13. The antigen-binding molecule according to any one of claims 1 to 12, wherein the HER3-binding moiety comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:40

HC-CDR2 having the amino acid sequence of SEQ ID NO:43

HC-CDR3 having the amino acid sequence of SEQ ID NO:48; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:66

LC-CDR2 having the amino acid sequence of SEQ ID NO:69

LC-CDR3 having the amino acid sequence of SEQ ID NO:74.

14. The antigen-binding molecule according to any one of claims 1 to 13, wherein the HER3-binding moiety comprises:

(i) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:38

HC-CDR2 having the amino acid sequence of SEQ ID NO:42

HC-CDR3 having the amino acid sequence of SEQ ID NO:45; and

(ii) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:63

LC-CDR2 having the amino acid sequence of SEQ ID NO:67

LC-CDR3 having the amino acid sequence of SEQ ID NO:70.

15. The antigen-binding molecule according to any one of claims 1 to 14, wherein the antigen-binding moiety that binds to HER3 comprises:

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:33; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:58.

16. The antigen-binding molecule according to any one of claims 1 to 15, wherein the antigen-binding moiety that binds to HER3 comprises:

a polypeptide comprising, or consisting of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:75; and

a polypeptide comprising, or consisting of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:76.

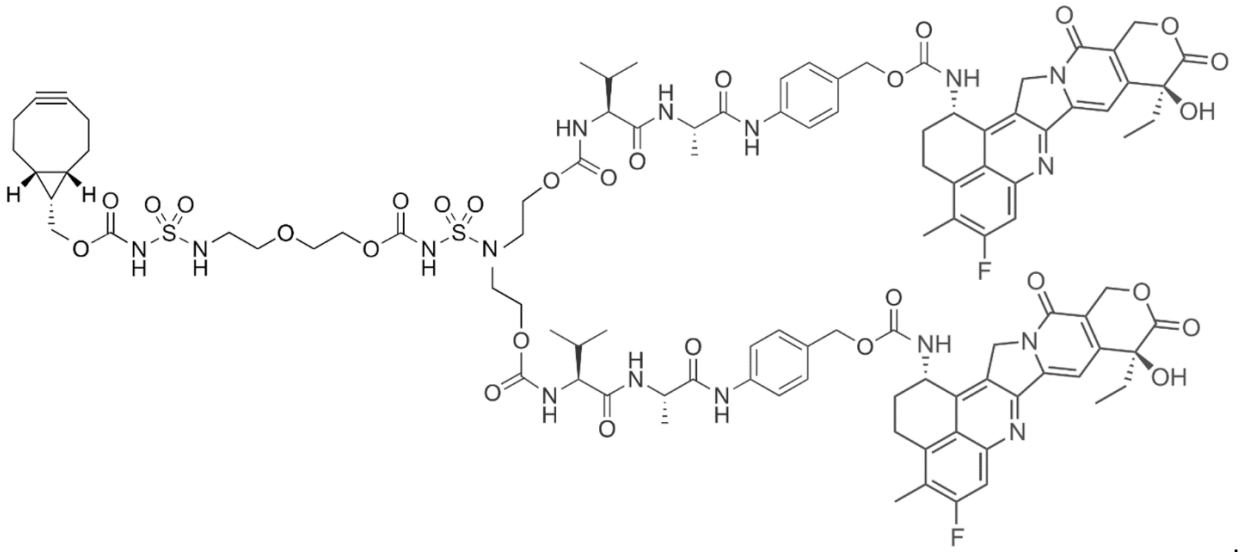
17. The antigen-binding molecule according to any one of claims 1 to 16, wherein the antigen-binding moiety that binds to HER3 comprises:

a polypeptide comprising, or consisting of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:80, 81, 82 or 91; and

a polypeptide comprising, or consisting of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:76.

18. A method for producing an antigen-binding molecule, comprising contacting a HER3-binding moiety comprising an azido moiety with a compound having structure (F):

(F)



19. An antigen-binding molecule obtained or obtainable by the method of claim 18.

20. A composition comprising an antigen-binding molecule according to any one of claims 1 to 17 or claim 19, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

21. An antigen-binding molecule according to any one of claims 1 to 17 or claim 19, or a composition according to claim 20, for use in a method of medical treatment or prophylaxis.

22. Use of an antigen-binding molecule according to any one of claims 1 to 17 or claim 19, or a composition according to claim 20, in the manufacture of a medicament for treating or preventing a cancer.

23. The use according to claim 22, wherein the cancer is selected from: a cancer comprising cells expressing/overexpressing an EGFR family member, a cancer comprising cells expressing/overexpressing HER3, a cancer comprising cells having a mutation resulting in increased expression of a ligand for HER3, a cancer comprising cells having an NRG gene fusion, a solid tumor, a hematological cancer, a squamous cell cancer, breast cancer, breast carcinoma, breast invasive carcinoma, ductal carcinoma, metastatic breast cancer, triple-negative breast cancer, HER2-positive breast cancer, HER2-negative breast cancer, hormone receptor-positive breast cancer, HER2-negative/hormone receptor-positive breast cancer, gastric cancer, gastric carcinoma, gastric adenocarcinoma, gastrointestinal adenocarcinoma, colorectal cancer, metastatic colorectal cancer, colon cancer, colorectal carcinoma, colorectal adenocarcinoma, colon adenocarcinoma, head and neck cancer, head and neck squamous cell carcinoma (HNSCC), lung cancer, non-small cell lung cancer, lung adenocarcinoma, invasive mucinous lung adenocarcinoma, lung squamous cell carcinoma (LUSC), ovarian cancer, ovarian carcinoma, ovarian serous adenocarcinoma, ovarian serous cystadenocarcinoma, fallopian tube cancer, renal cancer, renal cell carcinoma, renal clear cell carcinoma, renal cell adenocarcinoma, renal papillary cell carcinoma, pancreatic cancer, pancreatic adenocarcinoma, pancreatic ductal adenocarcinoma, cervical cancer, cervical squamous cell carcinoma, skin cancer, melanoma, oral cavity cancer, oropharyngeal cancer, esophageal cancer, esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma, liver cancer, hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer, biliary tract cancer, uterine cancer, endometrial cancer, uterine

corpus endometrial carcinoma, uterine carcinosarcoma, thyroid cancer, thyroid carcinoma, pheochromocytoma, paraganglioma, bladder cancer, bladder urothelial carcinoma, prostate cancer, prostate adenocarcinoma, castration-resistant prostate cancer, metastatic prostate cancer, metastatic castration-resistant prostate cancer, retinoblastoma, sarcoma, soft tissue sarcoma, peritoneal cancer, thymoma, neuroendocrine tumor, neuroendocrine tumor of the nasopharynx and homologous recombination deficiency (HRD) cancer.

24. Use of an antigen-binding molecule according to any one of claims 1 to 17 or claim 19, or a composition according to claim 20, to deplete or increase killing of cells expressing HER3.

25. An *in vitro* complex, optionally isolated, comprising an antigen-binding molecule according to any one of claims 1 to 17 or claim 19 bound to HER3.

26. A method for detecting HER3 in a sample, comprising contacting a sample containing, or suspected to contain, HER3 *in vitro* with an antigen-binding molecule according to any one of claims 1 to 17 or claim 19, and detecting the formation of a complex of the antigen-binding molecule with HER3.

27. A method of selecting or stratifying a subject for treatment with a HER3-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with an antigen-binding molecule according to any one of claims 1 to 17 or claim 19, and detecting the formation of a complex of the antigen-binding molecule with HER3.

28. Use of an antigen-binding molecule according to any one of claims 1 to 17 or claim 19, or a composition according to claim 20, as an *in vitro* diagnostic or prognostic agent.