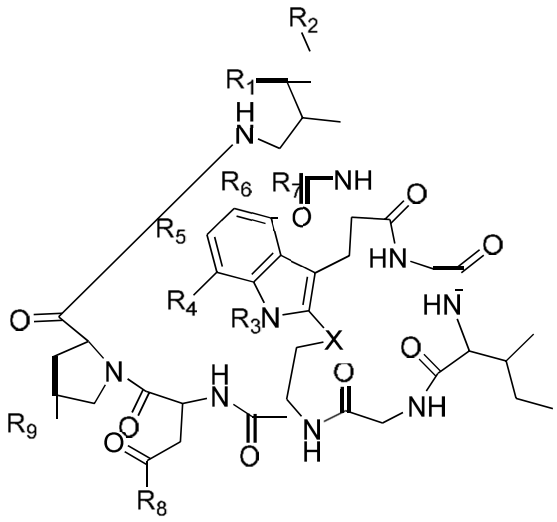
CLAIMS

1. Use of an effective amount of an antibody drug conjugate (ADC) in the manufacture of a medicament for depleting a population of CD137 positive cells in a human patient having graft-versus-host disease (GVHD) or at risk for developing GVHD, wherein the ADC comprises an anti-CD137 antibody conjugated at a cysteine residue to an amatoxin via a linker, wherein the anti-CD137 antibody binds to human CD137, and wherein the amatoxin is represented by formula (**IV**)



(**IV**)

wherein R_1 is H, OH, or OR_A;

R_2 is H, OH, or OR_B;

R_A and R_B, together with the oxygen atoms to which they are bound, combine to form a 5-membered heterocyclolalkyl group;

R_3 is H or R_D;

R_4, R_6, and R_7 are each independently H, OH, OR_D, or R_D;

R_5 is H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, or OR_D;

X is -S-, -S(O)-, or $-SO_2-$;

R_C is -L-Z;

R_D is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 heteroalkenyl, C_2-C_6 alkynyl, C_2-C_6 heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

L is C_1-C_6 alkylene, C_1-C_6 heteroalkylene, C_2-C_6 alkenylene, C_2-C_6 heteroalkenylene, C_2-C_6 alkynylene, C_2-C_6 heteroalkynylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or comprises a dipeptide; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody,

wherein the amatoxin comprises exactly one R_C substituent.

2. The use of claim 1, wherein the amatoxin is an amanitin.

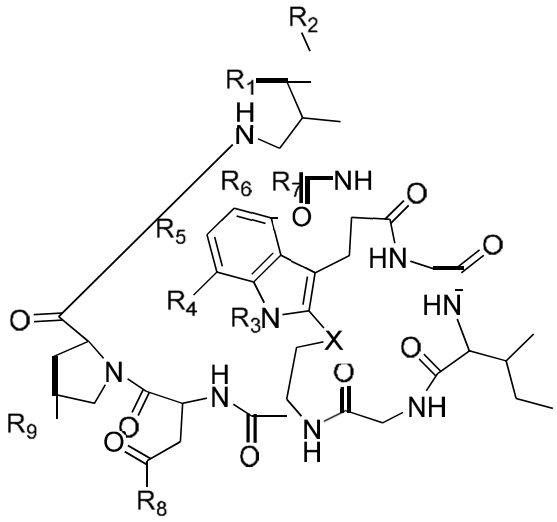
3. The use of claim 2, wherein the amanitin is selected from the group consisting of α-amanitin, β-amanitin, γ-amanitin, ε-amanitin, amanin, amaninamide, amanullin, amanullinic acid, and proamanullin.

4. The use of claim 1, wherein the ADC is for use in the patient prior to, concomitantly with, or after receipt of an allogeneic transplant comprising hematopoietic stem cells.

5. The use of claim 4, wherein the ADC is for use in the patient about 1 hour to 10 days after receipt of the allogeneic transplant comprising hematopoietic stem cells.

6. The use of claim 1, wherein the antibody comprises a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 having an amino acid sequence as set forth in SEQ ID NOs: 25, 26, and 27, respectively, and comprising a light chain variable region comprising a CDR1, a CDR2, and a CDR3 having an amino acid sequence as set forth in SEQ ID NOs: 29, 30, and 31, respectively.

7. Use of an effective amount of an antibody drug conjugate (ADC) in the manufacture of a medicament for treating graft-versus-host disease (GVHD) in a human patient in need thereof, wherein the ADC comprises an anti-CD137 antibody linked at a cysteine residue to an amatoxin, wherein the anti-CD137 antibody binds to human CD137, and wherein the amatoxin is represented by formula (**IV**)



(**IV**)

wherein R_1 is H, OH, or OR_A;

R_2 is H, OH, or OR_B;

R_A and R_B, together with the oxygen atoms to which they are bound, combine to form a 5-membered heterocyclolalkyl group;

R_3 is H or R_D;

R_4, R_6, and R_7 are each independently H, OH, OR_D, or R_D;

R_5 is H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, or OR_D;

X is -S-, -S(O)-, or $-SO_2$-;

R_C is -L-Z;

R_D is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 heteroalkenyl, C_2-C_6 alkynyl, C_2-C_6 heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

L is C_1-C_6 alkylene, C_1-C_6 heteroalkylene, C_2-C_6 alkenylene, C_2-C_6 heteroalkenylene, C_2-C_6 alkynylene, C_2-C_6 heteroalkynylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or comprises a dipeptide; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody,

wherein the amatoxin comprises exactly one R_C substituent.

8. The use of claim 7, wherein the ADC is administered to the patient prior to, concomitantly with, or after receipt of an allogeneic transplant comprising hematopoietic stem cells.

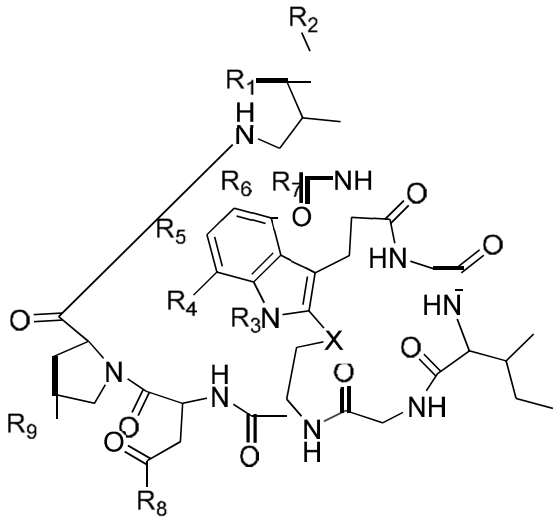
9. The use of claim 7, wherein the ADC is for use in the patient about three days prior to the patient receiving an allogeneic transplant comprising hematopoietic stem cells.

10. The use of claim 7, wherein the anti-CD137 antibody comprises a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 having an amino acid sequence as set forth in SEQ ID NOs: 25, 26, and 27, respectively, and comprising a light chain variable region comprising a CDR1, a CDR2, and a CDR3 having an amino acid sequence as set forth in SEQ ID NOs: 29, 30, and 31, respectively.

11. The use of claim 7, wherein the amatoxin is an amanitin.

12. The use of claim 11, wherein the amanitin is selected from the group consisting of α-amanitin, β-amanitin, γ-amanitin, ε-amanitin, amanin, amaninamide, amanullin, amanullinic acid, and proamanullin.

13. Use of an effective amount of an antibody drug conjugate (ADC) in the manufacture of a medicament for depleting allo-reactive T cells in a human patient who received an allogeneic transplant, wherein the ADC comprises an anti-CD137 antibody linked at a cysteine residue to an amatoxin, wherein the anti-CD137 antibody binds to human CD137, and wherein the amatoxin is represented by formula (**IV**)



(**IV**)

wherein R_1 is H, OH, or OR_A;

R_2 is H, OH, or OR_B;

R_A and R_B, together with the oxygen atoms to which they are bound, combine to form a 5-membered heterocyclolalkyl group;

R_3 is H or R_D;

R_4, R_6, and R_7 are each independently H, OH, OR_D, or R_D;

R_5 is H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, or OR_D;

X is -S-, -S(O)-, or $-SO_2$-;

R_C is -L-Z;

R_D is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 heteroalkenyl, C_2-C_6 alkynyl, C_2-C_6 heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

L is C_1-C_6 alkylene, C_1-C_6 heteroalkylene, C_2-C_6 alkenylene, C_2-C_6 heteroalkenylene, C_2-C_6 alkynylene, C_2-C_6 heteroalkynylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or comprises a dipeptide; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody,

wherein the amatoxin comprises exactly one R_C substituent.

14. The use of claim 13, wherein the transplant is selected from the group consisting of a bone marrow transplant, a peripheral blood transplant and a cord blood transplant.

15. The use of claim 13, wherein the transplant comprises hematopoietic cells.

16. The use of claim 13, wherein the amatoxin is an amanitin.

17. The use of claim 16, wherein the amanitin is selected from the group consisting of α-amanitin, β-amanitin, γ-amanitin, ε-amanitin, amanin, amaninamide, amanullin, amanullinic acid, and proamanullin.

18. The use of any one of claims 1, 7, and 13, wherein R_5 is OR_c.

19. The use of any one of claims 1, 7, and 13, wherein R_5 is R_C.

20. The use of any one of claims 1, 7, and 13, wherein R_8 is OR_c.

21. The use of any one of claims 1, 7, and 13, wherein R_8 is NHR_C.

22. The use of any one of claims 1, 7, or 13, wherein R_8 is NR_CR_D.

23. The use of any one of claims 1, 7, and 13, wherein R_1 and R_2 are each OH.

24. The use of any one of claims 1, 7, and 13, wherein L is C_1-C_6 alkylene, C_1-C_6 heteroalkylene, C_2-C_6 alkenylene, C_2-C_6 heteroalkenylene, C_2-C_6 alkynylene, C_2-C_6 heteroalkynylene, or comprises a dipeptide.

25. The use of claim 24, wherein L is C_1-C_6 alkylene, C_1-C_6 heteroalkylene, C_2-C_6 alkenylene, C_2-C_6 heteroalkenylene, C_2-C_6 alkynylene, or C_2-C_6 heteroalkynylene.

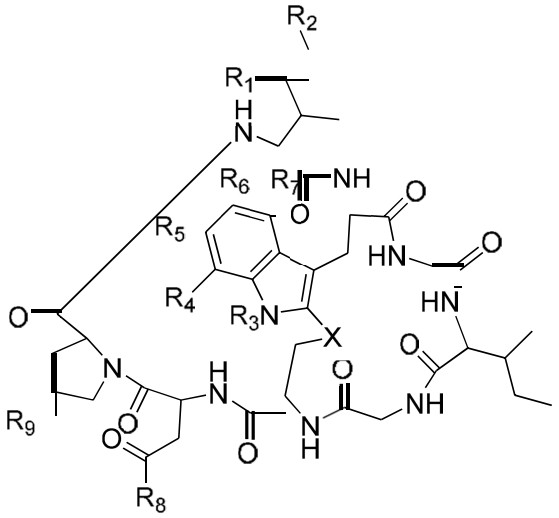
26. The use of claim 24, wherein L comprises a dipeptide.

27. The use of any one of claims 1, 7, and 13, wherein X is -S-.

28. The use of any one of claims 1, 7, and 13, wherein X is -S(O)-.

29. The use of any one of claims 1, 7, and 13, wherein X is -SO_2-.

30. An antibody drug conjugate (ADC) comprising an anti-CD137 antibody conjugated to an amatoxin, wherein the amatoxin is represented by formula (**IV**):



(**IV**)

wherein R_1 is H, OH, or OR_A;

R_2 is H, OH, or OR_B;

R_A and R_B, together with the oxygen atoms to which they are bound, combine to form a 5-membered heterocyclolalkyl group;

R_3 is H or R_D;

R_4, R_6, and R_7 are each independently H, OH, OR_D, or R_D;

R_5 is H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, or OR_D;

X is -S-, -S(O)-, or -SO_2-;

R_C is -L-Z;

R_D is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 heteroalkenyl, C_2-C_6 alkynyl, C_2-C_6 heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

L is C_1-C_6 alkylene, C_1-C_6 heteroalkylene, C_2-C_6 alkenylene, C_2-C_6 heteroalkenylene, C_2-C_6 alkynylene, C_2-C_6 heteroalkynylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or comprises a dipeptide; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof,

wherein the amatoxin comprises exactly one R_C substituent.

31. The ADC of claim 30, wherein the amatoxin is an amanitin.

32. The ADC of claim 31, wherein the amanitin is selected from the group consisting of α-amanitin, β-amanitin, γ-amanitin, ε-amanitin, amanin, amaninamide, amanullin, amanullinic acid, and proamanullin.

33. The ADC of claim 30, wherein R_5 is OR_C.

34. The ADC of claim 30, wherein R_8 is OR_C.

35. The ADC of claim 30, wherein R_8 is NHR_C.

36. The ADC of claim 30, wherein R_8 is NR_CR_D.

37. The ADC of claim 30, wherein R_1 and R_2 are each OH.

38. The ADC of claim 30, wherein L is C_1-C_6 alkylene, C_1-C_6 heteroalkylene, C_2-C_6 alkenylene, C_2-C_6 heteroalkenylene, C_2-C_6 alkynylene, C_2-C_6 heteroalkynylene, or comprises a dipeptide.

39. The ADC of claim 38, wherein L is C_1-C_6 alkylene, C_1-C_6 heteroalkylene, C_2-C_6 alkenylene, C_2-C_6 heteroalkenylene, C_2-C_6 alkynylene, or C_2-C_6 heteroalkynylene.

40. The ADC of claim 38, wherein L comprises a dipeptide.

41. The ADC of claim 30, wherein X is -S-.

42. The ADC of claim 30, wherein X is -S(O)-.

43. The ADC of claim 30, wherein X is -SO_2-.