CLAIMS

1. A Ligand-Functional Agent Conjugate that is a Ligand Drug Conjugate, for use in treating a cancer, the cells of which express a target antigen, in which the Ligand-Functional Agent Conjugate comprises:

a Ligand unit and at least one Functional Agent in which the Functional Agent is a Drug unit, in which

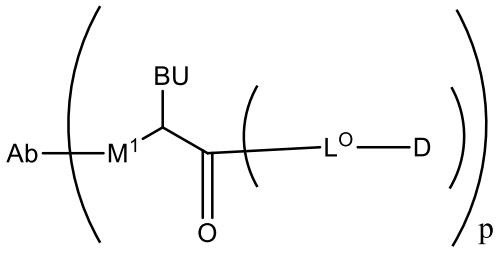
the Ligand unit and each of the Drug Unit(s) are joined by a self-stabilizing linker assembly comprising a hydrolyzed succinimide directly conjugated to the Ligand unit via a thioether linkage; and

a basic functional group of a Base unit and an electron withdrawing group, each of which is operably linked to stabilize the conjugate in plasma relative to a Ligand-Functional Agent Conjugate lacking the self-stabilizing linker assembly,

in which there are between 2 and 6 intervening atoms between the basic functional group of the Basic unit and the nitrogen atom of the hydrolyzed succinimide and between 2 and 5 carbon atoms between the electron withdrawing group and the nitrogen atom of the hydrolyzed succinimide ring;

in which the Ligand unit is a monoclonal antibody that specifically binds to the target antigen, and

in which the Ligand Drug Conjugate compound is represented by the structure of:



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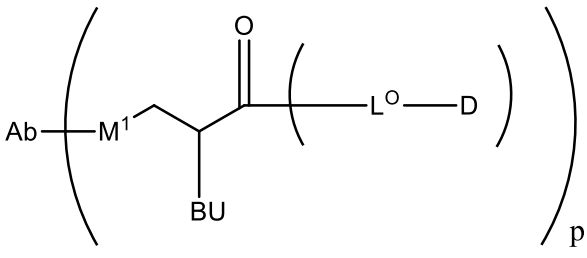
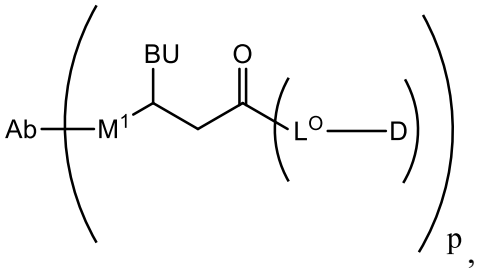


, or



or a salt thereof, in which

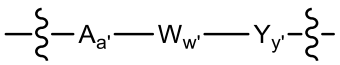
D is the Drug unit;

Ab is a monoclonal antibody that specifically binds to the target antigen;

M^1 is a the hydrolyzed succinimide;

BU is the Basic unit;

L^O is an optional secondary linker assembly, in which L^O when present has the formula:



in which –A- is an optional Stretcher unit, the subscript a' is 0 or 1; -W- is an optional Cleavable unit, the subscript w' is 0 or 1; and -Y- is an optional Spacer unit, and the subscript y' is 0 or 1;

subscript p ranges from 1 to 20; and

the wavy lines indicate the points of attachment within the Ligand-Drug Conjugate compound formula.

2. A Ligand Drug Conjugate compound according to Claim 1, in which BU is selected from the group consisting of $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^a$, and $–(CH_2)_xNR^a_2$, in which x is an integer of from 0-4 and each R^a is independently selected from the group consisting of unsubstituted C_{1-6} alkyl and C_{1-6} haloalkyl, or two R^a groups are combined with the nitrogen to which they are attached to form an azetidinyl, pyrrolidinyl or piperidinyl group, provided that there are no less than 2 intervening atoms between the base of the Basic unit and the nitrogen atom of the hydrolyzed succinimide.

3. A Ligand-Drug Conjugate compound according to Claim 1, in which the subscript w' is 1, and W is conjugated directly to the Drug unit.

4. A Ligand-Drug Conjugate compound according to Claim 1, in which w' is 1 and W is conjugated directly to the Spacer unit.

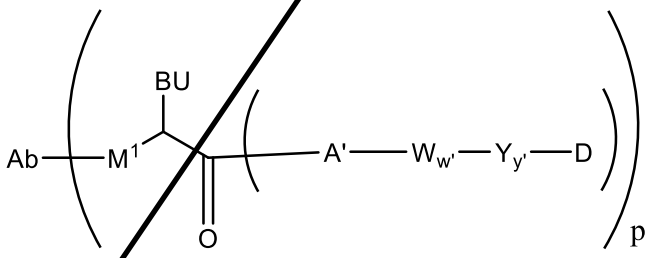
5. A Ligand-Drug Conjugate compound according to Claim 1, in which w' is 1, and W is conjugated directly to the Drug unit or Spacer unit via a cleavable peptide, disulfide or hydrazine bond.

6. A Ligand-Drug Conjugate compound according to Claim 1, in which W is absent.

7. A Ligand-Drug Conjugate compound according to Claim 1, in which W is present and the Spacer unit and Stretcher unit are absent.

8. A Ligand-Drug Conjugate compound according to Claim 1, in which D is selected from the group consisting of auristatins and PBDs.

9. A Ligand-Drug Conjugate compound according to Claim 1, in which the Ligand-Drug Conjugate has the formula:

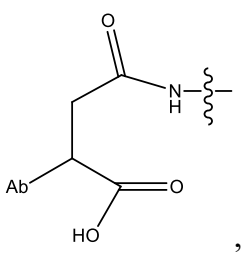


or a salt thereof, in which

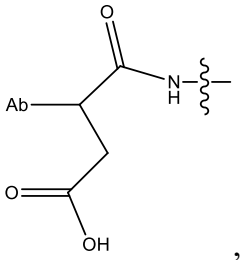
BU is selected from the group consisting of $–CH_2NH_2$, $–CH_2CH_2NH_2$, $–CH_2CH_2CH_2NH_2$, and $–CH_2CH_2CH_2CH_2NH_2$; and

the subscript p ranges from 1 to 12.

10. A Ligand-Drug Conjugate compound according to Claim 9, in which Ab-M^1- has the structure:



, or



,

or a salt thereof, in which the wavy line indicates the point of attachment to the remainder of the Ligand Drug Conjugate compound formula.

11. A Ligand-Drug Conjugate compound according to Claim 9, in which a' is 0, and $W_{w'}$ is a dipeptide.

12. A Ligand-Drug Conjugate compound according to Claim 11, in which $W_{w'}$ is selected from the group consisting of Val-Cit, Phe-Lys and Val-Ala.

13. A Ligand-Drug Conjugate compound according to Claim 9, in which D is a cytotoxic agent.

14. A Ligand-Drug Conjugate compound according to Claim 13, in which the cytotoxic agent is an auristatin selected from the group consisting of AE, AFP, AEB, AEVB, MMAF and MMAE.

15. A Ligand-Drug Conjugate compound according to Claim 9, in which $Y_{y'}$ is a PAB unit.

16. A Ligand-Drug Conjugate compound according to Claim 9, in which the subscript a' is 0; $W_{w'}$ is Val-Cit; and $Y_{y'}$ is a PAB unit.

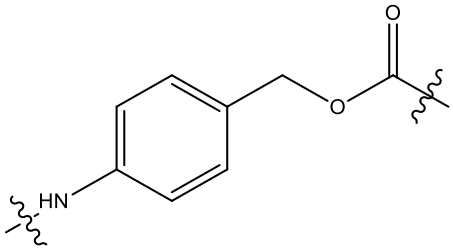
17. A Ligand-Drug Conjugate compound according to Claim 9, in which the subscript a' is 0; $W_{w'}$ is Val-Cit; $Y_{y'}$ is a PAB unit; and D is a cytotoxic agent.

18. A Ligand-Drug Conjugate compound according to Claim 9, in which the subscript a' is 0; $W_{w'}$ is Val-Cit; $Y_{y'}$ is PAB; D is a cytotoxic agent; and the subscript p ranges from 1 to 8.

19. A Ligand-Drug Conjugate compound according to Claim 17 or 18, in which the cytotoxic agent is MMAE.

20. A Ligand-Drug Conjugate compound according to Claim 9, in which the subscript a' is 0; $W_{w'}$ is Val-Cit; $Y_{y'}$ is a PAB unit; and D is MMAE.

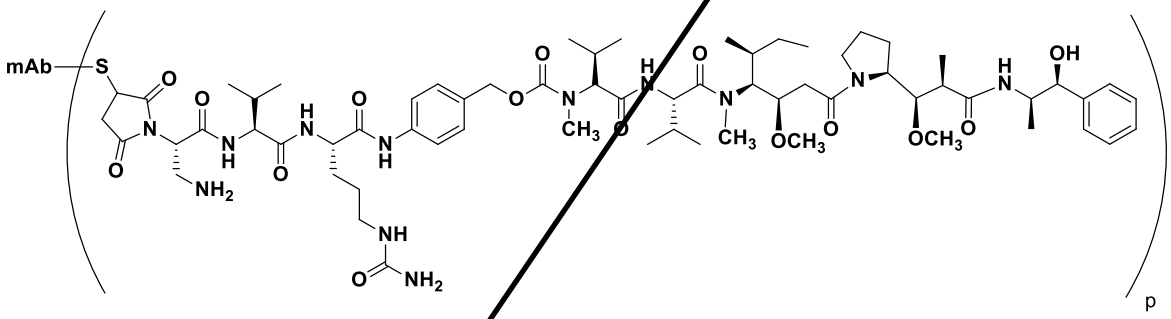
21. A Ligand-Drug Conjugate compound according to any of Claims 15 to 18 and 20, in which the PAB unit has the structure:



,

in which the wavy lines indicate the points of attachment within the remainder of the Ligand-Drug Conjugate compound formula.

22. A Ligand-Drug Conjugate compound according to Claim 1, in which the Ligand-Drug Conjugate has the structure:



,

in which the succinimide is hydrolyzed, or a salt thereof; in which

mAb is a monoclonal antibody and S is a sulfur atom from the monoclonal antibody.

23. A Ligand-Drug Conjugate compound according to Claim 22, in which the subscript p is about 4.

CLAIMS

1. A Ligand-Functional Agent Conjugate that is a Ligand Drug Conjugate, for use in treating a cancer, the cells of which express a target antigen, in which the Ligand-Functional Agent Conjugate comprises:

a Ligand unit and at least one Functional Agent in which the Functional Agent is a Drug unit, in which

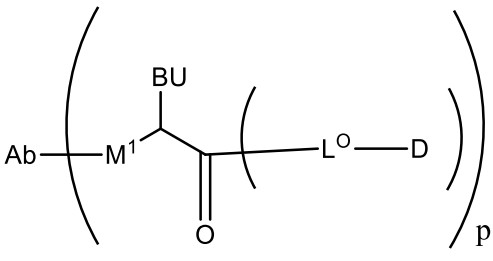
the Ligand unit and each of the Drug Unit(s) are joined by a self-stabilizing linker assembly comprising a hydrolyzed succinimide directly conjugated to the Ligand unit via a thioether linkage; and

a basic functional group of a Base unit and an electron withdrawing group, each of which is operably linked to stabilize the conjugate in plasma relative to a Ligand-Functional Agent Conjugate lacking the self-stabilizing linker assembly,

in which there are between 2 and 6 intervening atoms between the basic functional group of the Basic unit and the nitrogen atom of the hydrolyzed succinimide and between 2 and 5 carbon atoms between the electron withdrawing group and the nitrogen atom of the hydrolyzed succinimide ring;

in which the Ligand unit is a monoclonal antibody that specifically binds to the target antigen, and

in which the Ligand Drug Conjugate compound is represented by the structure of:



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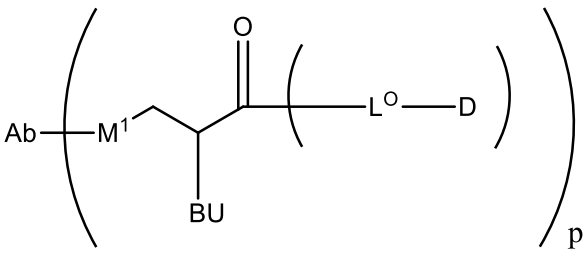
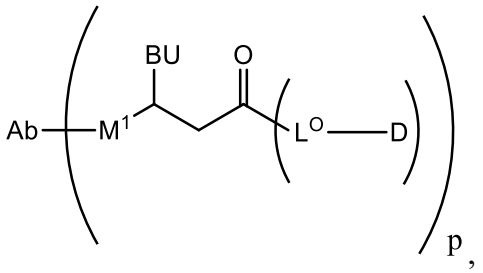


, or



or a salt thereof, in which

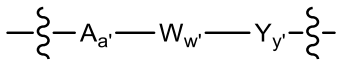
D is the Drug unit;

Ab is a monoclonal antibody that specifically binds to the target antigen;

M^1 is a the hydrolyzed succinimide;

BU is the Basic unit selected from the group consisting of $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^a$, and $–(CH_2)_xNR^a{}_2$, in which x is an integer of from 0-4 and each R^a is independently selected from the group consisting of unsubstituted C_{1-6} alkyl and C_{1-6} haloalkyl, or two R^a groups are combined with the nitrogen to which they are attached to form an azetidinyl, pyrrolidinyl or piperidinyl group, provided that there are no less than 2 intervening atoms between the base of the Basic unit and the nitrogen atom of the hydrolyzed succinimide;

L^O is an optional secondary linker assembly, in which L^O when present has the formula:



in which –A- is an optional Stretcher unit, the subscript a' is 0 or 1; -W- is an optional Cleavable unit, the subscript w' is 0 or 1; and -Y- is an optional Spacer unit, and the subscript y' is 0 or 1;

subscript p ranges from 1 to 20; and

the wavy lines indicate the points of attachment within the Ligand-Drug Conjugate compound formula.

2. A Ligand-Drug Conjugate compound according to Claim 1, in which the subscript w' is 1, and W is conjugated directly to the Drug unit.

3. A Ligand-Drug Conjugate compound according to Claim 1, in which w' is 1 and W is conjugated directly to the Spacer unit.

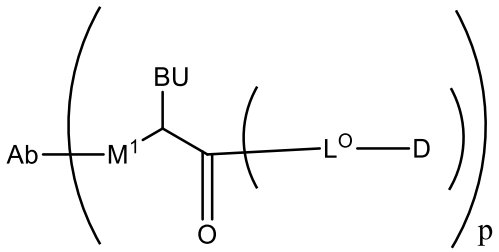
4. A Ligand-Drug Conjugate compound according to Claim 1, in which w' is 1, and W is conjugated directly to the Drug unit or Spacer unit via a cleavable peptide, disulfide or hydrazine bond.

5. A Ligand-Drug Conjugate compound according to Claim 1, in which W is absent.

6. A Ligand-Drug Conjugate compound according to Claim 1**,** in which W is present and the Spacer unit and Stretcher unit are absent.

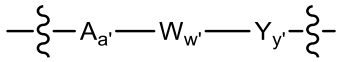
7. A Ligand-Drug Conjugate compound according to Claim 1, in which D is selected from the group consisting of auristatins and PBDs.

8. A Ligand-Drug Conjugate compound according to Claim 1, in which the Ligand-Drug Conjugate has the formula:



or a salt thereof, in which

L^O is a secondary linker assembly having the formula:



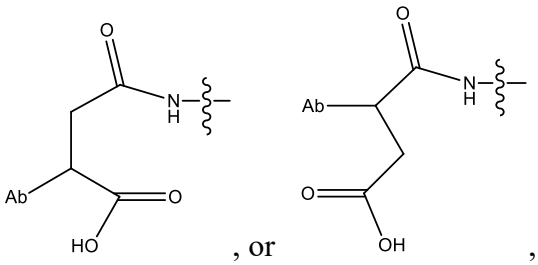
BU is selected from the group consisting of $–CH_2NH_2$, $–CH_2CH_2NH_2$,

$–CH_2CH_2CH_2NH_2$, and $–CH_2CH_2CH_2CH_2NH_2$;

the wavy lines indicate the points of attachment within the Ligand-Drug Conjugate compound formula; and

the subscript p ranges from 1 to 12.

9. A Ligand-Drug Conjugate compound according to Claim 8, in which Ab-M^1- has the structure:



, or ,

or a salt thereof, in which the wavy line indicates the point of attachment to the remainder of the Ligand Drug Conjugate compound formula.

10. A Ligand-Drug Conjugate compound according to Claim 8, in which a' is 0, and $W_{w'}$ is a dipeptide.

11. A Ligand-Drug Conjugate compound according to Claim 10, in which $W_{w'}$ is selected from the group consisting of Val-Cit, Phe-Lys and Val-Ala.

12. A Ligand-Drug Conjugate compound according to Claim 8, in which D is a cytotoxic agent.

13. A Ligand-Drug Conjugate compound according to Claim 12, in which the cytotoxic agent is an auristatin selected from the group consisting of AE, AFP, AEB, AEVB, MMAF and MMAE.

14. A Ligand-Drug Conjugate compound according to Claim 8, in which $Y_{y'}$ is a PAB unit.

15. A Ligand-Drug Conjugate compound according to Claim 8, in which the subscript a' is 0; $W_{w'}$ is Val-Cit; and $Y_{y'}$ is a PAB unit.

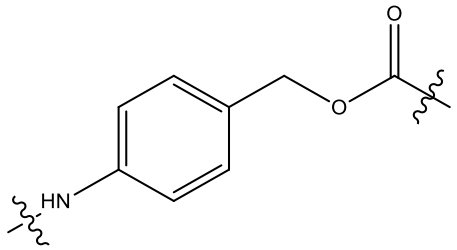
16. A Ligand-Drug Conjugate compound according to Claim 8, in which the subscript a' is 0; $W_{w'}$ is Val-Cit; $Y_{y'}$ is a PAB unit; and D is a cytotoxic agent.

17. A Ligand-Drug Conjugate compound according to Claim 8, in which the subscript a' is 0; $W_{w'}$ is Val-Cit; $Y_{y'}$ is PAB; D is a cytotoxic agent; and the subscript p ranges from 1 to 8.

18. A Ligand-Drug Conjugate compound according to Claim 16 or 17, in which the cytotoxic agent is MMAE.

19. A Ligand-Drug Conjugate compound according to Claim 8, in which the subscript a' is 0; $W_{w'}$ is Val-Cit; $Y_{y'}$ is a PAB unit; and D is MMAE.

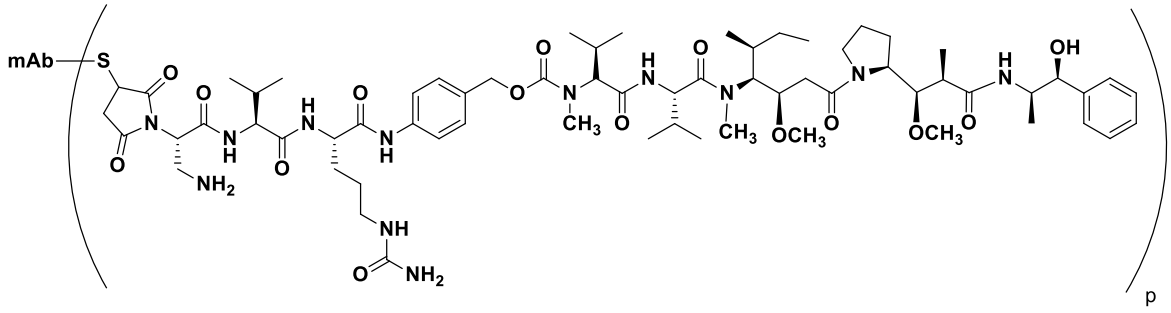
20. A Ligand-Drug Conjugate compound according to any of Claims 14 to 17 and 19, in which the PAB unit has the structure:



,

in which the wavy lines indicate the points of attachment within the remainder of the Ligand-Drug Conjugate compound formula.

21. A Ligand-Drug Conjugate compound according to Claim 1, in which the Ligand-Drug Conjugate has the structure:



,

in which the succinimide is hydrolyzed, or a salt thereof; in which

mAb is a monoclonal antibody and S is a sulfur atom from the monoclonal antibody.

22. A Ligand-Drug Conjugate compound according to Claim 21, in which the subscript p is 4.