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

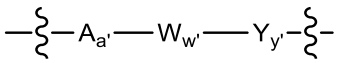
a basic functional group of a Base unit and optionally an electron withdrawing group, each of which is operably linked to stabilize the conjugate in plasma relative to a Ligand-Functional Agent Conjugate lacking the self-stabilizing linker assembly,

in which there are 2 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 optional electron withdrawing group and the nitrogen atom of the hydrolyzed succinimide ring; and

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

2. A Ligand-Functional Agent Conjugate according to Claim 1, comprising a linker assembly that joins each Drug unit to a self-stabilizing linker assembly.

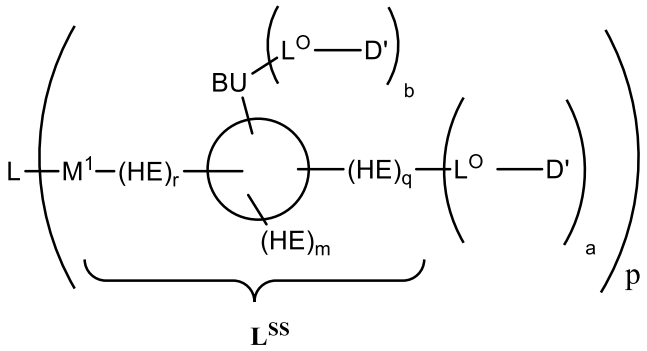
3. A Ligand-Functional Agent Conjugate according to Claim 2, in which the linker assembly has the formula:



in which -A- is an optional Stretcher unit, subscript a' is 0 or 1; -W- is an optional Cleavable unit, subscript w' is 0 or 1; and -Y- is an optional Spacer unit, and subscript y' is 0 or 1; and the wavy lines indicate the points of attachment to the self-stabilizing linker assembly and the Drug unit.

4. A Ligand-Functional Agent Conjugate according to Claim 3, in which the subscript w' is 1, and W is a dipeptide, tripeptide or tetrapeptide.

5. 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 has the formula:



or a salt thereof, in which

L is a Ligand unit;

D' is a Drug unit;

L^O is an optional secondary linker assembly; and

L^{SS} is the self-stabilizing linker assembly, in which

M^1 is a hydrolyzed succinimide;

BU is a Basic unit;

HE is a hydrolysis enhancer comprising an electron withdrawing group;

the circle represents a scaffold that is a C_{1-8} alkylene, or a C_{1-8} heteroalkylene comprising 1 to 8 carbon atoms and 1 to 3 oxygen atoms, or a C_{6-10} arylene, or C_{4-10} heteroarylene;

subscripts m, q and r are each 0 or 1, and the sum of subscripts m + q + r is 0, 1 or 2 provided that if subscripts m + q + r is 0, the scaffold is a C_{6-10} arylene or C_{4-10} heteroarylene;

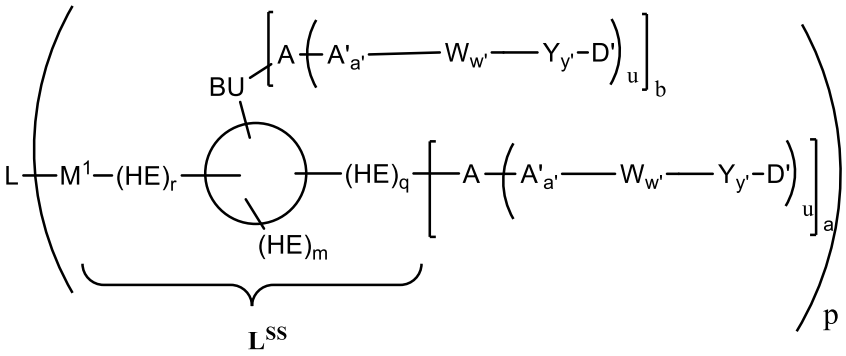
subscripts a and b are each 0 or 1, and the sum of subscripts a+b is 1; and

the subscript p ranges from 1 to 20; and

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

in which the Basic unit and the hydrolysis enhancer are operably linked to stabilize the conjugate in plasma relative to a Ligand-Functional Agent Conjugate lacking the self-stabilizing linker assembly.

6. 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, wherein the Ligand- Functional Agent Conjugate has the formula:



or a salt thereof, in which

L is a Ligand unit;

D' is a Drug unit;

L^{SS} is a self-stabilizing linker assembly, in which

M^1 is a hydrolyzed succinimide;

BU is a Basic unit;

HE is a hydrolysis enhancer comprising an electron withdrawing group;

the circle represents a scaffold that is C_{1-8} alkylene, or a C_{1-8} heteroalkylene comprising 1 to 8 carbon atoms and 1 to 3 oxygen atoms, or C_{4-10} heteroarylene;

subscripts m, q and r are each 0 or 1, and the sum of subscripts m + q + r is 0, 1 or 2 provided that if subscripts m + q + r is 0, the scaffold is a C_{4-10} heteroarylene;

the subscripts a and b are each 0 or 1, and the sum of a+b is 1;

subscript p ranges from 1 to 20;

-W- is an optional Cleavable unit,

subscript w' is 0 or 1;

-Y- is an optional Spacer unit,

subscript y' is 0 or 1,

A is a Stretcher unit,

A' is an optional Stretcher unit that is a component of A at the terminus of A;

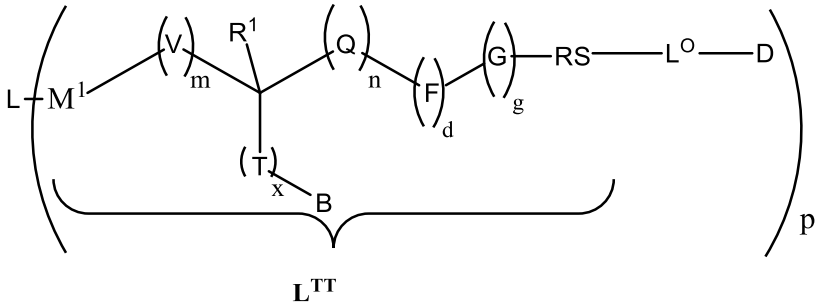
subscript a' is 0 or 1; and

subscript u is from 1 to 20, in which when subscript u is from 2 to 20, A is present and when subscript u is 1, A is either present or absent; and

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

in which the Basic unit and the hydrolysis enhancer are operably linked to stabilize the conjugate in plasma relative to a Ligand-Functional Agent Conjugate lacking the self-stabilizing linker assembly.

7. 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, wherein the Ligand- Functional Agent Conjugate has the formula:



$\mathbf{L^{TT}}$

or a pharmaceutically acceptable salt thereof in which L is a Ligand unit;

D is a Drug unit;

L^O is an optional secondary linker assembly;

L^{TT} is a self-stabilizing linker assembly, in which

M^1 is a succinimide ring or hydrolyzed succinimide or together with B forms a dilactam;

V, Q, T, and G are independently–(C(R^9)(R^{10}))-;

R^1 is H or C_{1-3} alkyl;

R^9 and R^{10} are, in each occurrence, independently H or C_{1-3} alkyl;

F is $C(E^1)(E^2)$ in which E^1 and E^2 are each hydrogen or E^1 and E^2 together are (=O);

RS is from a reactive functional group that was used for conjugation to a component of the optional secondary linker assembly or Drug unit;

subscript g is 0 to 5;

subscript m is 0 to 5;

subscript n is 0 to 5;

subscript d is 0 or 1;

subscript x is 0 to 4, provided that when subscript m is 0, subscript x is 1 to 4;

and B is a basic functional group of a Basic unit; and

provided that when subscript d is zero or E^1 and E^2 are hydrogen and RS is an electron withdrawing group; and

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

in which the Basic unit and the hydrolysis enhancer are operably linked to stabilize the conjugate in plasma relative to a Ligand-Functional Agent Conjugate lacking the self-stabilizing linker assembly.

8. Use of a Ligand-Functional Agent Conjugate that is a Ligand Drug Conjugate in the preparation of a medicament for the treatment of a cancer, the cells of which express a target antigen, in which the cancer is a blood-borne cancer, an acute or chronic leukemia or a lymphoma, 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

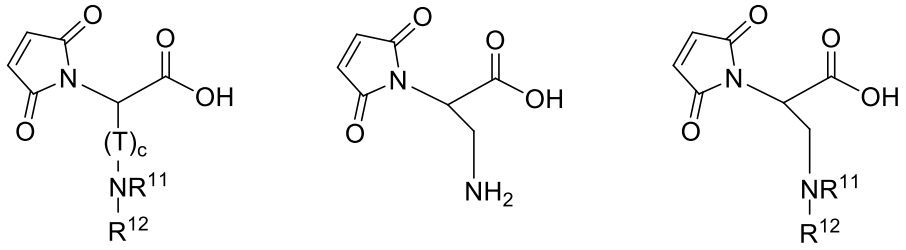
the Ligand unit and each of the Drug Unit(s) are joined by a self-stabilizing linker assembly comprising a hydrolyzed succinimide directly conjugated to the Ligand unit via a thioether linkage; and

a basic functional group of a Basic unit and optionally 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 2 intervening carbon atoms between the base of the basic functional group of the Basic unit and the nitrogen atom of the hydrolyzed succinimide and between 2 and 5 intervening carbon atoms between the electron withdrawing group and the nitrogen atom of the hydrolyzed succinimide; and

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

9. A Linker intermediate having a formula selected from the group consisting of (a), (b) and (c):



(a) (b) (c)

or a protected form thereof, in which,

T is $–(C(R^9)(R^{10}))-$;

R^9 and R^{10} are, in each occurrence, independently selected from the group consisting of H and C_{1-3} alkyl;

subscript c is 1 to 4;

R^{11} and R^{12} are independently selected from the group consisting of H and C_{1-6} alkyl.

10. A Linker intermediate according to Claim 9, having formula (a).

11. A Linker intermediate according to Claim 9, having formula (b).

12. A Linker intermediate according to Claim 9, having formula (c).

13. A Linker intermediate according to Claim 9, having formula (a) in a protected form in which the protecting group is an acid labile amine-protecting group.

14. A Linker intermediate according to Claim 13, in which the acid labile amine-protecting group is a Boc-protecting group.

15. A Linker intermediate according to Claim 9, having formula (b) in a protected form in which the protecting group is an acid labile amine-protecting group.

16. A Linker intermediate according to Claim 15, in which the acid labile amine-protecting group is a Boc-protecting group.

17. A Linker intermediate according to Claim 9, having formula (c) in a protected form in which the protecting group is an acid labile amine-protecting group.

18. A Linker intermediate according to Claim 17, in which the acid labile amine-protecting group is a Boc-protecting group.