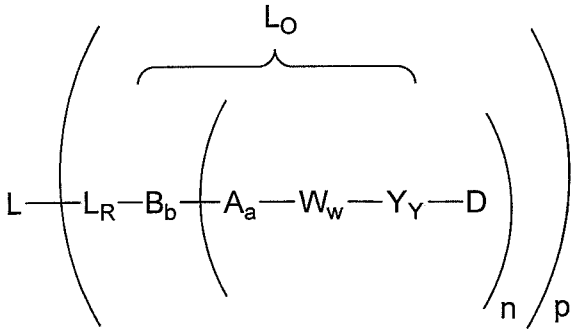
Conjugates described herein having a NAMPT inhibitor compound or derivative thereof as a Drug Unit and whose Ligand Unit targets those abnormal cells, or the vicinity of such cells, address that unmet need.

SUMMARY

[0007] Principle embodiments of the disclosure are Ligand Drug Conjugate (LDC) compositions that are represented by Formula 1:



(Formula 1)

[0008] or a pharmaceutically acceptable salt thereof, wherein L is a Ligand Unit; D is a NAMPT Drug Unit represented by the general structure of:



[0009] or a pharmaceutically acceptable salt thereof, wherein the wavy line indicates the site of covalent attachment to L_O or L_R, depending on the presence or absence of L_O; H_N is a NAMPT Head Unit, wherein the NAMPT Head Unit is a C_5-C_{24} heteroaryl or partially aromatic C_9-C_{24} heterocyclyl, optionally substituted, wherein the C_5-C_{24} heteroaryl or partially aromatic C_9-C_{24} heterocyclyl is comprised of an optionally substituted 5- or 6-membered nitrogen-containing heteroaromatic ring system corresponding to the heterocycle of nicotinamide, and is capable of interacting with enzymatically competent NAMPT homodimer at its nicotinamide mononucleotide binding site when the NAMPT Drug Unit is released from a Ligand Drug Conjugate compound of the composition as a NAMPT inhibitor (NAMPTi) compound or derivative thereof;

[0010] DA is a Donor-Acceptor Unit wherein the Donor-Acceptor Unit is or is comprised of a hydrogen bond donor or acceptor functional group and is bonded to a carbon skeletal atom at position 2 or 3 of the 5-membered nitrogen-containing heteroaromatic ring system or at position 3 or 4 of the 6-membered nitrogen-containing

[0017] In some embodiments, W is a Peptide Cleavable Unit and subscript y is 0, 1 or 2, or W is a Glucuronide Unit of structure –Y(W')-, so that subscript y is 1 or 2, wherein Y is a self-immolative Spacer Unit and W' is a carbohydrate moiety (Su) with attachment to Y by glycosidic bonding through an optionally substituted heteroatom (E') wherein D is attached directly to Y when subscript y is 1 or D is attached indirectly to Y through Y' when subscript y is 2.

[0018] In some embodiments in which subscript y is 2, Y and Y' are both self-immolative Spacer Units, which undergo self-immolation upon enzymatic processing of the Peptide Cleavable Unit or Glucuronide Unit as, for example, when one self-immolative Spacer Unit (Y) is capable of 1,4- or 1,6-elimination and the other self-immolative Spacer Unit (Y') is a methylene carbamate unit or a carbamate functional group as described herein.

[0019] In other embodiments, when subscript y is 1, Y undergoes self-immolation upon conditional enzymatic processing of the Peptide or Glucuronide Unit to release D as a NAMPTi compound or derivative thereof, or releases Y'-D, when subscript y is 2 and Y bonded to Y' undergoes self-immolation. In some of those embodiments Y' of –Y'-D so released also can undergo self-immolation to release D as a NAMPTi compound or derivative thereof. In still other embodiments, W is a Cleavable Unit that is not reliant upon enzymatic cleavage for release of the NAMPTi compound or derivative thereof and in some instances is acted upon non-enzymatically for that release.

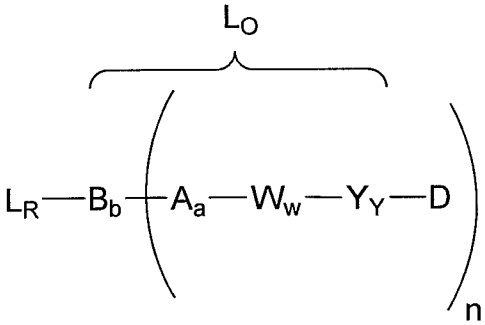
[0020] In other embodiments, the Ligand Unit of a Ligand Drug Conjugate composition is that of an antibody, thereby defining an Antibody Drug Conjugate (ADC) composition, and the targeted moiety recognized by its targeting antibody Ligand Unit is an cell-surface antigen of abnormal cells, wherein the targeted antigen so bound from said recognition is capable of cellular internalization of a Ligand Drug Conjugate compound of the composition, wherein the antigen is typically present on the abnormal cells in greater copy number in comparison to that of normal cells.

[0021] In still other embodiments, the antibody Ligand Unit of a Ligand Drug Conjugate composition recognizes an antigen present within the vicinity of abnormal cells in which the antigen is typically present in greater copy number in comparison to that of normal cells or the vicinity of these cells distant from the site of the abnormal cells, wherein bonding to the targeted antigen culminates in release of the NAMPT Drug Unit in proximity to the abnormal cells, which is followed by entry of the NAMPTi compound or its derivative from that release into the abnormal cells.

[0022] In any one of those embodiments, a NAMPT Drug Unit is released from a Ligand Drug Conjugate compound of the composition as a NAMPTi compound or derivative thereof within abnormal cells, or is released in the vicinity of the abnormal cells targeted by the Ligand Drug Conjugate, to exert a therapeutic effect due intracellular inhibition of NAMPT in the abnormal cells.

[0023] Those and other embodiments of Ligand Drug Conjugates and NAMPT Drug Units therein are further described by the embodiments of the disclosure.

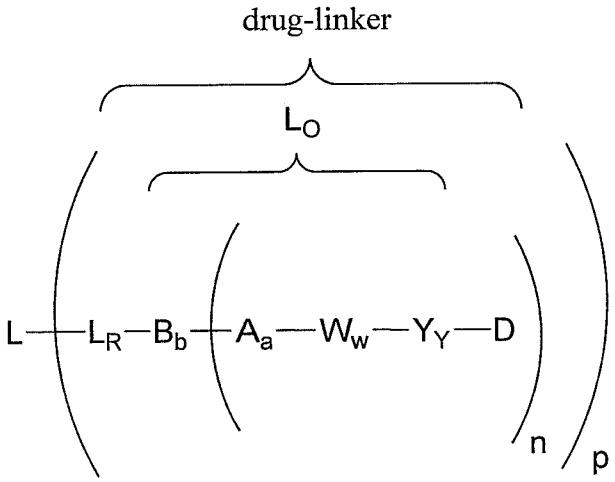
[0024] Other principle embodiments of the disclosure provide for compounds having the structure of Formula I:



(Formula I),

[0025] or a salt thereof, wherein L_R is a primary linker having a functional group capable of forming a covalent bond to a targeting moeity that becomes the Ligand Unit of a Ligand Drug Conjugate of Formula 1 wherein the other variable groups of Formula I are as defined for Formula 1.

[0025a] In one aspect, there is provided a Ligand Drug Conjugate (LDC) composition, wherein the composition is represented by the structure of:



or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

D is a NAMPT Drug Unit represented by the general structure of:



or a pharmaceutically acceptable salt thereof, wherein

the wavy line indicates the site of covalent attachment to L_O or L_R, depending on the presence or absence of L_O;

H_N is a NAMPT Head Unit, wherein the NAMPT Head Unit is a C_5-C_{24} heteroaryl or partially aromatic C_9-C_{24} heterocyclyl, optionally substituted, wherein the C_5-C_{24} heteroaryl or partially aromatic C_9-C_{24} heterocyclyl is comprised of an optionally substituted 5- or 6-membered nitrogen-containing heteroaromatic ring system corresponding to the heterocycle of nicotinamide, and is capable of interacting with enzymatically competent NAMPT homodimer at its nicotinamide mononucleotide binding site when the NAMPT Drug Unit is released from a Ligand Drug Conjugate compound of the composition as a NAMPT inhibitor (NAMPTi) compound or derivative thereof;

DA is a Donor-Acceptor Unit wherein the Donor-Acceptor Unit is or is comprised of a hydrogen bond donor or acceptor functional group and is bonded to a carbon skeletal atom at position 2 or 3 of the 5-membered nitrogen-containing heteroaromatic ring system or at position 3 or 4 of the 6-membered nitrogen-containing heteroaromatic ring system, with optional formal cyclization of DA back to an adjacent skeletal carbon atom of the 6-membered nitrogen-containing heteroaromatic ring system through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted nitrogen, oxygen or sulfur atom resulting in a partially aromatic or fully aromatic fused 6,5- or 6,6-ring system,

wherein said bonding of DA is in relation to a skeletal nitrogen atom of the 5- or 6 membered nitrogen-containing heteroaromatic ring system and wherein said formal cyclization to the adjacent carbon atom of the 6-membered nitrogen-containing heteroaromatic ring system substantially retains the hydrogen bonding capability of the donor or acceptor functional group of DA in absence of said cyclization;

I_N is an Interconnecting Unit, wherein the Interconnecting Unit is or is comprised of -X^1-$[C(=O)]_{0,1}$-, –X^1-$S(=O)_{1,2}$-, –X^2-C_6-C_{24} arylene-$[C(=O)]_{0,1}$-, –X^2-C_6-C_{24} arylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_6-C_{24} arylene-O-, -X^2-C_5-C_{24} heteroarylene-$[C(=O)_{0,1}]$-, –X^2-C_5-C_{24} heteroarylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_5-C_{24} heteroarylene-O- or -X^2-C_3-C_{20} heterocyclo-$[C(=O)_{0,1}]$-, wherein the arylene, heteroarylene and heterocyclo are optionally substituted;

X^1 is optionally substituted C_5-C_7 alkylene;

X^2 is absent or is an optionally substituted C_1-C_4 alkylene;

T_N is a NAMPT Tail Unit, wherein the NAMPT Tail Unit is or is comprised of an optionally substituted amino-alcohol residue or a carboxylic acid-alcohol residue, the –O- or optionally substituted nitrogen of which is the site of covalent attachment to L_O, or or L_R, depending on the presence or absence of L_O, or

T_N is or is comprised of an optionally substituted benzamide moiety, the amide nitrogen atom of which is bonded to I_N with optional cyclization of that atom back to I_N or to the remainder of T_N, and the aromatic ring of which is at least substituted with a hydroxyl, thiol or amino residue, the –O-, -S- or optionally substituted nitrogen atom of which at position 3 or 4 relative to the site at which the amide carbonyl carbon atom is attached is the site of covalent attachment to L_O or L_R, depending on the presence or absence of L_O, or

T_N is or is comprised of an optionally substituted aryl or biaryl moiety, an aromatic skeletal atom of which is bonded to I_N, or to the remainder of T_N, and wherein an aromatic ring of which is at least substituted with a hydroxyl, thiol or an amino residue, the –O-, -S- or optionally substituted nitrogen of which is the site of covalent attachment to L_O or or L_R, depending on the presence or absence of L_O, respectively; and

wherein T_N or the remainder thereof is bonded to I_N, wherein said remainder is an optionally substituted C_2-C_7 heteroalkylene or an optionally substituted C_5-C_6 heterocyclo,

L_R is a primary linker, which interconnects the Ligand Unit and Drug Unit optionally through L_O, as indicated, which is an optional secondary linker;

subscripts a and b independently are 0 or 1, indicating the absence or presence, respectively, of A or B;

subscript n is 1, 2, 3 or 4;

A is an first optional Stretcher; and

B is a Branching Unit, when subscript b is 1 and subscript n is 2, 3 or 4, or B is absent, so that subscript b is 0, when subscript n is 1,

wherein each of A and B is an independently selected single unit or is optionally comprised or consists of at least two, three or four independently selected subunits;

Y is a Spacer Unit; and subscript y is 0, 1 or 2, indicating the absence or presence of one or two of Y, respectively,

provided that when subscript y is 1, Y is a Spacer Unit covalently attached to a heteroatom or moiety thereof of T_N selected from the group consisting of –O-, -S- and optionally substituted nitrogen,

provided that when subscript y is 2 so that Y_y is –Y-Y, Y is a first Spacer Unit and Y' is a second Spacer Unit or a functional group comprised of the optionally substituted heteroatom from T_N; and

provided that subscript y is 1 or 2 when W is a Glucuronide Unit of formula Y(W'), in which instance subscript y is inclusive of a first Spacer Unit Y, wherein that Spacer Unit is a required self-immolative Spacer Unit; and

subscript w is 0 or 1, indicating the absence or presence, respectively, of W; wherein

when subscript w is 1, W is a Peptide Cleavable Unit or said Glucuronide Unit in which W' represents a carbohydrate moiety with glycosidic bonding to the required self-immolative Spacer Unit through an optionally substituted heteroatom, wherein enzymatic or non-enzymatic cleavage of either Unit initiates release of the NAMPT Drug Unit as a NAMPTi compound or derivative thereof from a drug linker moiety of a compound comprising the Ligand Drug Conjugate composition; and

when subscript w is 0, which indicates the absence of a Cleavable Unit, enzymatic or non-enzymatic cleavage of the bond between L_R and L_O, when L_O is present, or the bond between L_R and D, when L_O is absent, initiates release of the NAMPT Drug Unit as a NAMPTi compound or derivative thereof;

subscript p is an average drug linker moiety loading when subscript n is other than 1 or an average drug loading when subscript n is 1, wherein subscript p in either instance is a number ranging from about 1 to about 24; and

wherein a compound comprising the Ligand Drug Conjugate composition corresponds in structure to that of Formula 1 or Formula 2 in which p is replaced by p', wherein p' is an integer ranging from 1 to 24.

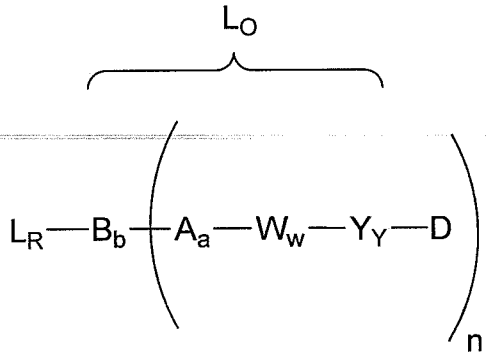
[0025b] In another aspect, there is provided a formulation comprising a Ligand Drug Conjugate composition disclosed herein and at least one, two, three or more excipients, in particular, wherein the formulation is a pharmaceutically acceptable formulation or a precursor thereof, particularly wherein the pharmaceutically acceptable formulation precursor is a solid suitable for reconstitution as a solution for intravenous injection to a

subject in need thereof, or the pharmaceutically acceptable formulation is a liquid suitable for intravenous injection to a subject in need thereof, more particularly in which the Ligand Drug Conjugate composition is present in an effective amount for treatment of a hyperproliferative disease or condition in said solid or liquid formulation.

[0025c] In another aspect, there is provided use of an effective amount of a Ligand Drug Conjugate composition disclosed herein in the manufacture of a medicament for treating a hyperproliferative disease or condition in a subject in need thereof having said disease or condition, in particular having a cancer, more particularly a leukemia or lymphoma.

[0025d] In another aspect, there is provided a method of inhibiting the multiplication of a tumor cell or cancer cell, or causing apoptosis in a tumor or cancer cell by exposing said cell to an effective amount of a Ligand Drug Conjugate composition or a compound thereof disclosed herein.

[0025e] In another aspect, there is provided a Drug Linker compound, wherein the compound is represented by the structure of:



or a salt thereof, wherein

L_R is a primary linker having a functional group capable interacting with a targeting agent to form a covalent bond to a Ligand Unit corresponding to or incorporating the targeting agent in a Ligand Drug Conjugate composition;

D is a NAMPT Drug Unit represented by the general structure of:



or a salt thereof, wherein

the wavy line indicates the site of covalent attachment to L_O, as indicated, which is an optional secondary linker, or L_R, depending on the presence or absence of L_O, respectively;

H_N is a NAMPT Head Unit, wherein the NAMPT Head Unit is a C_5-C_{24} heteroaryl or partially aromatic C_9-C_{24} heterocyclyl, optionally substituted, wherein the C_5-C_{24} heteroaryl or partially aromatic C_9-C_{24} heterocyclyl is comprised of an optionally substituted 5- or 6-membered nitrogen-containing heteroaromatic ring system corresponding to the heterocycle of nicotinamide, and is capable of interacting with enzymatically competent NAMPT homodimer at its nicotinamide mononucleotide binding site when the NAMPT Drug Unit is released from a Ligand Drug Conjugate compound of the composition as a NAMPT inhibitor (NAMPTi) compound or derivative thereof;

DA is a Donor-Acceptor Unit wherein the Donor-Acceptor Unit is or is comprised of a hydrogen bond donor or acceptor functional group and is bonded to a carbon skeletal atom at position 2 or 3 of the 5-membered nitrogen-containing heteroaromatic ring system or at position 3 or 4 of the 6-membered nitrogen-containing heteroaromatic ring system, with optional formal cyclization of DA back to an adjacent skeletal carbon atom of the 6-membered nitrogen-containing heteroaromatic ring system through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted nitrogen, oxygen or sulfur atom resulting in a partially aromatic or fully aromatic fused 6,5- or 6,6-ring system,

wherein said bonding of DA is in relation to a skeletal nitrogen atom of the 5- or 6 membered nitrogen-containing heteroaromatic ring system and wherein said formal cyclization to the adjacent carbon atom of the 6-membered nitrogen-containing heteroaromatic ring system substantially retains the hydrogen bonding capability of the donor or acceptor functional group of DA in absence of said cyclization;

I_N is an Interconnecting Unit, wherein the Interconnecting Unit is or is comprised of -X^1-$[C(=O)]_{0,1}$-, –X^1-$S(=O)_{1,2}$-, –X^2-C_6-C_{24} arylene-$[C(=O)]_{0,1}$-, –X^2-C_6-C_{24} arylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_6-C_{24} arylene-O-, -X^2-C_5-C_{24} heteroarylene-$[C(=O)_{0,1}]$-, –X^2-C_5-C_{24} heteroarylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_5-C_{24} heteroarylene-O- or -X^2-C_3-C_{20} heterocyclo-$[C(=O)_{0,1}]$-, wherein the arylene, heteroarylene and heterocyclo are optionally substituted;

X^1 is optionally substituted C_5-C_7 alkylene;

X^2 is absent or is an optionally substituted C_1-C_4 alkylene;

T_N is a NAMPT Tail Unit, wherein the NAMPT Tail Unit is or is comprised of an optionally substituted amino-alcohol residue or a carboxylic acid-alcohol residue, the –O- or optionally substituted nitrogen of which is the site of covalent attachment to L_O, or L_R, depending on the presence or absence of L_O, or

T_N is or is comprised of an optionally substituted benzamide moiety, the amide nitrogen atom of which is bonded to I_N with optional cyclization of that atom back to I_N or to the remainder of T_N, and the aromatic ring of which is at least substituted with a hydroxyl, thiol or amino residue, the –O-, -S- or optionally substituted nitrogen atom of which at position 3 or 4 relative to the site at which the amide carbonyl carbon atom is attached is the site of covalent attachment to L_O or L_R, depending on the presence or absence of L_O, or

T_N is or is comprised of an optionally substituted aryl or biaryl moiety, an aromatic skeletal atom of which is bonded to I_N, or to the remainder of T_N, and wherein an aromatic ring of which is at least substituted with a hydroxyl, thiol or an amino residue, the –O-, -S- or optionally substituted nitrogen of which is the site of covalent attachment to L_O or L_R, depending on the presence or absence of L_O, respectively; and

wherein T_N or the remainder thereof is bonded to I_N, wherein said remainder is an optionally substituted C_2-C_7 heteroalkylene or an optionally substituted C_5-C_6 heterocyclo,

subscripts a and b independently are 0 or 1, indicating the absence or presence, respectively, of A or B;

subscript n is 1, 2, 3 or 4;

A is an first optional Stretcher; and

B is a Branching Unit, when subscript b is 1 and subscript n is 2, 3 or 4, or B is absent, so that subscript b is 0, when subscript n is 1,

wherein each of A and B is an independently selected single unit or is optionally comprised or consists of at least two, three or four independently selected subunits;

subscript y is 0, 1 or 2, indicating the absence or presence of one or two of Y, respectively;

Y is a Spacer Unit; and subscript y is 0, 1 or 2, indicating the absence or presence of one or two of Y, respectively,

provided that when subscript y is 1, Y is a Spacer Unit covalently attached to a heteroatom or moiety thereof of T_N selected from the group consisting of –O-, -S- and optionally substituted nitrogen,

provided that when subscript y is 2 so that Y_y is –Y-Y, Y is a first Spacer Unit and Y' is a second Spacer Unit or a functional group comprised of the optionally substituted heteroatom from T_N; and

provided that subscript y is 1 or 2 when W is a Glucuronide Unit of formula Y(W'), in which instance subscript y is inclusive of a first Spacer Unit Y, wherein that Spacer Unit is a required self-immolative Spacer Unit; and

subscript w is 0 or 1, indicating the absence or presence, respectively, of W; wherein

when subscript w is 1, W is a Peptide Cleavable Unit or said Glucuronide Unit in which W' represents a carbohydrate moiety with glycosidic bonding to the required self-immolative Spacer Unit through an optionally substituted heteroatom, enzymatic or non-enzymatic cleavage of that Unit in the Drug Linker Compound, or in a drug linker moiety of a Ligand Drug Conjugate compound or a N-acetyl-cysteine (NAC)conjugate prepared from the Drug Linker compound initiates release of the NAMPT Drug Unit as a NAMPTi compound or derivative therefrom, and

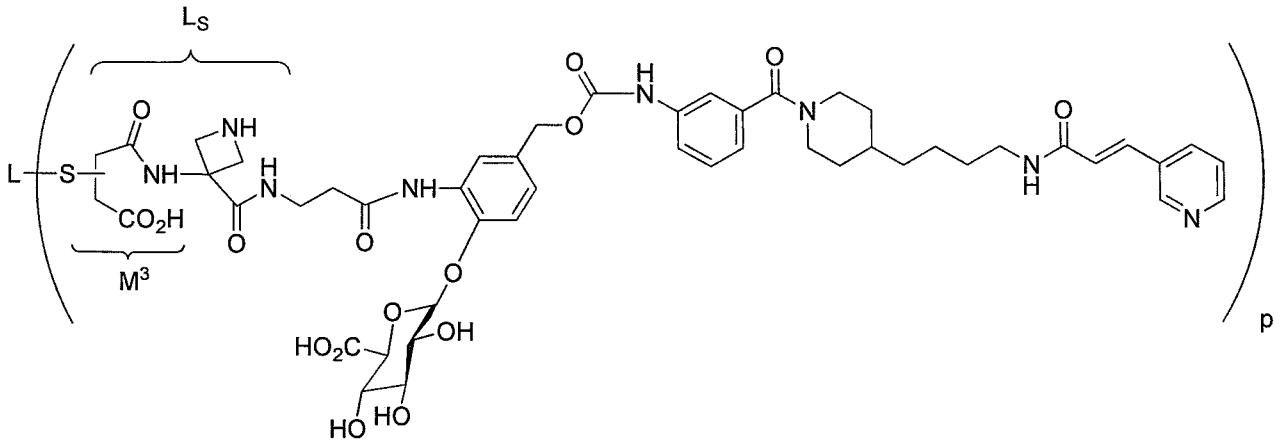
when subscript w is 0, which indicates the absence of a Cleavable Unit, enzymatic or non-enzymatic cleavage of the bond between the indicated L_R and L_O moieties, when L_O is present, or the bond between L_R and D, when L_O is absent, initiates release of the NAMPT Drug Unit as a NAMPTi compound or derivative thereof from the Drug Linker compound or said drug linker moiety or NAC conjugate.

[0025f] In another aspect, there is provided a method of preparing a Ligand Drug Conjugate composition or compound disclosed herein, the method comprising the step of: contacting a Drug Linker compound disclosed herein with a targeting agent having a reactive function group capable of interacting with the reactive functional group of the primary linker of the Drug Linker compound so as to form a covalent bond to between the Ligand Unit corresponding to the targeting agent and the primary linker of the Ligand Drug Conjugate corresponding in structure to the the primary linker of the Drug Linker compound.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Figure 1 shows variation over time (days) in tumor volume (mm^3) in a L450cy xenograft model post tumor implant in untreated SCID mice in comparison to those treated with 1, 3 or 10 mg/Kg (i.p.) of an Antibody Drug Conjugate (8 NAMPT Drug Units/Ab) prepared from chimeric antibody cAC10, which targets Ag2 (CD30) expressed by the implanted L450cy tumor cells, and Drug Linker compound **21**.

[0027] Figure 2 shows variation over time (days) in tumor volume (mm^3) in a L450cy xenograft model post tumor implant in untreated SCID mice in comparison to those treated with 10 mg/Kg (i.p.) Antibody Drug Conjugates (8 NAMPT Drug Units/Ab) prepared from chimeric antibody cAC10, which targets Ag2 (CD30) expressed by the implanted L450cy tumor cells, and Drug Linker compound **21** or Drug Linker compound **51**.



or pharmaceutical acceptable salt(s) thereof,

wherein

L is an antibody, thereby defining an antibody Ligand Unit of an antibody drug conjugate (ADC), and S is a sulfur atom of the antibody, wherein the antibody is a monoclonal antibody in particular a humanized or chimeric antibody.

28. A formulation comprising a Ligand Drug Conjugate composition of any one of claims 1-13, 15-19 and 27 and at least one, two, three or more excipients,

in particular, wherein the formulation is a pharmaceutically acceptable formulation or a precursor thereof, particularly wherein the pharmaceutically acceptable formulation precursor is a solid suitable for reconstitution as a solution for intravenous injection to a subject in need thereof, or the pharmaceutically acceptable formulation is a liquid suitable for intravenous injection to a subject in need thereof, more particularly in which the Ligand Drug Conjugate composition is present in an effective amount for treatment of a hyperproliferative disease or condition in said solid or liquid formulation.

29. Use of an effective amount of a Ligand Drug Conjugate composition of any one of claims 1-13, 15-19 and 27 in the manufacture of a medicament for treating a hyperproliferative disease or condition in a subject in need thereof having said disease or condition, in particular having a cancer, more particularly a leukemia or lymphoma.

30. A method of inhibiting the multiplication of a tumor cell or cancer cell, or causing apoptosis in a tumor or cancer cell by exposing said cell to an effective amount of a Ligand Drug Conjugate composition or a compound thereof of any one of claims 1-13, 15-19 and 27.