

What is claimed:

1. ~~A method of~~Use of an antibody-drug conjugate (ADC) comprising a bispecific antigen-binding molecule and a cytotoxin in the manufacture of a medicament for treating an uveal melanoma, reducing uveal melanoma tumor growth, and/or causing regression of an uveal melanoma in a subject, ~~the method comprising administering to a~~wherein the subject in need thereof is to be administered the medicament~~an antibody-drug conjugate (ADC) comprising a bispecific antigen-binding molecule and a cytotoxin~~, wherein the bispecific antigen-binding molecule comprises:

a first antigen-binding domain (D1); and

a second antigen-binding domain (D2);

wherein D1 specifically binds a first epitope of human MET; and

wherein D2 specifically binds a second epitope of human MET; and

wherein D1 comprises three heavy chain complementarity determining regions comprising: an HCDR1 comprising the amino acid sequence of SEQ ID NO: 60; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 62; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; and three light chain complementarity determining regions comprising: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144; and

wherein D2 comprises three heavy chain complementarity determining regions comprising: an HCDR1 comprising the amino acid sequence of SEQ ID NO: 84; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 86; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 88; and three light chain complementarity determining regions comprising: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144.

2. The ~~method~~use of claim 1, wherein the uveal melanoma expresses MET.

3. The [methoduse](#) of claim 1, wherein D1 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 58 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 138.

4. The [methoduse](#) of claim 1, wherein D2 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 82 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 138.

5. The [methoduse](#) of claim 1, wherein the bispecific antigen-binding molecule comprises the CDRs within the D1-HCVR amino acid sequence of SEQ ID NO: 58 and the CDRs within the D2-HCVR amino acid sequence of SEQ ID NO: 82.

6. The [methoduse](#) of claim 1, wherein the first epitope of human MET comprises amino acids 192-204 of SEQ ID NO: 155.

7. The [methoduse](#) of claim 1, wherein the second epitope of human MET comprises amino acids 305-315 and 421-455 of SEQ ID NO: 155.

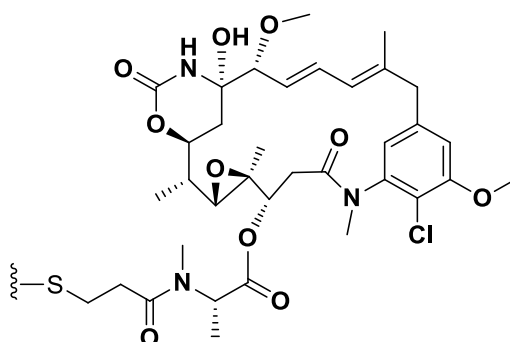
8. The [methoduse](#) of claim 1, wherein the first epitope of human MET comprises amino acids 192-204 of SEQ ID NO: 155; and wherein the second epitope of human MET comprises amino acids 305-315 and 421-455 of SEQ ID NO: 155.

9. The [methoduse](#) of claim 1, wherein the cytotoxin is selected from the group consisting of biotoxins, chemotherapeutic agents, and radioisotopes.

10. The [methoduse](#) of claim 1, wherein the cytotoxin is selected from the group consisting of maytansinoids, auristatins, tomaymycins, duocarmycins, ²²⁵Ac, [and](#) ²²⁷Th, ~~and any derivatives thereof~~.

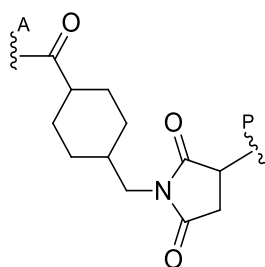
11. The [methoduse](#) of claim 1, wherein the cytotoxin is conjugated to the

bispecific antigen-binding molecule through a linker, and wherein the cytotoxin is:



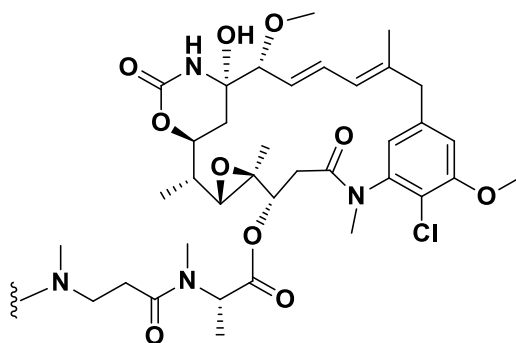
wherein the  is the bond to a linker.

12. The [method use](#) of claim 11, wherein the linker is:



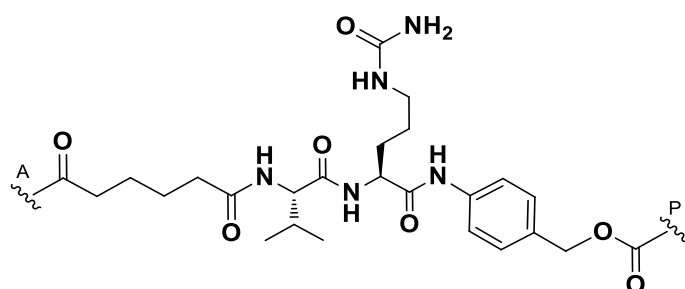
wherein the bond noted with  represents the bond to the bispecific antigen-binding molecule and the bond noted with  represents the bond to the cytotoxin.

13. The [method use](#) of claim 1, wherein the cytotoxin is conjugated to the bispecific antigen-binding molecule through a linker, and wherein the cytotoxin is:



wherein the  is the bond to the linker.

14. The ~~method~~use of claim 13, wherein the linker is



wherein the bond noted with $\sim^A$ represents the bond to the bispecific antigen-binding molecule and the bond noted with $\sim^P$ represents the bond to the cytotoxin.

15. ~~A method of~~Use of an antibody-drug conjugate (ADC) comprising a bispecific antigen-binding molecule and a cytotoxin in the manufacture of a medicament for inhibiting proliferation, inhibiting invasion, causing apoptosis, and/or decreasing viability of a uveal melanoma cell, ~~the method comprising contacting~~wherein the cell is to be contacted with an antibody-drug conjugate (ADC) comprising a bispecific antigen-binding molecule and a cytotoxin~~the medicament~~, wherein the bispecific antigen-binding molecule comprises:

a first antigen-binding domain (D1); and

a second antigen-binding domain (D2);

wherein D1 specifically binds a first epitope of human MET; and

wherein D2 specifically binds a second epitope of human MET; and

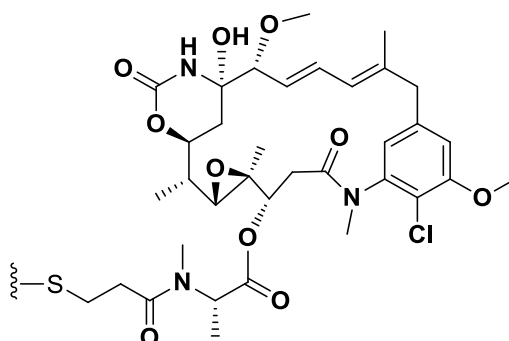
wherein D1 comprises three heavy chain complementarity determining regions comprising: an HCDR1 comprising the amino acid sequence of SEQ ID NO: 60; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 62; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; and three light chain complementarity determining regions comprising: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144; and

wherein D2 comprises three heavy chain complementarity determining regions comprising: an HCDR1 comprising the amino acid sequence of SEQ ID NO: 84; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 86; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 88; and three light chain complementarity determining regions comprising: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144.

16. The methoduse of claim 15, wherein D1 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 58 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 138.

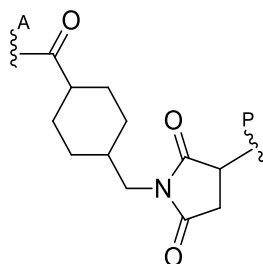
17. The methoduse of claim 15, wherein D2 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 82 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 138.

18. The methoduse of claim 15, wherein the cytotoxin is conjugated to the bispecific antigen-binding molecule through a linker, and wherein the cytotoxin is:



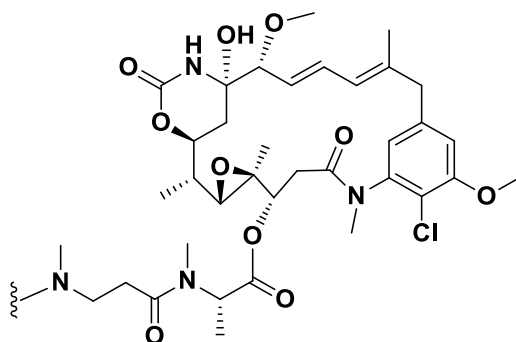
wherein the  is the bond to a linker.

19. The methoduse of claim 18, wherein the linker is:



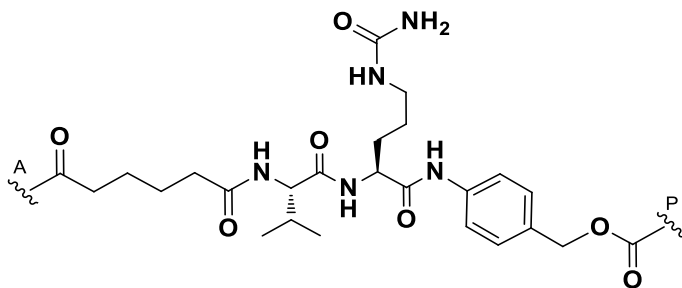
wherein the bond noted with $\overset{\text{A}}{\sim}$ represents the bond to the bispecific antigen-binding molecule and the bond noted with $\overset{\text{P}}{\sim}$ represents the bond to the cytotoxin.

20. The methoduse of claim 15, wherein the cytotoxin is conjugated to the bispecific antigen-binding molecule through a linker, and wherein the cytotoxin is:



wherein the  is the bond to the linker.

21. The methoduse of claim 20, wherein the linker is



wherein the bond noted with ~^{A} represents the bond to the bispecific antigen-binding molecule and the bond noted with ~^{P} represents the bond to the cytotoxin.

22. ~~A method of~~Use of an antibody-drug conjugate (ADC) comprising a bispecific antigen-binding molecule and a cytotoxin in the manufacture of a medicament for inducing mitotic arrest of an uveal melanoma cell, ~~the method comprising contacting~~wherein the cell is to be contacted *in vivo* with ~~an antibody-drug conjugate (ADC) comprising a bispecific antigen-binding molecule and a cytotoxin~~the medicament, wherein the bispecific antigen-binding molecule comprises:

a first antigen-binding domain (D1); and

a second antigen-binding domain (D2);

wherein D1 specifically binds a first epitope of human MET; and

wherein D2 specifically binds a second epitope of human MET; and

wherein D1 comprises three heavy chain complementarity determining regions comprising: an HCDR1 comprising the amino acid sequence of SEQ ID NO: 60; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 62; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; and three light chain complementarity determining regions comprising: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144; and

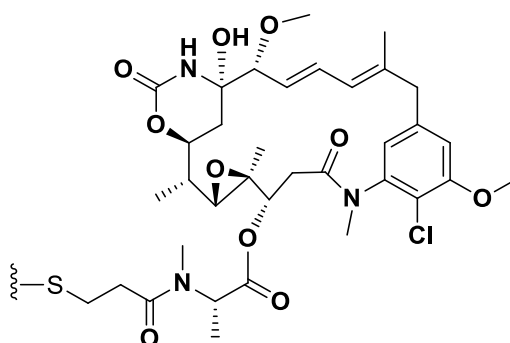
wherein D2 comprises three heavy chain complementarity determining regions comprising: an HCDR1 comprising the amino acid sequence of SEQ ID NO: 84; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 86; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 88; and three light chain complementarity determining regions comprising: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144.

23. The ~~method~~use of claim 22, wherein D1 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy

chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 58 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 138.

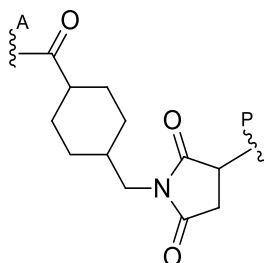
24. The [method use](#) of claim 22, wherein D2 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 82 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 138.

25. The [method use](#) of claim 22, wherein the cytotoxin is conjugated to the bispecific antigen-binding molecule through a linker, and wherein the cytotoxin is:



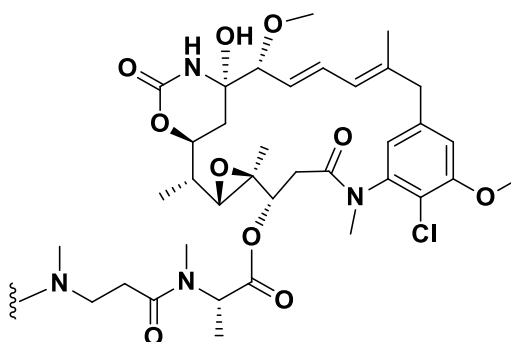
wherein the  is the bond to a linker.

26. The [method use](#) of claim 25, wherein the linker is:



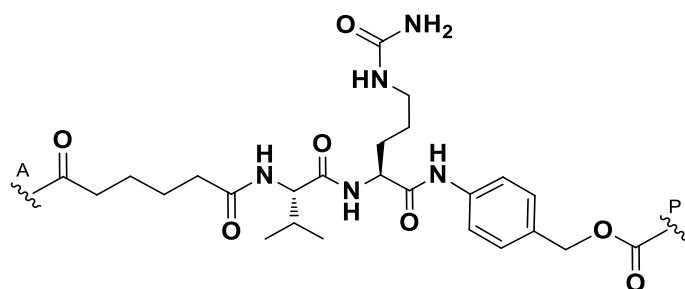
wherein the bond noted with  represents the bond to the bispecific antigen-binding molecule and the bond noted with  represents the bond to the cytotoxin.

27. The [method use](#) of claim 22, wherein the cytotoxin is conjugated to the bispecific antigen-binding molecule through a linker, and wherein the cytotoxin is:



wherein the  is the bond to the linker.

28. The [method use](#) of claim 27, wherein the linker is



wherein the bond noted with  represents the bond to the bispecific antigen-binding molecule and the bond noted with  represents the bond to the cytotoxin.

29. [A method of Use of a bispecific antigen-binding molecule in the manufacture of a medicament for](#) treating eye cancer or inhibiting metastasis in a subject suffering from a c-Met expressing tumor, [the method comprising administering to wherein](#) the subject [is to be administered the medicament, and wherein the a](#) bispecific antigen-binding molecule [comprising comprises](#):

a first antigen-binding domain (D1); and

a second antigen-binding domain (D2);

wherein D1 specifically binds a first epitope of human MET; and

wherein D2 specifically binds a second epitope of human MET; [and](#)

wherein D1 comprises three heavy chain complementarity determining regions comprising: an HCDR1 comprising the amino acid sequence of SEQ ID NO: 60; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 62; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; and three light chain complementarity determining regions comprising: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144; and

wherein D2 comprises three heavy chain complementarity determining regions comprising: an HCDR1 comprising the amino acid sequence of SEQ ID NO: 84; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 86; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 88; and three light chain complementarity determining regions comprising: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144.

30. The methoduse of claim 29, wherein the eye cancer is selected from the group consisting of uveal melanoma, orbital lymphoma, retinoblastoma, and medulloepithelioma.

31. The methoduse of claim 29, further comprising administering to the subject a second anti-cancer therapeutic agent.

32. The methoduse of claim 29, wherein D1 and D2 do not compete with one another for binding to human MET.

33. The methoduse of claim 29, wherein D1 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 58 or an amino acid sequence that is at least 95% identical thereto and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 138 or an amino acid sequence that is at least 95% identical thereto.

~~34. The method of claim 29, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO:60; HCDR2 comprises the amino acid sequence of SEQ ID NO:62; HCDR3 comprises the amino acid sequence of SEQ ID NO:64; LCDR1 comprises the amino acid sequence of SEQ ID NO:140; LCDR2 comprises the amino acid sequence of SEQ ID NO:142; and LCDR3 comprises the amino acid sequence of SEQ ID NO:144.~~

~~35~~34. The ~~method~~use of claim ~~34~~29, wherein the bispecific antigen-binding molecule comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 58 or an amino acid sequence that is at least 95% identical thereto; and an LCVR comprising the amino acid sequence of SEQ ID NO: 138 or an amino acid sequence that is at least 95% identical thereto.

~~36~~35. The ~~method~~use of claim ~~35~~34, wherein the bispecific antigen-binding molecule comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 58; and an LCVR comprising the amino acid sequence of SEQ ID NO: 138.

~~37~~36. The ~~method~~use of claim ~~36~~29, wherein D2 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 82 or an amino acid sequence that is at least 95% identical thereto and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 138 or an amino acid sequence that is at least 95% identical thereto.

~~38. The method of claim 37, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO:84; HCDR2 comprises the amino acid sequence of SEQ ID NO:86; HCDR3 comprises the amino acid sequence of SEQ ID NO:88; LCDR1 comprises the amino acid sequence of SEQ ID NO:140; LCDR2 comprises the amino acid sequence of SEQ ID NO:142; and LCDR3 comprises the amino acid sequence of SEQ ID NO:144.~~

~~39~~37. The ~~method~~use of claim ~~38~~29, wherein the bispecific antigen-binding molecule comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 82 or an amino acid sequence that is at least 95% identical thereto; and an LCVR comprising the amino acid sequence of SEQ ID NO: 138 or an amino acid sequence

that is at least 95% identical thereto.

~~4038~~. The ~~method~~use of claim ~~3937~~, wherein the bispecific antigen-binding molecule comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 82; and an LCVR comprising the amino acid sequence of SEQ ID NO: 138.

~~4139~~. The ~~method~~use of claim 29, wherein the bispecific antigen-binding molecule is conjugated to a cytotoxin to form an antibody-drug conjugate (ADC), and wherein the cytotoxin is a maytansinoid.