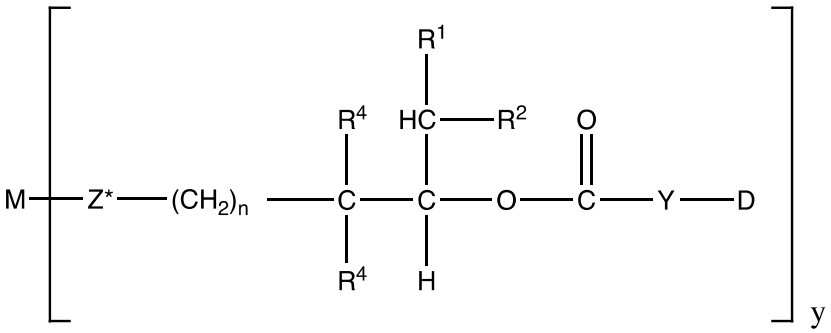
## CLAIMS

1. A conjugate having the formula

$M\text{-}(Z^*\text{-}L\text{-}D)_y$

wherein M is a macromolecular carrier;
y is a number describing the number of linker-drugs L-D attached to M;
Z* is a connecting group;
L is a releasable linker; and
D is an inhibitor of the DNA damage response.

2. The conjugate of Claim 1 having the formula




wherein Z* is a connecting group;
n = 0-6;
$R^1$ and $R^2$ are each independently H, CN, or $SO_2R^5$, wherein at least one of $R^1$ and $R^2$ is other than H;

wherein $R^5$ is optionally substituted $C_1$-$C_6$ alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $N(R^6)_2$,

wherein each $R^6$ is independently optionally substituted $C_1$-$C_6$ alkyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein $N(R^6)_2$ forms a ring of 4-8 atoms;

each $R^4$ is independently H or $C_1$-$C_3$ alkyl or both $R^4$ are taken together form a 3-6 member ring; and
Y is either absent or has the formula $N(R^7)CH_2$,

wherein $R^7$ is optionally substituted $C_1$-$C_4$ alkyl or optionally substituted aryl.

3. The conjugate of Claim 1 or 2 wherein D is a PARP inhibitor, ATM inhibitor, or ATR inhibitor.

4. The conjugate of Claim 2 wherein Y is absent and D is connected through a primary or secondary amine nitrogen atom of D.

5. The conjugate of any one of Claims 1-4 wherein D is rucaparib, veliparib, niraparib, or berzosertib.

6. The conjugate of Claim 2 wherein Y has the formula $N(R^7)CH_2$ and D is connected through a non-basic nitrogen atom of D.

7. The conjugate of Claim 6 wherein D is talazoparib, olaparib, tamiparib, E7016, or CEP-9722.

8. The conjugate of any one of Claims 1-7 wherein M is a PEG of molecular weight between 1,000 and 100,000 Daltons, and y = 1-8.

9. The conjugate of any one of Claims 1-8 wherein M has a hydrodynamic radius between 5 and 50 nm.

10. The conjugate of any one of Claims 1-7 wherein M is an insoluble macromolecular carrier.

11. The conjugate of any one of Claims 1-10 wherein Z* is a carboxamide, carbamate, urea, oxime, thioether, or 1,2,3-triazole.

12. The conjugate of any one of Claims 2-10 wherein $R^1$ and $R^2$ are selected to provide a half-life for D release between 100-1000 hours at a pH of 7.4 and a temperature of 37 $^oC$.

13. The conjugate of claim 2, wherein Z* is a triazole, n is 4, $R^1$ is $MeSO_2$, $R^2$ is H, each $R^4$ is H, Y is $N(R^7)CH_2$, $R^7$ is 2-methoxyethyl, y is 4, and D is talazoparib.

14. The conjugate of claim 2, wherein Z* is a triazole, n is 4, $R^1$ is $MeSO_2$, $R^2$ is H, each $R^4$ is H, Y is $N(R^7)CH_2$, $R^7$ is 2-methoxyethyl, y is 4, and D is olaparib.

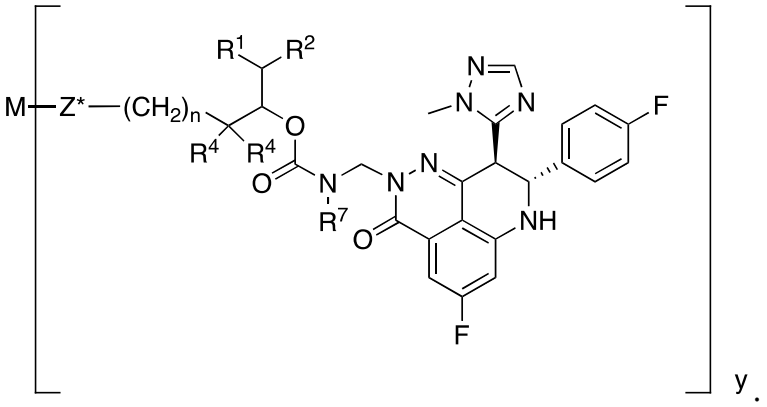
15. The conjugate of claim 13 or 14, wherein M is 40 kDa PEG.

16. The conjugate of claim 2, wherein Z* is a triazole, n is 2, $R^1$ is $MeSO_2$, $R^2$ is H, each $R^4$ is Me, Y is $N(R^7)CH_2$, $R^7$ is 2-methoxyethyl, y is 1, and D is talazoparib.

17. The conjugate of claim 2, wherein Z* is a triazole, n is 4, $R^1$ is $MeSO_2$, $R^2$ is H, each $R^4$ is H, Y is absent, $R^7$ is methyl, y is 1, and D is rucaparib

18. The conjugate of claim 16 or 17, wherein M is 20 kDa PEG.

19. The conjugate of Claim 1 having the formula




wherein M is a macromolecular carrier;

n = 0-6;

Z* is a connecting group;

$R^1$ and $R^2$ are each independently H, CN, or $SO_2R^5$, wherein at least one of $R^1$ and $R^2$ is other than H,

wherein $R^5$ is optionally substituted $C_1$-$C_6$ alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $N(R^6)_2$,

wherein each $R^6$ is independently optionally substituted $C_1$-$C_6$ alkyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein $N(R^6)_2$ forms a ring of 4-8 atoms;

each $R^4$ is independently H or $C_1$-$C_3$ alkyl or both $R^4$ are taken together form a 3-6 member ring;

$R^7$ is optionally substituted $C_1$-$C_3$ alkyl or optionally substituted aryl; and

y = 1 to 8.

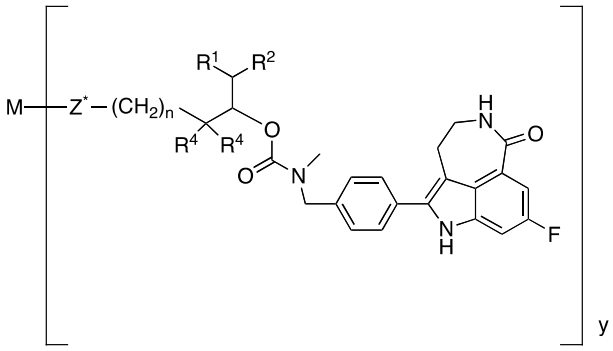
20. The conjugate of Claim 19 wherein M is a 40-kDa 4-armed PEG and y = 4.

21. The conjugate of Claim 19 or 20 wherein Z* is carboxamide, carbamate, oxime, thioether, or triazole.

22. The conjugate of claim 19, wherein Z* is a triazole, n is 4, $R^1$ is $MeSO_2$, $R^2$ is H, each $R^4$ is H, $R^7$ is 2-methoxyethyl, and y is 4.

23. The conjugate of claim 19, wherein Z* is a triazole, n is 2, $R^1$ is $MeSO_2$, $R^2$ is H, each $R^4$ is Me, and $R^7$ is 2-methoxyethyl, and y is 1.

24. The conjugate of Claim 1 having the formula




wherein M is a macromolecular carrier;

n = 0-6;

Z* is a connecting group;

$R^1$ and $R^2$ are each independently H, CN, or $SO_2R^5$, wherein at least one of $R^1$ and $R^2$ is other than H,

wherein $R^5$ is optionally substituted $C_1$-$C_6$ alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $N(R^6)_2$,

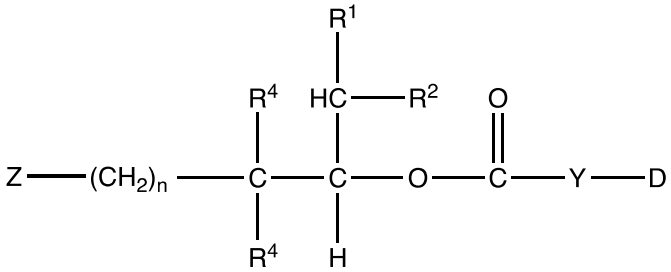
wherein each $R^6$ is independently optionally substituted $C_1$-$C_6$ alkyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein $N(R^6)_2$ forms a ring of 4-8 atoms;

each $R^4$ is independently H or $C_1$-$C_3$ alkyl or both $R^4$ are taken together form a 3-6 member ring; and
y = 1 to 8.

25. The conjugate of Claim 24 wherein M is a 40-kDa 4-armed PEG and y = 4.

26. The conjugate of any one of Claims 1-25, wherein Z* is a triazole resulting from the cycloaddition of an azide with a cyclooctyne selected from an azadibenzocyclooctyne (DBCO), a bicyclo[6.1.0]non-4-yne (BCN), or 5-hydroxycyclooctyne (5HCO).

27. A linker-drug of the formula




wherein Z is a functional group allowing for conjugation to a macromolecular carrier;
n = 0-6;
$R^1$ and $R^2$ are each independently H, CN, or $SO_2R^5$, wherein at least one of $R^1$ and $R^2$ is other than H,

wherein $R^5$ is optionally substituted $C_1$-$C_6$ alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $N(R^6)_2$,

wherein each $R^6$ is independently optionally substituted $C_1$-$C_6$ alkyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein $N(R^6)_2$ forms a ring of 4-8 atoms;

each $R^4$ is independently H or $C_1$-$C_3$ alkyl or taken together form a 3-6 member ring;
Y is either absent or has the formula $N(R^7)CH_2$, wherein $R^7$ is optionally substituted $C_1$-$C_4$ alkyl or optionally substituted aryl; and
D is an inhibitor of DNA damage response.

28. The linker-drug of claim 27, wherein:

a) Z is azide, n is 4, $R^1$ is $MeSO_2$, $R^2$ is H, each $R^4$ is H, Y is $N(R^7)CH_2$, $R^7$ is 2-methoxyethyl, and D is talazoparib;

b) Z is azide, n is 4, $R^1$ is $MeSO_2$, $R^2$ is H, each $R^4$ is H, Y is $N(R^7)CH_2$, $R^7$ is 2-methoxyethyl, and D is olaparib;

c) Z is azide, n is 4, $R^1$ is $MeSO_2$, $R^2$ is H, each $R^4$ is H, Y is $N(R^7)CH_2$, $R^7$ is 4-(N,N-diethylcarboxamido)phenyl, and D is talazoparib; or

d) Z is azide, n is 2, $R^1$ is thiomorpholine-$SO_2$, $R^2$ is H, each $R^4$ is Me, Y is $N(R^7)CH_2$, $R^7$ is 2-methoxyethyl, and D is talazoparib.

29. Use of a conjugate of any one of Claims 1-26 for the manufacture of a medicament for treating cancer.

30. A conjugate of any one of claims 1-26 for use in therapy.

31. A method of preparing a conjugated inhibitor of DNA damage response, said method comprising the step of contacting a linker-drug of Claim 27 or 28 with an activated macromolecular carrier comprising a cognate functional group Z' capable of reacting with functional group Z under conditions such that connecting group Z* is formed, and optionally isolating the conjugate.