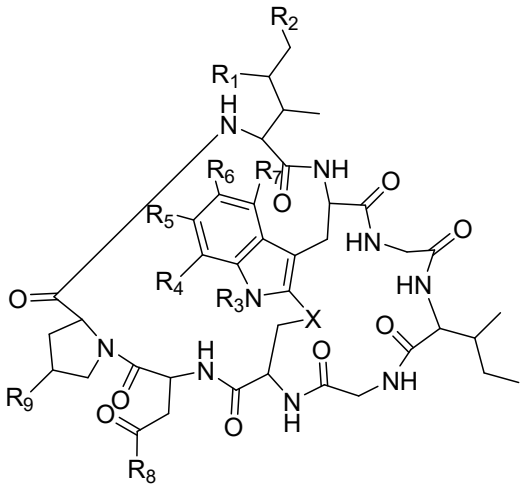
CLAIMS

1. Use of an effective amount of a conjugate comprising an anti-CD117 antibody, or an antigen-binding fragment thereof, and an amatoxin, in the manufacture of a medicament for depleting a population of CD117+ cells in a human patient in need of a hematopoietic stem cell transplant, wherein the antibody, or the antigen-binding fragment thereof, is internalized by a CD117+ cell, wherein the antibody, or the antigen-binding fragment thereof, is conjugated to the amatoxin by way of a cysteine residue in the Fc domain of the antibody or antigen-binding fragment thereof, and wherein the amatoxin is represented by formula (I)



wherein R_1 is H, OH, OR_A, or OR_C;

R_2 is H, OH, OR_B, or OR_C;

when present, 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, R_C, or R_D;

R_4, R_5, R_6, and R_7 are each independently 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_C, 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 a peptide; 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 one R_C substituent.

2~~1a~~. The use of claim 1,

wherein R_1 is H or OH,

R_2 is H or OH,

R_3 is H, and

R_9 is H or OH.

3~~1b~~. The use of claim 2~~1a~~,

wherein R_4, R_5, R_6, and R_7 are each independently H, OH, OR_C, or R_C, and

R_8 is OH, NH_2, OR_C, or NHR_C.

4~~2~~. The use of any one of claims 1, 2~~1a~~ or 3~~1b~~, wherein the cysteine residue is introduced by way of a mutation in the Fc domain of the antibody or antigen-binding fragment thereof.

5~~3~~. The use of any one of claims 1, 2~~1a~~ or 3~~1b~~, wherein the cysteine residue is naturally occurring in the Fc domain of the antibody, or the antigen-binding fragment thereof.

6~~4~~. The use of any one of claims 1, 2~~1a~~, 3~~1b~~, 4~~2~~ or 5~~3~~, wherein the population of CD117+ cells comprises hematopoietic stem cells.

7~~5~~. The use of any one of claims 1, 2~~1a~~, 3~~1b~~, 4~~2~~, 5~~3~~ or 6~~4~~, wherein the antibody, or the antigen-binding fragment thereof, binds CD117 with a K_d of from 0.1 pM to 1 μM.

8~~6~~. The use of any one of claims 1, 2~~1a~~, 3~~1b~~, 4~~2~~, 5~~3~~ or 6~~4~~, wherein the antibody, or the antigen-binding fragment thereof, binds CD117 with a k_{on} of from $9 \times 10^{-2}\ M^{-1}s^{-1}$ to $1 \times 10^{-2}\ M^{-1}s^{-1}$.

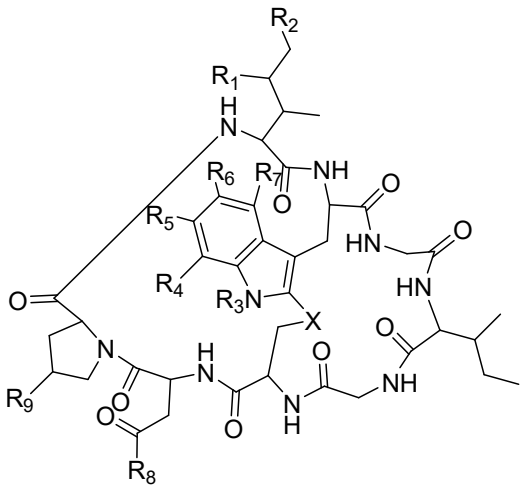
9~~7~~. The use of any one of claims 1, 2~~1a~~, 3~~1b~~, 4~~2~~, 5~~3~~, 6~~4~~, 7~~5~~ or 8~~6~~, wherein the antibody, or the antigen-binding fragment thereof, competitively inhibits the binding of CD117 to a second antibody comprising the following complementarity determining regions (CDRs):

a CDR-H1 having the amino acid sequence SYWIG (SEQ ID NO: 1);
a CDR-H2 having the amino acid sequence IIYPGDSDTRYSPSFQG (SEQ ID NO: 2);
a CDR-H3 having the amino acid sequence HGRGYNGYEGAFDI (SEQ ID NO: 3);
a CDR-L1 having the amino acid sequence RASQGISSALA (SEQ ID NO: 4);
a CDR-L2 having the amino acid sequence DASSLES (SEQ ID NO: 5); and
a CDR-L3 having the amino acid sequence CQQFNSYPLT (SEQ ID NO: 6).

108. The use of any one of claims 1, 21a, 31b, 42, 53, 64, 75, 86 or 97, wherein the antibody is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a humanized antibody, a bispecific antibody, and a dual-variable immunoglobulin domain.

119. The use of any one of claims 1, 21a, 31b, 42, 53, 64, 75, 86 or 97, wherein the antigen-binding fragment is selected from the group consisting of a single-chain Fv molecule (scFv), a diabody, a triabody, a nanobody, a Fv fragment, a Fab fragment, a $F(ab')_2$ molecule, a domain antibody, and a tandem di-scFV.

1210. Use of an effective amount of a conjugate comprising an anti-CD117 antibody, or an antigen-binding fragment thereof, covalently conjugated to an amatoxin, in the manufacture of a medicament for conditioning prior to a hematopoietic stem cell (HSC) transplantation for a hematological cancer, wherein the antibody, or the antigen-binding fragment thereof, is internalized by a CD117+ cell, wherein the antibody, or the antigen-binding fragment thereof, is conjugated to the amatoxin by way of a cysteine residue in the Fc domain of the antibody or antigen-binding fragment thereof, and wherein the amatoxin is represented by formula (I)



wherein R_1 is H, OH, OR_A, or OR_C;

R_2 is H, OH, OR_B, or OR_C;

when present, 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, R_C, or R_D;

R_4, R_5, R_6, and R_7 are each independently 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_C, 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 a peptide; 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 one R_C substituent.

13~~10a~~. The use of claim 12~~10~~,

wherein R_1 is H or OH,

R_2 is H or OH,

R_3 is H, and

R_9 is H or OH.

14~~10b~~. The use of claim 13~~10a~~,

wherein R_4, R_5, R_6, and R_7 are each independently H, OH, OR_C, or R_C, and

R_8 is OH, NH_2, OR_C, or NHR_C.

15~~11~~. The use of any one of claims 12~~10~~, 13~~10a~~, 14~~10b~~, or, wherein the hematological cancer is selected from the group consisting of acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, multiple myeloma, diffuse large B-cell lymphoma, and nonHodgkin's lymphoma.

16~~12~~. The use of any one of claims 12~~10~~, 13~~10a~~, 14~~10b~~, or, wherein the cancer is leukemia.

17~~13~~. The use of any one of claims 12~~10~~, 13~~10a~~, 14~~10b~~ or 16~~12~~, wherein a population of endogenous CD117+ cells are depleted following administration of the conjugate.

18~~14~~. The use of claim 17~~13~~, wherein the CD117+ cells are HSCs.

19~~15~~. The use of any one of claims 12~~10~~, 13~~10a~~, 14~~10b~~, 15~~11~~, 16~~12~~ or18~~14~~, wherein the anti-CD117 antibody or antigen binding fragment thereof binds CD117 with a K_d of from 0.1 pM to 1 μM.

20~~16~~. The use of any one of claims 12~~10~~, 13~~10a~~, 14~~10b~~, 15~~11~~, 16~~12~~ or 18~~14~~, wherein the antibody or antigen-binding fragment thereof binds CD117 with a k_{on} of from 9 x 10^{-2} M^{-1} s^{-1} to 1 x 10^{2} M^{-1} s^{-1}.

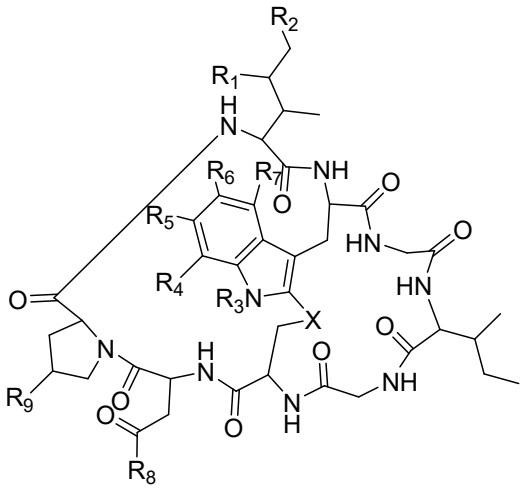
21~~17~~. The use of any one of claims 12~~10~~, 13~~10a~~, 14~~10b~~, 15~~11~~, 16~~12~~, 17~~13~~, 18~~14~~, 19~~15~~ or 20~~16~~, wherein the anti-CD117 antibody or antigen binding fragment thereof competitively inhibits the binding of CD117 to a second anti-CD117 antibody comprising the following CDRs:

a CDR-H1 having the amino acid sequence SYWIG (SEQ ID NO: 1);
a CDR-H2 having the amino acid sequence IIYPGDSDTRYSPSFQG (SEQ ID NO: 2);
a CDR-H3 having the amino acid sequence HGRGYNGYEGAFDI (SEQ ID NO: 3);
a CDR-L1 having the amino acid sequence RASQGISSALA (SEQ ID NO: 4);
a CDR-L2 having the amino acid sequence DASSLES (SEQ ID NO: 5); and
a CDR-L3 having the amino acid sequence CQQFNSYPLT (SEQ ID NO: 6).

22~~18~~. The use of any one of claims 12~~10~~, 13~~10a~~, 14~~10b~~, 15~~11~~, 16~~12~~, 17~~13~~, 18~~14~~, 19~~15~~, 20~~16~~ or 21~~17~~, wherein the anti-CD117 antibody is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a humanized antibody, a bispecific antibody, and a dual-variable immunoglobulin domain.

23~~19~~. Use of an effective amount of a conjugate, wherein the conjugate comprises a monoclonal anti-CD117 antibody, or an antigen-binding fragment thereof, covalently conjugated to an amatoxin, in the manufacture of a medicament for conditioning a human patient for receiving a hematopoietic stem cell (HSC) transplantation, wherein the human patient has a hematological cancer, and wherein the antibody, or the antigen-binding fragment thereof, is internalized by a CD117+ cell, wherein the antibody, or the antigen-binding fragment thereof, is conjugated to the amatoxin by way of a cysteine residue in the

Fc domain of the antibody or antigen-binding fragment thereof, and wherein the amatoxin is represented by formula (I)



wherein R_1 is H, OH, OR_A, or OR_C;

R_2 is H, OH, OR_B, or OR_C;

when present, 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, R_C, or R_D;

R_4, R_5, R_6, and R_7 are each independently 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_C, 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 a peptide; 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 one R_C substituent.

2420. The use of claim 2319,

wherein R_1 is H or OH,

R_2 is H or OH,

R_3 is H, and

R_9 is H or OH.

2521. The use of claim 2420,

wherein R_4, R_5, R_6, and R_7 are each independently H, OH, OR_C, or R_C, and

R_8 is OH, NH_2, OR_C, or NHR_C.

2622. The use of any one of claims 2319-2521, wherein the cysteine residue is introduced by way of a mutation in the Fc domain of the antibody or antigen-binding fragment thereof.

2723. The use of any one of claims 2319-2521, wherein the cysteine residue is naturally occurring in the Fc domain of the antibody, or the antigen-binding fragment thereof.

2824. The use of any one of claims 2319-2723, wherein the population of CD117+ cells comprises hematopoietic stem cells.

2925. The use of any one of claims 2319-2824, wherein the hematological cancer is selected from the group consisting of acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, multiple myeloma, diffuse large B-cell lymphoma, and nonHodgkin's lymphoma.

3026. The use of any one of claims 2319-2824, wherein the cancer is leukemia.

3127. The use of any one of claims 2319-3026, wherein a population of endogenous CD117+ cells are depleted following administration of the conjugate.

3228. The use of claim 3127, wherein the CD117+ cells are HSCs.