## CLAIMS

1. A conjugate of formula (I)

$$M\text{-}[Z^*\text{-}L\text{-}D]_q \quad (I)$$

wherein M is a macromolecular carrier;

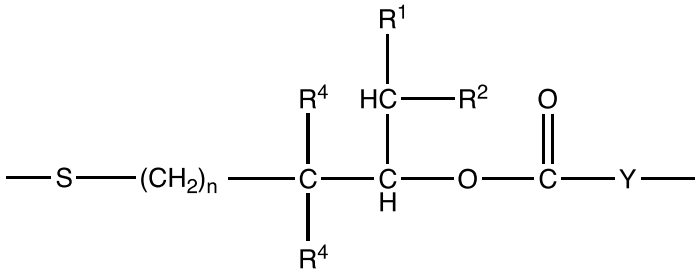
Z* is a connecting functionality;

L is a cleavable linker;

D is the amine residue of a cytokine or variant thereof; and

q is an integer from 1 to 10 when M is a soluble macromolecular carrier or q is a multiplicity when M is an insoluble macromolecular carrier;

wherein L is of the formula below,



wherein

n is an integer from 0 to 6;

$R^1$ and $R^2$ are independently an electron-withdrawing group, alkyl, or H, and wherein at least one of $R^1$ and $R^2$ is an electron-withdrawing group;

each $R^4$ is independently $C_1$-$C_3$ alkyl or the two $R^4$ are taken together with the carbon atom to which they attach to form a 3-6 member ring;

S is absent or $(CH_2CH_2O)_h(CH_2)_gCONH$ wherein g = 1-6 and h = 0-1000; and

Y is absent or $NH(CH_2CH_2O)_p(CH_2)_m$ wherein m = 2-6 and p = 0-1000.

2. The conjugate of claim 1, wherein Z* comprises a carboxamide, amide, oxime, triazole, thioether, thiosuccinimide, or ether.

3. The conjugate of claim 2, wherein Z* comprises a carboxamide, oxime, thioether, or triazole.

4. The conjugate of any one of claims 1-3, wherein:

$R^1$ is -CN or $-SO_2R^5$, wherein $R^5$ is $C_1$-$C_6$ alkyl, aryl, heteroaryl, or $NR^6_2$, wherein each $R^6$ is independently $C_1$-$C_6$ alkyl, aryl, or heteroaryl;

$R^2$ is H; and

wherein each of $R^5$ and $R^6$ is independently optionally substituted.

5. The conjugate of any one of claims 1-4, wherein M is a soluble polyethylene glycol of average molecular weight between 1,000 and 100,000 daltons, and q is an integer from 1 to 10.

6. The conjugate of any one of claims 1-4, wherein M is an insoluble hydrogel or surgical device, and q is a multiplicity.

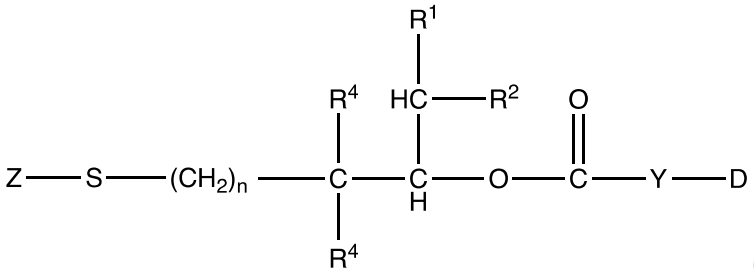
7. The conjugate of any one of claims 1-6, wherein D is IL-2, IL-7, IL-9, IL-10, IL-15, an IL-15•IL-15RαSu fusion protein, IL-21 or a variant thereof.

8. The conjugate of claim 7, wherein D is an IL-2 variant having selective binding for the trimeric αβγ-receptor over the dimeric βγ receptor or is an IL-2 variant having selective binding for the dimeric βγ-receptor over the trimeric αβγ-receptor.

9. The conjugate of claim 7, wherein D is an IL-15, an IL-15•IL-15RαSu fusion protein, or a variant thereof.

10. The conjugate of claim 7, wherein D is an IL-15 or an IL-15•IL-15RαSu fusion protein variant stabilized against deamidation.

11. A linker-drug of formula (Ia)



(Ia),

wherein:

n is an integer from 0 to 6;

$R^1$ and $R^2$ are independently an electron-withdrawing group, alkyl, or H, and wherein at least one of $R^1$ and $R^2$ is an electron-withdrawing group;

each $R^4$ is independently $C_1$-$C_3$ alkyl or the two $R^4$ are taken together with the carbon atom to which they attach to form a 3-6 member ring;

Z is a group for connecting the linker to a macromolecular carrier;

S is absent or is $(CH_2CH_2O)_h(CH_2)_gCONH$, wherein g is an integer from 1 to 6 and h is an integer from 0 to 1000;

Y is absent or is $NH(CH_2CH_2O)_p(CH_2)_m$, wherein m is an integer from 2 to 6 and p is an integer from 0 to 1000; and

D is an amine residue of a cytokine or variant thereof.

12. The linker-drug of claim 11, wherein $R^1$ is -CN or $-SO_2R^5$, wherein $R^5$ is $C_1$-$C_6$ alkyl, aryl, heteroaryl, or $NR^6_2$, wherein each $R^6$ is independently $C_1$-$C_6$ alkyl, aryl, or heteroaryl, and $R^2$ is H, and wherein each of $R^5$ and $R^6$ is independently optionally substituted.

13. The linker-drug of claim 11 or 12, wherein D is IL-2, IL-7, IL-9, IL-10, IL-15, an IL-15•IL-15RαSu fusion protein, IL-21 or a variant thereof.

14. The linker-drug of claim 13, wherein D is an IL-2 variant having selective binding for the trimeric αβγ-receptor over the dimeric βγ receptor, or is an IL-2 variant having selective binding for the dimeric βγ-receptor over the trimeric αβγ-receptor.

15. The linker-drug of claim 14, wherein D is selected from the group consisting of IL-2, IL-2 [N88R], IL-2 [N88D], IL-2 [N88R,C125S], and IL-2 [N88D,C125S].

16. The linker-drug of claim 11 or 12, wherein D is IL-15, IL-15 N77A, IL-15-[N71S,N72A,N77A], an IL-15•IL-15RαSu fusion protein, or a variant thereof.

17. The linker-drug of claim 11 or 12, wherein D is selected from the group consisting of IL-2, IL-7, IL-9, IL-10, IL-15, an IL-15•IL-15RαSu fusion protein, IL-21, or a cytokine variant thereof wherein the N-alpha amine group is modified by addition of $NH_2(CH_2CH_2O)_p(CH_2)_m$, wherein m is an integer from 2 to 6 and p is an integer from 0 to 1000.

18. Use of the conjugate of any one of claims 1-10 for the manufacture of a medicament for treating a disease or a condition in a subject in need thereof, wherein the disease or condition is an autoimmune disease; chronic graft-vs-host disease (cGVHD) associated with inadequate reconstitution of tolerogenic $CD4^+$ $CD25^+$ $FOXP3^+$ regulatory T cells; systemic lupus erythrematosis; sarcoidosis; Hepatitis C-induced vasculitis; alopecia; rheumatoid arthritis; inflammatory bowel disease; multiple sclerosis; or type-1 diabetes.

19. A cytokine or cytokine variant modified at the N-terminal alpha amine by the addition of $NH_2(CH_2CH_2O)_p(CH_2)_m$, wherein m is an integer from 2 to 6 and p is an integer from 0 to 1000.