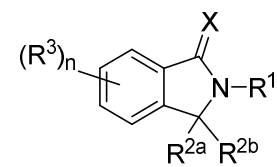


What is claimed is:

1. A method of identifying a genetic element associated with a specific biological phenotype, e.g., a genetic element associated with the development and/or progression of a cancer, the method comprising the steps of:

i) modulating the expression of a fusion polypeptide in cells by exposing said cell to a stabilization compound, e.g., bazedoxifene, or a pharmaceutically acceptable salt thereof, and then to COF1 or COF2, e.g., lenalidomide, or a pharmaceutically acceptable salt thereof, wherein the fusion polypeptide comprises:

a compound of Formula (I) (COF1)/CRBN (cereblon)-binding polypeptide and a heterologous polypeptide, e.g., a heterologous mammalian, bacterial, or viral polypeptide, wherein the compound of Formula (I) is:



(I)

or a pharmaceutically acceptable salt, ester, hydrate, solvate, or tautomer thereof, wherein:

X is O or S;

R¹ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted by one or more R⁴;

each of R^{2a} and R^{2b} is independently hydrogen or C₁-C₆ alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a carbonyl group or a thiocarbonyl group;

each of R³ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, -C(O)R^A, -C(O)OR^B, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), -N(R^C)C(O)R^A, -S(O)_xR^E, -S(O)_xN(R^C)(R^D), or -N(R^C)S(O)_xR^E, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R⁶;

each R⁴ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, oxo, -C(O)R^A, -C(O)OR^B, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), -N(R^C)C(O)R^A, -S(O)_xR^E, -S(O)_xN(R^C)(R^D), -N(R^C)S(O)_xR^E, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R⁷;

each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C₁-C₆ alkyl;

each R⁶ is independently C₁-C₆ alkyl, oxo, cyano, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), -N(R^C)C(O)R^A, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R⁸;

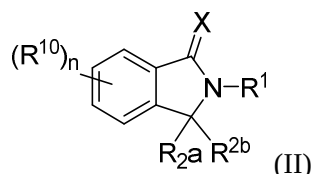
each R⁷ is independently halo, oxo, cyano, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), or -N(R^C)C(O)R^A;

each R⁸ is independently C₁-C₆ alkyl, cyano, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), or -N(R^C)C(O)R^A;

n is 0, 1, 2, 3 or 4; and

x is 0, 1, or 2; or

a first domain and a second domain separated by a heterologous protease cleavage site, wherein the first domain comprises a degradation domain and the second domain comprises a compound of Formula (II) (COF2)/CRBN (cereblon)-binding polypeptide and a heterologous polypeptide, e.g., a heterologous mammalian, bacterial, or viral polypeptide, wherein the compound of Formula (II) is:



or a pharmaceutically acceptable salt, ester, hydrate, tautomer, or prodrug thereof, wherein:

X is O or S;

R¹ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted by one or more R⁴;

each of R^{2a} and R^{2b} is independently hydrogen or C₁-C₆ alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached to form carbonyl group or thiocarbonyl group;

each of R¹⁰ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, -C(O)R^A, -C(O)OR^B, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), -N(R^C)C(O)R^A, -S(O)_xR^E, -S(O)_xN(R^C)(R^D), or -N(R^C)S(O)_xR^E, or L-Tag; wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R¹¹;

each R⁴ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, oxo, C(O)R^A, -C(O)OR^B, OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), -N(R^C)C(O)R^A, S(O)_xR^E, -S(O)_xN(R^C)(R^D), -N(R^C)S(O)_xR^E, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R⁷;

each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C₁-C₆ alkyl;

each R¹¹ is independently C₁-C₆ alkyl, halo, oxo, cyano, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), -N(R^C)C(O)R^A, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R⁸;

each R⁷ is independently halo, oxo, cyano, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), or -N(R^C)C(O)R^A;

each R⁸ is independently C₁-C₆ alkyl, halo, cyano, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), or -N(R^C)C(O)R^A;

each L is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, -C(O)R^{A1}, -C(O)OR^{B1}, -OR^{B1}, -N(R^{C1})(R^{D1}), -C(O)N(R^{C1})(R^{D1}), -N(R^{C1})C(O)R^{A1}, -S(O)_xR^{E1}, -S(O)_xN(R^{C1})(R^{D1}), or -N(R^{C1})S(O)_xR^{E1}, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R¹²;

each Tag is a targeting moiety capable of binding to a target protein;

each of R^{A1}, R^{B1}, R^{C1}, R^{D1}, and R^{E1} is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R¹²;

each R¹² is independently C₁-C₆ alkyl, halo, cyano, carbocyclyl, or heterocyclyl;

n is 0, 1, 2, 3 or 4; and

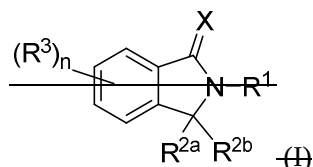
x is 0, 1, or 2,

(ii) selecting for cells with a phenotype of interest, e.g., a phenotype associated with the development and/or progression of a cancer, and

(iii) identifying said fusion polypeptide that induces said phenotype of interest,

wherein exposure of said cell to the stabilization compound, e.g., bazedoxifene, or a pharmaceutically acceptable salt thereof, increases, e.g., by at least about 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide prior to exposure to the stabilization compound, e.g., bazedoxifene, or a pharmaceutically acceptable salt thereof, and wherein exposure of said cell to COF1 or COF2, e.g., lenalidomide, or a pharmaceutically acceptable salt thereof, decreases, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, the expression level of said fusion polypeptide relative to the expression level of said fusion polypeptide after exposure to the stabilization compound and prior to exposure to COF1 or COF2, e.g., lenalidomide, or a pharmaceutically acceptable salt thereof.

1. A fusion polypeptide comprising a compound of Formula (I) (COF1)/CRBN (cereblon)-binding polypeptide and a heterologous polypeptide, e.g., a heterologous mammalian, bacterial, or viral polypeptide, wherein the compound of Formula (I) is:



or a pharmaceutically acceptable salt, ester, hydrate, solvate, or tautomer thereof, wherein:

—— X is O or S;

—— R¹ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted by one or more R⁴;

—— each of R^{2a} and R^{2b} is independently hydrogen or C₁-C₆ alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a carbonyl group or a thiocarbonyl group;

—— each of R³ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), or N(R^C)S(O)_xR^E, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R⁶;

—— each R⁴ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, oxo, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), N(R^C)S(O)_xR^E, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R⁷;

each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C₁-C₆ alkyl;

each R⁶ is independently C₁-C₆ alkyl, oxo, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R⁸;

each R⁷ is independently halo, oxo, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), or N(R^C)C(O)R^A;

each R⁸ is independently C₁-C₆ alkyl, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), or N(R^C)C(O)R^A;

n is 0, 1, 2, 3 or 4; and

x is 0, 1, or 2.

2. The fusion polypeptide of claim 1, wherein the COF1/CRBN-binding polypeptide is fused to the heterologous polypeptide.
3. The fusion polypeptide of claim 1 or 2, wherein the COF1/CRBN-binding polypeptide and the heterologous polypeptide are linked by a peptide bond.
4. The fusion polypeptide of claim 1 or 2, wherein the COF1/CRBN-binding polypeptide and the heterologous polypeptide are linked by a bond other than a peptide bond.
5. The fusion polypeptide of any one of claims 1-4, wherein the heterologous polypeptide is linked directly to the COF1/CRBN-binding polypeptide.
6. The fusion polypeptide of any one of claims 1-4, wherein the heterologous polypeptide is linked indirectly to the COF1/CRBN-binding polypeptide.
7. The fusion polypeptide of any one of claims 1-6, wherein the COF1/CRBN-binding polypeptide and the heterologous polypeptide are operatively linked via a linker, e.g., a glycine-serine linker, e.g., a linker comprising the amino acid sequence of SEQ ID NO: 28.
8. The fusion polypeptide of any one of claims 1-7, wherein the COF1/CRBN-binding polypeptide is linked to the C-terminus or N-terminus of the heterologous polypeptide.
9. The fusion polypeptide of any one of claims 1-8, wherein the association of the COF1/CRBN-binding polypeptide with cereblon (CRBN) in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF1/CRBN-binding polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation.
10. The fusion polypeptide of any one of claims 1-9, wherein the COF1/CRBN-binding polypeptide does not bind to CRBN in the absence of COF1.
11. The fusion polypeptide of any one of claims 1-10, wherein the association of the fusion polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of

~~the association of the fusion polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation.~~

~~12. The fusion polypeptide of any one of claims 1-11, wherein the fusion polypeptide does not bind to CRBN in the absence of COF1.~~

~~13. The fusion polypeptide of any one of claims 1-12, wherein the ubiquitination of the heterologous polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein.~~

~~14. The fusion polypeptide of any one of claims 1-13, wherein the ubiquitination of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein.~~

~~15. The fusion polypeptide of claim 13 or 14, wherein the heterologous polypeptide or the fusion polypeptide is ubiquitinated at one or more lysine or methionine residues in the presence of COF1.~~

~~16. The fusion polypeptide of any one of claims 1-15, wherein the degradation of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70% of the degradation of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.~~

~~17. The fusion polypeptide of claim 16, wherein the degradation of the fusion polypeptide is mediated by ubiquitination in the presence of COF1.~~

~~18. The fusion polypeptide of any one of claims 9-17, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.~~

~~19. The fusion polypeptide of any one of claims 1-18, wherein the COF1/CRBN binding polypeptide is between 10 and 95 amino acid residues in length, between 15 and 90 amino acid residues in length, between 20 and 85 amino acid residues in length, between 25 and 80 amino acid residues in length, between 30 and 75 amino acid residues in length, between 35 and 70 amino acid residues in length,~~

between 40 and 65 amino acid residues in length, between 45 and 65 amino acid residues in length, between 50 and 65 amino acid residues in length, or between 55 and 65 amino acid residues in length.

20. The fusion polypeptide of any one of claims 1-19, wherein the COF1/CRBN binding polypeptide comprises a beta turn.

21. The fusion polypeptide of any one of claims 1-20, wherein the COF1/CRBN binding polypeptide comprises a beta hairpin.

22. The fusion polypeptide of any one of claims 1-21, wherein the COF1/CRBN binding polypeptide comprises a beta strand.

23. The fusion polypeptide of any one of claims 1-22, wherein the COF1/CRBN binding polypeptide comprises an alpha helix.

24. The fusion polypeptide of any one of claims 1-23, wherein the COF1/CRBN binding polypeptide comprises, from N-terminus to C-terminus, a first beta strand, a beta hairpin, a second beta strand, and a first alpha helix.

25. The fusion polypeptide of any one of claims 1-24, wherein the COF1/CRBN binding polypeptide comprises, from N-terminus to C-terminus, a first beta strand, a beta hairpin, a second beta strand, a first alpha helix, and a second alpha helix.

26. The fusion polypeptide of claim 25, wherein the beta hairpin and the second alpha helix are separated by no more than 60, 50, 40, or 30 amino acid residues.

27. The fusion polypeptide of any one of claims 1-26, wherein the COF1/CRBN binding polypeptide comprises a COF1/CRBN binding sequence from a naturally occurring polypeptide or a COF1/CRBN binding variant thereof, e.g., a naturally occurring IKZF polypeptide or a COF1/CRBN binding variant thereof, e.g., a naturally occurring IKZF1, IKZF2, IKZF3, IKZF4, IKZF5, or a COF1/CRBN binding variant thereof.

28. The fusion polypeptide of claim 27, wherein the COF1/CRBN binding sequence comprises two or more discontinuous sequences from the naturally occurring polypeptide, e.g., a naturally occurring IKZF polypeptide, e.g., a naturally occurring IKZF1, IKZF2, IKZF3, IKZF4, or IKZF5.

29. The fusion polypeptide of any one of claims 1-28, wherein the COF1/CRBN binding polypeptide comprises an IKZF polypeptide or a structural motif thereof.

30. The fusion polypeptide of claim 29, wherein the IKZF polypeptide is an IKZF1 polypeptide, an IKZF3 polypeptide, an IKZF2 polypeptide having H141Q substitution (numbered according to SEQ ID NO: 21), or an IKZF4 polypeptide having H188Q substitution (numbered according to SEQ ID NO: 22).

31. The fusion polypeptide of any one of claims 1-30, wherein the COF1/CRBN binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from IKZF (e.g., IKZF1 or IKZF3) that:

i) the association of the COF1/CRBN binding polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF1/CRBN binding polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

ii) the association of the fusion polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

iii) the ubiquitination of the heterologous polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein;

iv) the ubiquitination of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein; or

v) the degradation of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

32. The fusion polypeptide of claim 31, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

33. The fusion polypeptide of any one of claims 1-32, wherein the COF1/CRBN binding polypeptide comprises about 10 to about 95 amino acid residues, about 15 to about 90 amino acid residues, about 20 to about 85 amino acid residues, about 25 to about 80 amino acid residues, about 30 to about 75 amino acid residues, about 35 to about 70 amino acid residues, about 40 to about 65 amino acid residues, about 45 to about 65 amino acid residues, about 50 to about 65 amino acid residues, or about 55 to about 65 amino acid residues of IKZF1 or IKZF3.

34. The fusion polypeptide of any one of claims 1-33, wherein the COF1/CRBN binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., sufficient amino acid sequence and/or a structural motif from amino acid residues 136-180 of SEQ ID NO: 19) that:

- i) the association of the COF1/CRBN binding polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF1/CRBN binding polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- ii) the association of the fusion polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- iii) the ubiquitination of the heterologous polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein;
- iv) the ubiquitination of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein; or
- v) the degradation of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

35. The fusion polypeptide of claim 34, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

36. The fusion polypeptide of any one of claims 1-35, wherein the COF1/CRBN binding polypeptide comprises amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., the COF1/CRBN binding polypeptide comprises the amino acid sequence of SEQ ID NO: 5) or a sequence that differs from amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues (e.g., a sequence that differs from amino acid residues 136-180 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues) (e.g., a sequence having no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid substitutions from amino acid residues 136-180 of SEQ ID NO: 19).

37. The fusion polypeptide of any one of claims 1-33, wherein the COF1/CRBN binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., sufficient amino acid sequence and/or a structural motif from amino acid residues 136-170 of SEQ ID NO: 19) that:

i) the association of the COF1/CRBN binding polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF1/CRBN binding polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

ii) the association of the fusion polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

iii) the ubiquitination of the heterologous polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein;

iv) the ubiquitination of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein; or

v) the degradation of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the

presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

38. The fusion polypeptide of claim 37, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

39. The fusion polypeptide of any one of claims 1-33, 37, or 38, wherein the COF1/CRBN-binding polypeptide comprises amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., the COF1/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 6) or a sequence that differs from amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 amino acid residues (e.g., a sequence that differs from amino acid residues 136-170 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 amino acid residues) (e.g., a sequence having no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 amino acid substitutions from amino acid residues 136-170 of SEQ ID NO: 19).

40. The fusion polypeptide of any one of claims 36-39, wherein one, two, three or all of the following amino acid residues remain unaltered: glutamine at position 147, cysteine at position 148, glutamine at position 150, glycine at position 152, leucine at position 161, or leucine at position 162, numbered according to SEQ ID NO: 19.

41. The fusion polypeptide of claim 40, wherein glutamine at position 147 remains unaltered, numbered according to SEQ ID NO: 19.

42. The fusion polypeptide of claim 40, wherein cysteine at position 148 remains unaltered, numbered according to SEQ ID NO: 19.

43. The fusion polypeptide of claim 40, wherein glycine at position 152 remains unaltered, numbered according to SEQ ID NO: 19.

44. The fusion polypeptide of any one of claims 1-43, wherein the COF1/CRBN-binding polypeptide comprises amino acid residues 136-139 of IKZF3 (numbered according to SEQ ID NO: 19), e.g., the COF1/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 40.

45. The fusion polypeptide of any one of claims 1-44, wherein the COF1/CRBN-binding polypeptide comprises amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19), e.g., the COF1/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 5 or 77.

46. The fusion polypeptide of any one of claims 1-44, wherein the COF1/CRBN-binding polypeptide comprises amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19), e.g., the COF1/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 6 or 78.

47. The fusion polypeptide of any one of claims 1-46, wherein the COF1/CRBN-binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., sufficient amino acid sequence and/or a structural motif from amino acid residues 236-249 of SEQ ID NO: 19) that:

- i) the association of the COF1/CRBN-binding polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF1/CRBN-binding polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- ii) the association of the fusion polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- iii) the ubiquitination of the heterologous polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein;
- iv) the ubiquitination of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein; or
- v) the degradation of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

48. The fusion polypeptide of claim 47, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

49. The fusion polypeptide of any one of claims 1-48, wherein the COF1/CRBN binding polypeptide comprises amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., the COF1/CRBN binding polypeptide comprises the amino acid sequence of SEQ ID NO: 11) or a sequence that differs from amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 6, or 7 amino acid residues (e.g., a sequence that differs from amino acid residues 236-249 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 6, or 7 amino acid residues) (e.g., a sequence having no more than 1, 2, 3, 4, 5, 6, or 7 amino acid substitutions from amino acid residues 236-249 of SEQ ID NO: 19).

50. The fusion polypeptide of any one of claims 1-49, wherein the COF1/CRBN binding polypeptide comprises amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19), e.g., the COF1/CRBN binding polypeptide comprises the amino acid sequence of SEQ ID NO: 11.

51. The fusion polypeptide of any one of claims 1-49, wherein the COF1/CRBN binding polypeptide comprises the amino acid sequence of MALEKMALEKMALE (SEQ ID NO: 91).

52. The fusion polypeptide of any one of claims 1-51, wherein the COF1/CRBN binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from amino acid residues 136-180 and 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., sufficient amino acid sequence and/or a structural motif from amino acid residues 136-180 and 236-249 of SEQ ID NO: 19) that:

i) the association of the COF1/CRBN binding polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF1/CRBN binding polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

ii) the association of the fusion polypeptide with CRBN in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

iii) the ubiquitination of the heterologous polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous

polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein;

iv) the ubiquitination of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein; or

v) the degradation of the fusion polypeptide in the absence of COF1 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF1, e.g., an excess of COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

53. The fusion polypeptide of claim 52, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

54. The fusion polypeptide of any one of claims 1-53, wherein the COF1/CRBN-binding polypeptide comprises a first sequence comprising amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., a first sequence comprising the amino acid sequence of SEQ ID NO: 5) or a first sequence that differs from amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues (e.g., a first sequence that differs from amino acid residues 136-180 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues); and a second sequence comprising amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., a second sequence comprising the amino acid sequence of SEQ ID NO: 11) or a second sequence that differs from amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 6, or 7 amino acid residues (e.g., a second sequence that differs from amino acid residues 236-249 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 6, or 7 amino acid residues).

55. The fusion polypeptide of any one of claims 1-54, wherein the COF1/CRBN-binding polypeptide comprises amino acid residues 136-180 and 236-249 of IKZF3 (numbered according to SEQ ID NO: 19), e.g., the COF1/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 1 or 3.

56. The fusion polypeptide of any one of claims 1-55, wherein the COF1/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 1 or 3.

57. The fusion polypeptide of any one of claims 1-56, wherein the COF1/CRBN-binding polypeptide comprises a first sequence comprising amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) and a second sequence comprising the amino acid sequence of MALEKMALEKMALE (SEQ ID NO: 91), e.g., the COF1/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 14 or 85.

58. The fusion polypeptide of any one of claims 1-56, wherein the COF1/CRBN-binding polypeptide comprises a first sequence comprising amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19) and a second sequence comprising the amino acid sequence of MALEKMALEKMALE (SEQ ID NO: 91), e.g., the COF1/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 15 or 86.

59. The fusion polypeptide of any one of claims 1-58, wherein the COF1/CRBN-binding polypeptide comprises at least one less lysine than the corresponding native sequence.

60. The fusion polypeptide of claim 59, wherein one or more lysine residues in the corresponding native sequence are replaced by a different amino acid, e.g., arginine.

61. The fusion polypeptide of claim 59 or 60, wherein the COF1/CRBN-binding polypeptide comprises less than 1, 2, 3, 4, or 5 lysine residues.

62. The fusion polypeptide of claim 61, wherein the COF1/CRBN-binding polypeptide does not comprise a lysine residue.

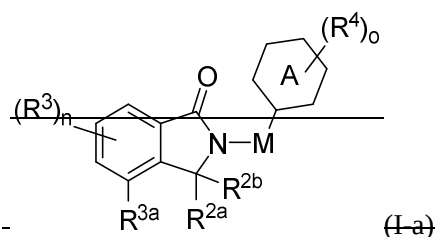
63. The fusion polypeptide of any one of claims 1-62, wherein the COF1/CRBN-binding polypeptide is not ubiquitinated, e.g., in the presence of COF1, e.g., as measured by an assay described herein, optionally wherein ubiquitination is as measured in a mammalian cell, e.g., a human cell.

64. The fusion polypeptide of any one of claims 1-63, wherein the COF1/CRBN-binding polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 41, 42, and 43.

65. The fusion polypeptide of any one of claims 1-63, wherein the COF1/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 2 or 4.

66. The fusion polypeptide of any one of claims 1-65, wherein the COF1 is an immunomodulatory imide drug (IMiD), or a pharmaceutically acceptable salt thereof.

67. The fusion polypeptide of any one of claims 1-65, wherein the COF1 has the structure of Formula (I-a):



or a pharmaceutically acceptable salt, ester, hydrate, or tautomer thereof, wherein:

—— Ring A is carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted with one or more R^4 ;

M is absent, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, or C_1 - C_6 heteroalkyl, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^4 ;

—— each of R^{2a} and R^{2b} is independently hydrogen or C_1 - C_6 alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached to form a carbonyl group or thiocarbonyl group;

—— R^{2a} is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, halo, cyano, $C(O)R^A$, $C(O)OR^B$, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, $N(R^C)C(O)R^A$, $S(O)_xR^E$, $S(O)_xN(R^C)(R^D)$, or $N(R^C)S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^6 ;

each of R^3 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, halo, cyano, $C(O)R^A$, $C(O)OR^B$, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, $N(R^C)C(O)R^A$, $S(O)_xR^E$, $S(O)_xN(R^C)(R^D)$, or $N(R^C)S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^6 ;

—— each R^4 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, halo, cyano, oxo, $C(O)R^A$, $C(O)OR^B$, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, $N(R^C)C(O)R^A$, $S(O)_xR^E$, $S(O)_xN(R^C)(R^D)$, $N(R^C)S(O)_xR^E$, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R^7 ;

each of R^A , R^B , R^C , R^D , and R^E is independently hydrogen or C_1 - C_6 alkyl;

each R^6 is independently C_1 - C_6 alkyl, oxo, cyano, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, $N(R^C)C(O)R^A$, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R^8 ;

each R^7 is independently halo, oxo, cyano, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, or $N(R^C)C(O)R^A$;

each R^8 is independently C_1 - C_6 alkyl, cyano, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, or $N(R^C)C(O)R^A$;

n is 0, 1, 2, or 3;

o is 0, 1, 2, 3, 4, or 5; and

x is 0, 1, or 2.

68. The fusion polypeptide of claim 67, wherein X is O.

69. The fusion polypeptide of claim 67 or 68, wherein M is absent.

70. The fusion polypeptide of any one of claims 67-69, wherein Ring A is heterocyclyl (e.g., a nitrogen-containing heterocyclyl, e.g., 2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione).

71. The fusion polypeptide of any one of claims 67-70, wherein R^4 is oxo or OR^B (e.g., OCH_3 or OCH_2CH_3) and o is 0, 1, or 2.

72. The fusion polypeptide of any one of claims 67-71, wherein each of R^{2a} and R^{2b} is independently hydrogen, or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a carbonyl group.

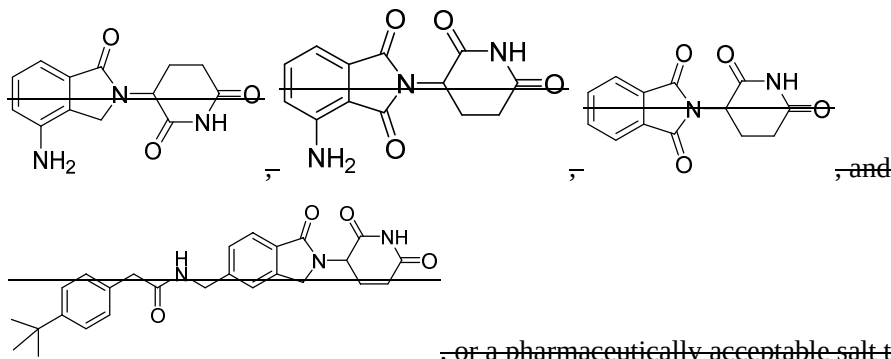
73. The fusion polypeptide of any one of claims 67-72, wherein R^{3a} is heteroalkyl (e.g., $CH_2NHC(O)CH_2$), $N(R^C)(R^D)$ (e.g., NH_2), or $N(R^C)C(O)R^A$ (e.g., $NHC(O)CH_3$).

74. The fusion polypeptide of any one of claims 67-73, wherein n is 0.

75. The fusion polypeptide of any one of claims 1-74, wherein the COF1 is thalidomide or analogue, or a pharmaceutically acceptable salt thereof.

76. The fusion polypeptide of any one of claims 1-74, wherein the COF1 is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, and 2-(4-(tert-butyl)phenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)acetamide, or a pharmaceutically acceptable salt thereof.

77. ~~The fusion polypeptide of any one of claims 1-74, wherein the COF1 is selected from the group consisting of:~~



78. ~~The fusion polypeptide of any one of claims 1-74, wherein the COF1 is lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof.~~

79. ~~The fusion polypeptide of any one of claims 1-74, wherein the COF1 is lenalidomide or analogue, or a pharmaceutically acceptable salt thereof.~~

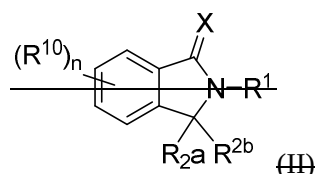
80. ~~The fusion polypeptide of any one of claims 1-79, wherein the fusion polypeptide further comprises a degradation domain, wherein the degradation domain is separated from the COF1/CRBN binding polypeptide and the heterologous polypeptide by a heterologous protease cleavage site.~~

81. ~~The fusion polypeptide of claim 80, wherein the fusion polypeptide comprises, from N-terminus to C-terminus:~~

- ~~i) the degradation domain, the heterologous protease cleavage site, the heterologous polypeptide, and the COF1/CRBN binding polypeptide;~~
- ~~ii) the degradation domain, the heterologous protease cleavage site, the COF1/CRBN binding polypeptide, and the heterologous polypeptide;~~
- ~~iii) the COF1/CRBN binding polypeptide, the heterologous polypeptide, the heterologous protease cleavage site, and the degradation domain; or~~
- ~~iv) the heterologous polypeptide, and the COF1/CRBN binding polypeptide, the heterologous protease cleavage site, and the degradation domain.~~

82. The fusion polypeptide of claim 80, wherein the fusion polypeptide comprises, from N-terminus to C-terminus, the degradation domain, the heterologous protease cleavage site, the heterologous polypeptide, and the COF1/CRBN-binding polypeptide.

83. A fusion polypeptide comprising a first domain and a second domain separated by a heterologous protease cleavage site, wherein the first domain comprises a degradation domain and the second domain comprises a compound of Formula (II) (COF2)/CRBN (cereblon)-binding polypeptide and a heterologous polypeptide, e.g., a heterologous mammalian, bacterial, or viral polypeptide, wherein the compound of Formula (II) is:



or a pharmaceutically acceptable salt, ester, hydrate, tautomer, or prodrug thereof, wherein:

—— X is O or S;

—— R¹ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted by one or more R⁴;

—— each of R^{2a} and R^{2b} is independently hydrogen or C₁-C₆ alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached to form carbonyl group or thiocarbonyl group;

—— each of R¹⁰ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), or N(R^C)S(O)_xR^E, or L-Tag; wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R¹¹;

—— each R⁴ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, oxo, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), N(R^C)S(O)_xR^E, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R⁷;

each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C₁-C₆ alkyl;

each R¹¹ is independently C₁-C₆ alkyl, halo, oxo, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R⁸;

each R⁷ is independently halo, oxo, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), or N(R^C)C(O)R^A;

each R^B is independently C_1 - C_6 alkyl, halo, cyano, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, or $N(R^C)C(O)R^A$;

each L is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, $C(O)R^{A1}$, $C(O)OR^{B1}$, OR^{B1} , $N(R^{C1})(R^{D1})$, $C(O)N(R^{C1})(R^{D1})$, $N(R^{C1})C(O)R^{A1}$, $S(O)_xR^{E1}$, $S(O)_xN(R^{C1})(R^{D1})$, or $N(R^{C1})S(O)_xR^{E1}$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^{12} ;

each Tag is a targeting moiety capable of binding to a target protein;

each of R^{A1} , R^{B1} , R^{C1} , R^{D1} , and R^{E1} is independently hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R^{12} ;

each R^{12} is independently C_1 - C_6 alkyl, halo, cyano, carbocyclyl, or heterocyclyl;

n is 0, 1, 2, 3 or 4; and

x is 0, 1, or 2.

84. The fusion polypeptide of any one of claims 80-83, wherein the degradation domain has a first state associated with a first level of expression of the fusion polypeptide and a second state associated with a second level of expression of the fusion polypeptide, wherein the second level is increased, e.g., by at least 2-, 3-, 4-, 5-, 10-, 20- or 30-fold over the first level in the presence of a stabilization compound.

85. The fusion polypeptide of claim 84, wherein in the absence of the stabilization compound, the fusion polypeptide is degraded by a cellular degradation pathway, e.g., at least 50%, 60%, 70%, 80%, 90% or greater of the fusion polypeptide is degraded, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

86. The fusion polypeptide of claim 84 or 85, wherein the level of expression, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

87. The fusion polypeptide of any one of claims 84-86, wherein in the presence of the stabilization compound:

- i) the degradation domain assumes a conformation more resistant to cellular degradation relative to a conformation in the absence of the stabilization compound; or
- ii) the conformation of the fusion polypeptide is more permissive to cleavage at the heterologous protease cleavage site relative to a conformation in the absence of the stabilization compound.

88. The fusion polypeptide of any one of claims 80-87, wherein the degradation domain is chosen from an estrogen receptor (ER) domain, an FKB protein (FKBP) domain, or a dihydrofolate reductase (DHFR) domain.

89. The fusion polypeptide of claim 88, wherein the degradation domain is an estrogen receptor (ER) domain.

90. The fusion polypeptide of claim 89, wherein the degradation domain comprises an amino acid sequence that is at least 90, 95, 97, 98, 99, or 100% identical to SEQ ID NO: 46 or 48.

91. The fusion polypeptide of claim 90, wherein the degradation domain comprises the amino acid sequence of SEQ ID NO: 46.

92. The fusion polypeptide of any one of claims 89-91, wherein the stabilization compound is bazedoxifene or 4 hydroxy tamoxifen (4 OHT), or a pharmaceutically acceptable salt thereof.

93. The fusion polypeptide of claim 88, wherein the degradation domain is an FKB protein (FKBP) domain.

94. The fusion polypeptide of claim 93, wherein the degradation domain comprises an amino acid sequence that is at least 90, 95, 97, 98, 99, or 100% identical to SEQ ID NO: 50.

95. The fusion polypeptide of claim 93 or 94, wherein the stabilization compound is Shield 1, or a pharmaceutically acceptable salt thereof.

96. The fusion polypeptide of claim 88, wherein the degradation domain is a dihydrofolate reductase (DHFR) domain.

97. The fusion polypeptide of claim 96, wherein the degradation domain comprises an amino acid sequence that is at least 90, 95, 97, 98, 99, or 100% identical to SEQ ID NO: 51.

98. The fusion polypeptide of claim 96 or 97, wherein the stabilization compound is trimethoprim, or a pharmaceutically acceptable salt thereof.

99. The fusion polypeptide of any one of claims 80-98, wherein the heterologous protease cleavage site is cleaved by a mammalian intracellular protease.

100. The fusion polypeptide of claim 99, wherein the heterologous protease cleavage site is cleaved by a protease selected from the group consisting of furin, PCSK1, PCSK5, PCSK6, PCSK7, cathepsin B, Granzyme B, Factor XA, Enterokinase, genenase, sortase, precision protease, thrombin, TEV protease, and elastase 1.

101. The fusion polypeptide of claim 99 or 100, wherein the heterologous protease cleavage site comprises a sequence having a cleavage motif selected from the group consisting of RX(K/R)R consensus motif (X can be any amino acid; SEQ ID NO: 52), RXXX[KR]R consensus motif (X can be any amino acid; SEQ ID NO: 53), RRX consensus motif (SEQ ID NO : 54), I-E-P-D-X consensus motif (SEQ ID NO: 55), Ile-Glu/Asp-Gly-Arg (SEQ IDNO : 56), Asp-Asp-Asp-Asp-Lys (SEQ ID NO: 57), Pro-Gly-Ala-Ala-His-Tyr (SEQ ID NO: 58), LPXTG/A consensus motif (SEQ ID NO: 59), Leu-Glu-Val-Phe-Gln-Gly-Pro (SEQ ID NO: 60), Leu-Val-Pro-Arg-Gly-Ser (SEQ ID NO: 61), E-N-L-Y-F-Q-G (SEQ ID NO: 62), and [AGSV]-X (X can be any amino acid; SEQ ID NO: 63).

102. The fusion polypeptide of claim 99, wherein the heterologous protease cleavage site is cleaved by furin.

103. The fusion polypeptide of claim 102, wherein the heterologous protease cleavage site comprises a furin cleavage site selected from the group consisting of RTKR (SEQ ID NO: 123); GTGAEDPRPSRKRRSLGDVG (SEQ ID NO: 125); GTGAEDPRPSRKRR (SEQ ID NO: 127); LQWLEQQVAKRRTKR (SEQ ID NO: 129); GTGAEDPRPSRKRRSLGG (SEQ ID NO: 131); GTGAEDPRPSRKRRSLG (SEQ ID NO: 133); SLNLTESHNSRKRR (SEQ ID NO: 135); CKINGYPKRGRKRR (SEQ ID NO: 137); and SARNRQKR (SEQ ID NO: 34).

104. The fusion polypeptide of claim 102, wherein the heterologous protease cleavage site comprises the furin cleavage site of GTGAEDPRPSRKRRSLGDVG (SEQ ID NO: 125).

105. The fusion polypeptide of any one of claims 80-98, wherein the heterologous protease cleavage site is cleaved by a mammalian extracellular protease.

106. The fusion polypeptide of claim 105, wherein the mammalian extracellular protease is selected from the group consisting of Factor XA, Enterokinase, genenase, sortase, precision protease, thrombin, TEV protease, and elastase 1.

107. The fusion polypeptide of claim 106, wherein the heterologous protease cleavage site comprises an amino acid sequence selected from the group consisting of Ile-Glu/Asp-Gly-Arg (SEQ ID NO: 56), Asp-Asp-Asp-Lys (SEQ ID NO: 57), Pro-Gly-Ala-Ala-His-Tyr (SEQ ID NO: 58), LPXTC/A consensus motif (SEQ ID NO: 59), Leu-Glu-Val-Phe-Gln-Gly-Pro (SEQ ID NO: 60), Leu-Val-Pro-Arg-Gly-Ser (SEQ ID NO: 61), E-N-L-Y-F-Q-G (SEQ ID NO: 62), and [AGSV]-X (X can be any amino acid; SEQ ID NO: 63).

108. The fusion polypeptide of any one of claims 83-107, wherein the degradation domain is fused to the heterologous protease cleavage site, which is further fused to the second domain.

109. The fusion polypeptide of any one of claims 83-108, comprising, from N-terminus to C-terminus:

- i) the degradation domain, the heterologous protease cleavage site, the heterologous polypeptide, and the COF2/CRBN-binding polypeptide;
- ii) the degradation domain, the heterologous protease cleavage site, the COF2/CRBN-binding polypeptide, and the heterologous polypeptide;
- iii) the COF2/CRBN-binding polypeptide, the heterologous polypeptide, the heterologous protease cleavage site, and the degradation domain; or
- iv) the heterologous polypeptide, and the COF2/CRBN-binding polypeptide, the heterologous protease cleavage site, and the degradation domain.

110. The fusion polypeptide of any one of claims 83-108, comprising, from N-terminus to C-terminus, the degradation domain, the heterologous protease cleavage site, the heterologous polypeptide, and the COF2/CRBN-binding polypeptide.

111. The fusion polypeptide of any one of claims 83-110, wherein the association of the COF2/CRBN-binding polypeptide with cereblon (CRBN) in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF2/CRBN-binding polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation.

112. The fusion polypeptide of any one of claims 83-111, wherein the COF2/CRBN-binding polypeptide does not bind to CRBN in the absence of COF2.

113. The fusion polypeptide of any one of claims 83-112, wherein the association of the fusion polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the fusion polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation.

114. The fusion polypeptide of any one of claims 83-113, wherein the fusion polypeptide does not bind to CRBN in the absence of COF2.

115. The fusion polypeptide of any one of claims 83-114, wherein the ubiquitination of the heterologous polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein.

116. The fusion polypeptide of any one of claims 83-115, wherein the ubiquitination of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein.

117. The fusion polypeptide of claim 115 or 116, wherein the heterologous polypeptide or the fusion polypeptide is ubiquitinated at one or more lysine or methionine residues in the presence of COF2.

118. The fusion polypeptide of any one of claims 83-117, wherein the degradation of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

119. The fusion polypeptide of claim 118, wherein the degradation of the fusion polypeptide is mediated by ubiquitination in the presence of COF2.

120. The fusion polypeptide of any one of claims 111-119, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

121. The fusion polypeptide of any one of claims 83-120, wherein the COF2/CRBN binding polypeptide is between 10 and 95 amino acid residues in length, between 15 and 90 amino acid residues in length, between 20 and 85 amino acid residues in length, between 25 and 80 amino acid residues in length, between 30 and 75 amino acid residues in length, between 35 and 70 amino acid residues in length, between 40 and 65 amino acid residues in length, between 45 and 65 amino acid residues in length, between 50 and 65 amino acid residues in length, or between 55 and 65 amino acid residues in length.

122. The fusion polypeptide of any one of claims 83-121, wherein the COF2/CRBN binding polypeptide comprises a beta turn.

123. The fusion polypeptide of any one of claims 83-122, wherein the COF2/CRBN binding polypeptide comprises a beta hairpin.

124. The fusion polypeptide of any one of claims 83-123, wherein the COF2/CRBN binding polypeptide comprises a beta strand.

125. The fusion polypeptide of any one of claims 83-124, wherein the COF2/CRBN binding polypeptide comprises an alpha helix.

126. The fusion polypeptide of any one of claims 83-125, wherein the COF2/CRBN binding polypeptide comprises, from N-terminus to C-terminus, a first beta strand, a beta hairpin, a second beta strand, and a first alpha helix.

127. The fusion polypeptide of any one of claims 83-126, wherein the COF2/CRBN binding polypeptide comprises, from N-terminus to C-terminus, a first beta strand, a beta hairpin, a second beta strand, a first alpha helix, and a second alpha helix.

128. The fusion polypeptide of claim 127, wherein the beta hairpin and the second alpha helix are separated by no more than 60, 50, 40, or 30 amino acid residues.

129. The fusion polypeptide of any one of claims 83-128, wherein the COF2/CRBN-binding polypeptide comprises a COF2/CRBN-binding sequence from a naturally occurring polypeptide or a COF2/CRBN-binding variant thereof, e.g., a naturally occurring IKZF polypeptide or a COF2/CRBN-binding variant thereof, e.g., a naturally occurring IKZF1, IKZF2, IKZF3, IKZF4, or IKZF5 a COF2/CRBN-binding variant thereof.

130. The fusion polypeptide of claim 129, wherein the COF2/CRBN-binding sequence comprises two or more discontinuous sequences from the naturally occurring polypeptide, e.g., a naturally occurring IKZF polypeptide, e.g., a naturally occurring IKZF1, IKZF2, IKZF3, IKZF4, or IKZF5.

131. The fusion polypeptide of any one of claims 83-130, wherein the COF2/CRBN-binding polypeptide comprises an IKZF polypeptide or a structural motif thereof.

132. The fusion polypeptide of claim 131, wherein the IKZF polypeptide is an IKZF1 polypeptide, an IKZF3 polypeptide, an IKZF2 polypeptide having H141Q substitution (numbered according to SEQ ID NO: 21), or an IKZF4 polypeptide having H188Q substitution (numbered according to SEQ ID NO: 22).

133. The fusion polypeptide of any one of claims 83-132, wherein the COF2/CRBN-binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from IKZF (e.g., IKZF1 or IKZF3) that:

- i) the association of the COF2/CRBN-binding polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF2/CRBN-binding polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- ii) the association of the fusion polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- iii) the ubiquitination of the heterologous polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein;

iv) the ubiquitination of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein; or
v) the degradation of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

134. The fusion polypeptide of claim 133, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

135. The fusion polypeptide of any one of claims 83-134, wherein the COF2/CRBN-binding polypeptide comprises about 10 to about 95 amino acid residues, about 15 to about 90 amino acid residues, about 20 to about 85 amino acid residues, about 25 to about 80 amino acid residues, about 30 to about 75 amino acid residues, about 35 to about 70 amino acid residues, about 40 to about 65 amino acid residues, about 45 to about 65 amino acid residues, about 50 to about 65 amino acid residues, or about 55 to about 65 amino acid residues of IKZF1 or IKZF3.

136. The fusion polypeptide of any one of claims 83-135, wherein the COF2/CRBN-binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., sufficient amino acid sequence and/or a structural motif from amino acid residues 136-180 of SEQ ID NO: 19) that:

- i) the association of the COF2/CRBN-binding polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF2/CRBN-binding polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- ii) the association of the fusion polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- iii) the ubiquitination of the heterologous polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein;

iv) the ubiquitination of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein; or
v) the degradation of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

137. The fusion polypeptide of claim 136, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

138. The fusion polypeptide of any one of claims 83-137, wherein the COF2/CRBN-binding polypeptide comprises amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., the COF2/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 5) or a sequence that differs from amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues (e.g., a sequence that differs from amino acid residues 136-180 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues) (e.g., a sequence having no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid substitutions from amino acid residues 136-180 of SEQ ID NO: 19).

139. The fusion polypeptide of any one of claims 83-137, wherein the COF2/CRBN-binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., sufficient amino acid sequence and/or a structural motif from amino acid residues 136-170 of SEQ ID NO: 19) that:

- i) the association of the COF2/CRBN-binding polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF2/CRBN-binding polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- ii) the association of the fusion polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- iii) the ubiquitination of the heterologous polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous

polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein;

iv) the ubiquitination of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein; or

v) the degradation of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

140. The fusion polypeptide of claim 139, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

141. The fusion polypeptide of any one of claims 83-137, 139, or 140, wherein the COF2/CRBN-binding polypeptide comprises amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., the COF2/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 6) or a sequence that differs from amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 amino acid residues (e.g., a sequence that differs from amino acid residues 136-170 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 amino acid residues) (e.g., a sequence having no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 amino acid substitutions from amino acid residues 136-170 of SEQ ID NO: 19).

142. The fusion polypeptide of any one of claims 138-141, wherein one, two, three or all of the following amino acid residues remain unaltered: glutamine at position 147, cysteine at position 148, glutamine at position 150, glycine at position 152, leucine at position 161, or leucine at position 162, numbered according to SEQ ID NO: 19.

143. The fusion polypeptide of claim 142, wherein glutamine at position 147 remains unaltered, numbered according to SEQ ID NO: 19.

144. The fusion polypeptide of claim 142, wherein cysteine at position 148 remains unaltered, numbered according to SEQ ID NO: 19.

145. The fusion polypeptide of claim 142, wherein glycine at position 152 remains unaltered, numbered according to SEQ ID NO: 19.

146. The fusion polypeptide of any one of claims 83-145, wherein the COF2/CRBN binding polypeptide comprises amino acid residues 136-139 of IKZF3 (numbered according to SEQ ID NO: 19), e.g., the COF2/CRBN binding polypeptide comprises the amino acid sequence of SEQ ID NO: 40.

147. The fusion polypeptide of any one of claims 83-146, wherein the COF2/CRBN binding polypeptide comprises amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19), e.g., the COF2/CRBN binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 5 or 77.

148. The fusion polypeptide of any one of claims 83-146, wherein the COF2/CRBN binding polypeptide comprises amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19), e.g., the COF2/CRBN binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 6 or 78.

149. The fusion polypeptide of any one of claims 83-148, wherein the COF2/CRBN binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., sufficient amino acid sequence and/or a structural motif from amino acid residues 236-249 of SEQ ID NO: 19) that:

i) the association of the COF2/CRBN binding polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF2/CRBN binding polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

ii) the association of the fusion polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

iii) the ubiquitination of the heterologous polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein;

iv) the ubiquitination of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein; or
v) the degradation of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

150. The fusion polypeptide of claim 149, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

151. The fusion polypeptide of any one of claims 83-150, wherein the COF2/CRBN-binding polypeptide comprises amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., the COF2/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 11) or a sequence that differs from amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 6, or 7 amino acid residues (e.g., a sequence that differs from amino acid residues 236-249 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 6, or 7 amino acid residues) (e.g., a sequence having no more than 1, 2, 3, 4, 5, 6, or 7 amino acid substitutions from amino acid residues 236-249 of SEQ ID NO: 19).

152. The fusion polypeptide of any one of claims 83-151, wherein the COF2/CRBN-binding polypeptide comprises amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19), e.g., the COF2/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 11.

153. The fusion polypeptide of any one of claims 83-152, wherein the COF2/CRBN-binding polypeptide comprises the amino acid sequence of MALEKMALEKMALE (SEQ ID NO: 91).

154. The fusion polypeptide of any one of claims 83-153, wherein the COF2/CRBN-binding polypeptide comprises sufficient amino acid sequence and/or a structural motif from amino acid residues 136-180 and 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., sufficient amino acid sequence and/or a structural motif from amino acid residues 136-180 and 236-249 of SEQ ID NO: 19) that:

i) the association of the COF2/CRBN-binding polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the COF2/CRBN-binding

polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

ii) the association of the fusion polypeptide with CRBN in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20% of the association of the fusion polypeptide with CRBN in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

iii) the ubiquitination of the heterologous polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the heterologous polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein;

iv) the ubiquitination of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein; or

v) the degradation of the fusion polypeptide in the absence of COF2 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the degradation of the fusion polypeptide in the presence of COF2, e.g., an excess of COF2, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

155. The fusion polypeptide of claim 154, wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

156. The fusion polypeptide of any one of claims 83-155, wherein the COF2/CRBN-binding polypeptide comprises a first sequence comprising amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., a first sequence comprising the amino acid sequence of SEQ ID NO: 5) or a first sequence that differs from amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues (e.g., a first sequence that differs from amino acid residues 136-180 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues); and a second sequence comprising amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) (e.g., a second sequence comprising the amino acid sequence of SEQ ID NO: 11) or a second sequence that differs from amino acid residues 236-249 of IKZF3 (numbered according to SEQ ID NO: 19) by no more than 1, 2, 3, 4, 5, 6, or 7 amino acid residues (e.g., a second sequence that differs from amino acid residues 236-249 of SEQ ID NO: 19 by no more than 1, 2, 3, 4, 5, 6, or 7 amino acid residues).

157. The fusion polypeptide of any one of claims 83-156, wherein the COF2/CRBN-binding polypeptide comprises amino acid residues 136-180 and 236-249 of IKZF3 (numbered according to SEQ ID NO: 19); e.g., the COF2/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 1 or 3.

158. The fusion polypeptide of any one of claims 83-157, wherein the COF2/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 1 or 3.

159. The fusion polypeptide of any one of claims 83-158, wherein the COF2/CRBN-binding polypeptide comprises a first sequence comprising amino acid residues 136-180 of IKZF3 (numbered according to SEQ ID NO: 19) and a second sequence comprising the amino acid sequence of MALEKMALEKMALE (SEQ ID NO: 91); e.g., the COF2/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 14 or 85.

160. The fusion polypeptide of any one of claims 83-159, wherein the COF2/CRBN-binding polypeptide comprises a first sequence comprising amino acid residues 136-170 of IKZF3 (numbered according to SEQ ID NO: 19) and a second sequence comprising the amino acid sequence of MALEKMALEKMALE (SEQ ID NO: 91); e.g., the COF2/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 15 or 86.

161. The fusion polypeptide of any one of claims 83-160, wherein the COF2/CRBN-binding polypeptide comprises at least one less lysine than the corresponding native sequence.

162. The fusion polypeptide of claim 161, wherein one or more lysine residues in the corresponding native sequence are replaced by a different amino acid, e.g., arginine.

163. The fusion polypeptide of claim 161 or 162, wherein the COF2/CRBN-binding polypeptide comprises less than 1, 2, 3, 4, or 5 lysine residues.

164. The fusion polypeptide of claim 163, wherein the COF2/CRBN-binding polypeptide does not comprise a lysine residue.

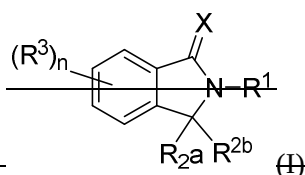
165. The fusion polypeptide of any one of claims 83-164, wherein the COF2/CRBN-binding polypeptide is not ubiquitinated, e.g., in the presence of COF2, e.g., as measured by an assay described herein, optionally wherein ubiquitination is as measured in a mammalian cell, e.g., a human cell.

166. The fusion polypeptide of any one of claims 83-165, wherein the COF2/CRBN-binding polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 41, 42, and 43.

167. The fusion polypeptide of any one of claims 83-165, wherein the COF2/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 2 or 4.

168. The fusion polypeptide of any one of claims 83-167, wherein the COF2 is an immunomodulatory imide drug (IMiD), or a pharmaceutically acceptable salt thereof.

169. The fusion polypeptide of any one of claims 83-167, wherein the COF2 has the structure of Formula (I):



or a pharmaceutically acceptable salt, ester, hydrate, solvate, or tautomer thereof, wherein:

—— X is O or S;

—— R¹ is C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₆-heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted by one or more R⁴;

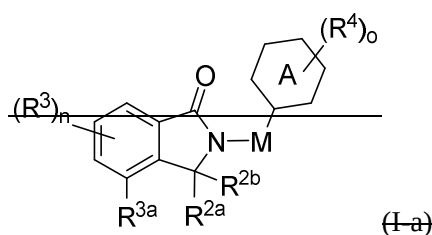
—— each of R^{2a} and R^{2b} is independently hydrogen or C₁-C₆-alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a carbonyl group or a thiocarbonyl group;

—— each of R³ is independently C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₆-heteroalkyl, halo, cyano, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), or N(R^C)S(O)_xR^E, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R⁶;

—— each R⁴ is independently C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₆-heteroalkyl, halo, cyano, oxo, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), N(R^C)S(O)_xR^E, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R⁷;

each of R^A , R^B , R^C , R^D , and R^E is independently hydrogen or C_1 - C_6 alkyl;
each R^6 is independently C_1 - C_6 alkyl, oxo, cyano, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R^8 ;
each R^7 is independently halo, oxo, cyano, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, or $-N(R^C)C(O)R^A$;
each R^8 is independently C_1 - C_6 alkyl, cyano, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, or $-N(R^C)C(O)R^A$;
n is 0, 1, 2, 3 or 4; and
x is 0, 1, or 2.

170. The fusion polypeptide of any one of claims 83-167, wherein the COF2 has the structure of Formula (I-a):



or a pharmaceutically acceptable salt, ester, hydrate, or tautomer thereof, wherein:

—— Ring A is carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted with one or more R^4 ;

M is absent, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, or C_1 - C_6 heteroalkyl, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^4 ;

—— each of R^{2a} and R^{2b} is independently hydrogen or C_1 - C_6 alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached to form a carbonyl group or thiocarbonyl group;

—— R^{3a} is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, halo, cyano, $-C(O)R^A$, $-C(O)OR^B$, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, $-S(O)_xR^E$, $-S(O)_xN(R^C)(R^D)$, or $-N(R^C)S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^6 ;

each of R^3 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, halo, cyano, $-C(O)R^A$, $-C(O)OR^B$, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, $-S(O)_xR^E$, $-S(O)_xN(R^C)(R^D)$, or $-N(R^C)S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^6 ;

~~each R⁴ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, oxo, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), N(R^C)S(O)_xR^E, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R⁷;~~

~~each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C₁-C₆ alkyl;~~

~~each R⁶ is independently C₁-C₆ alkyl, oxo, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R⁸;~~

~~each R⁷ is independently halo, oxo, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), or N(R^C)C(O)R^A;~~

~~each R⁸ is independently C₁-C₆ alkyl, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), or N(R^C)C(O)R^A;~~

~~n is 0, 1, 2, or 3;~~

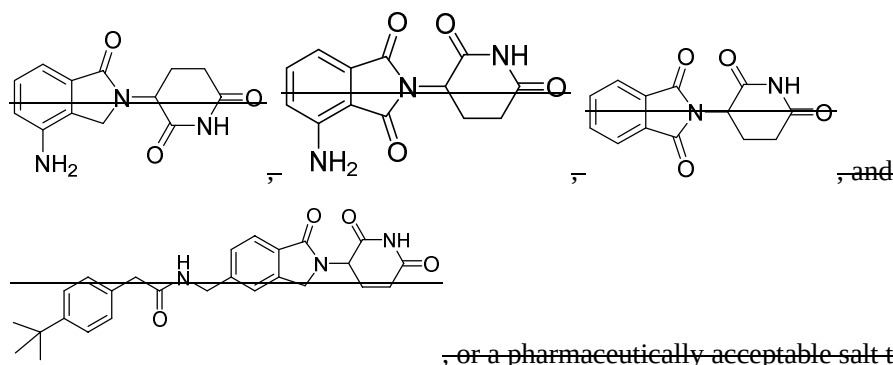
~~o is 0, 1, 2, 3, 4, or 5; and~~

~~x is 0, 1, or 2.~~

~~171. The fusion polypeptide of any one of claims 83-167, wherein the COF2 is thalidomide or analogue, or a pharmaceutically acceptable salt thereof.~~

~~172. The fusion polypeptide of any one of claims 83-167, wherein the COF2 is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, and 2-(4-(tert-butyl)phenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)acetamide, or a pharmaceutically acceptable salt thereof.~~

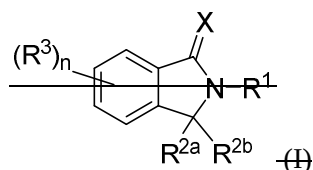
~~173. The fusion polypeptide of any one of claims 83-167, wherein the COF2 is selected from the group consisting of:~~



174. The fusion polypeptide of any one of claims 83-167, wherein the COF2 is lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof.

175. The fusion polypeptide of any one of claims 83-167, wherein the COF2 is lenalidomide or analogue, or a pharmaceutically acceptable salt thereof.

176. The fusion polypeptide of any one of claims 83-167, wherein the COF2 comprises the structure of Formula (I):



or a pharmaceutically acceptable salt, ester, hydrate, solvate, or tautomer thereof, wherein:

—— X is O or S;

—— R¹ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted by one or more R⁴;

—— each of R^{2a} and R^{2b} is independently hydrogen or C₁-C₆ alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a carbonyl group or a thiocarbonyl group;

—— each of R³ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), or N(R^C)S(O)_xR^E, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R⁶;

—— each R⁴ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, oxo, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), N(R^C)S(O)_xR^E, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl,

alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R^7 ;

each of R^A , R^B , R^C , R^D , and R^E is independently hydrogen or C_1 - C_6 alkyl;

each R^6 is independently C_1 - C_6 alkyl, oxo, cyano, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, $N(R^C)C(O)R^A$, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R^8 ;

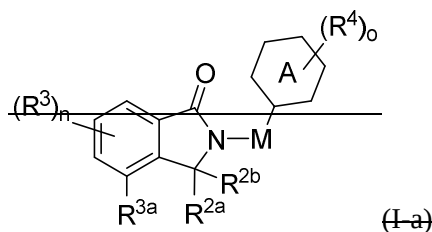
each R^7 is independently halo, oxo, cyano, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, or $N(R^C)C(O)R^A$;

each R^8 is independently C_1 - C_6 alkyl, cyano, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, or $N(R^C)C(O)R^A$;

n is 0, 1, 2, 3 or 4; and

x is 0, 1, or 2.

177. The fusion polypeptide of any one of claims 83-167, wherein the COF2 comprises the structure of Formula (I-a):



or a pharmaceutically acceptable salt, ester, hydrate, or tautomer thereof, wherein:

—— Ring A is carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted with one or more R^4 ;

M is absent, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, or C_1 - C_6 heteroalkyl, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one or more R^4 ;

—— each of R^{2a} and R^{2b} is independently hydrogen or C_1 - C_6 alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached to form a carbonyl group or thiocarbonyl group;

—— R^{3a} is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, halo, cyano, $C(O)R^A$, $C(O)OR^B$, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, $N(R^C)C(O)R^A$, $S(O)_xR^E$, $S(O)_xN(R^C)(R^D)$, or $N(R^C)S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^6 ;

each of R^3 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, halo, cyano, $C(O)R^A$, $C(O)OR^B$, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, $N(R^C)C(O)R^A$, $S(O)_xR^E$,

~~S(O)_xN(R^E)(R^D), or N(R^E)S(O)_xR^E, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R⁶;~~

~~—— each R⁴ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, oxo, C(O)R^A, C(O)OR^B, OR^B, N(R^E)(R^D), C(O)N(R^E)(R^D), N(R^E)C(O)R^A, S(O)_xR^E, S(O)_xN(R^E)(R^D), N(R^E)S(O)_xR^E, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R⁷;~~

~~each of R^A, R^B, R^E, R^D, and R^E is independently hydrogen or C₁-C₆ alkyl;~~

~~each R⁶ is independently C₁-C₆ alkyl, oxo, cyano, OR^B, N(R^E)(R^D), C(O)N(R^E)(R^D), N(R^E)C(O)R^A, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R⁸;~~

~~each R⁷ is independently halo, oxo, cyano, OR^B, N(R^E)(R^D), C(O)N(R^E)(R^D), or N(R^E)C(O)R^A;~~

~~each R⁸ is independently C₁-C₆ alkyl, cyano, OR^B, N(R^E)(R^D), C(O)N(R^E)(R^D), or N(R^E)C(O)R^A;~~

~~n is 0, 1, 2, or 3;~~

~~o is 0, 1, 2, 3, 4, or 5; and~~

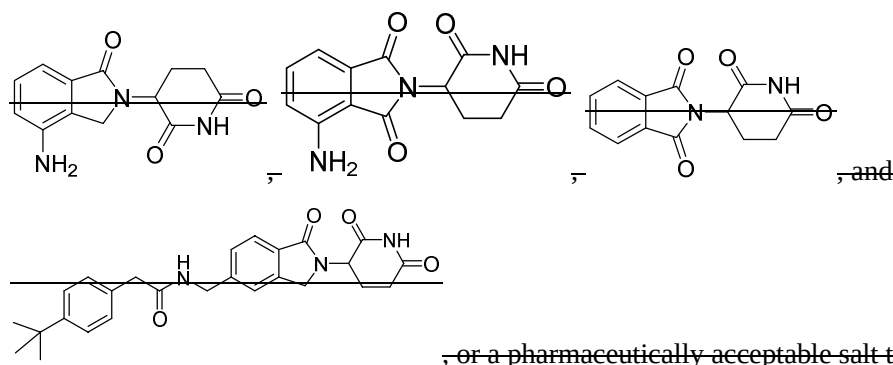
~~x is 0, 1, or 2.~~

~~178. The fusion polypeptide of any one of claims 83-167, wherein the COF2 comprises an immunomodulatory imide drug (IMiD), or a pharmaceutically acceptable salt thereof.~~

~~179. The fusion polypeptide of any one of claims 83-167, wherein the COF2 comprises thalidomide or analogue, or a pharmaceutically acceptable salt thereof.~~

~~180. The fusion polypeptide of any one of claims 83-167, wherein the COF2 comprises lenalidomide, pomalidomide, thalidomide, and 2-(4-(tert-butyl)phenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)acetamide, or a pharmaceutically acceptable salt thereof.~~

~~181. The fusion polypeptide of any one of claims 83-167, wherein the COF2 comprises a compound selected from the group consisting of:~~



182. The fusion polypeptide of any one of claims 83-167, wherein the COF2 comprises lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof.

183. The fusion polypeptide of any one of claims 83-167, wherein the COF2 comprises lenalidomide or analogue, or a pharmaceutically acceptable salt thereof.

184. The fusion polypeptide of any one of claims 176-183, wherein the COF2 further comprises a ligand (e.g., wherein R^{10} in Formula (II) is L-Tag).

185. The fusion polypeptide of any one of claims 176-184, wherein R^{10} in Formula (II) is L-Tag, L is a linker selected from a linker disclosed in International Patent Publication No. WO2017/024318 (e.g., Figures 28-31), and Tag is selected from a dTAG Targeting Ligand disclosed in International Patent Publication No. WO2017/024318 (e.g., Table T, pages 119-129).

186. The fusion polypeptide of any one of claims 83-184, wherein the COF2 comprises IMiD (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof) and a ligand, wherein the IMiD (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof) is linked to the ligand, e.g., via a linker.

187. The fusion polypeptide of any one of claims 184-186, wherein the COF2/CRBN-binding polypeptide binds to the ligand and wherein the binding between the COF2/CRBN-binding polypeptide and IMiD (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof) in the absence of the ligand is no more than 0.0001, 0.001, 0.01, 0.1, 1, or 10% of the binding between the COF2/CRBN-binding polypeptide and the ligand, e.g., the COF2/CRBN-binding polypeptide does not bind to IMiD (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof), optionally wherein

the COF2/CRBN-binding polypeptide is selected from a dTAG disclosed in International Patent Publication No. WO2017/024318 (e.g., pages 36-65).

~~188. The fusion polypeptide of any one of claims 1-187, wherein the heterologous polypeptide is chosen from a cytoplasmic and/or nuclear polypeptide, or a transmembrane polypeptide, e.g., a heterologous polypeptide in Table 2.~~

~~189. The fusion polypeptide of claim 188, wherein the cytoplasmic and/or nuclear polypeptide is selected from the group consisting of a component of the apoptosis pathway (e.g., Caspase 9), a component of a CRISPR/Cas system (e.g., Cas9), a transcription factor (e.g., MITF, c-Myc, STAT3, STAT5, NF-kappaB, beta-catenin, Notch, GLI, or c-JUN), Tet methylcytosine dioxygenase 2 (TET2), FKBP, and Tau.~~

~~190. The fusion polypeptide of claim 188, wherein the transmembrane polypeptide is selected from the group consisting of CD62L, CCR1, CCR2, CCR5, CCR7, CCR10, CXCR2, CXCR3, CXCR4, CXCR6, CTLA4, PD1, BTLA, VISTA, CD137L, CD80, CD86, TIGIT, CD3, CD8, CD19, CD22, CD20, BCMA, and a chimeric antigen receptor (CAR).~~

~~191. The fusion polypeptide of claim 188, wherein the heterologous polypeptide is selected from the group consisting of a chimeric antigen receptor (CAR), a component of a CRISPR/Cas system (e.g., Cas9), CD8, CD19, and CD22.~~

~~192. The fusion polypeptide of claim 191, wherein the heterologous polypeptide is a chimeric antigen receptor (CAR).~~

~~193. The fusion polypeptide of claim 192, wherein said CAR comprises, in a N-terminal to C-terminal direction, an antigen-binding domain, a transmembrane domain, and one or more intracellular signaling domains.~~

~~194. The fusion polypeptide of claim 193, wherein said intracellular signaling domain comprises one or more primary signaling domains.~~

~~195. The fusion polypeptide of claim 193 or 194, wherein said intracellular signaling domain comprises one or more costimulatory signaling domains.~~

196. The fusion polypeptide of claim 194, wherein one of said one or more primary signaling domains comprises a CD3-zeta stimulatory domain.

197. The fusion polypeptide of claim 195, wherein one or more of said costimulatory signaling domains is an intracellular domain from a costimulatory protein selected from the group consisting of CD27, CD28, 4-1BB (CD137), OX40, GITR, CD30, CD40, ICOS, BAFFR, HVEM, ICAM-1, lymphocyte function-associated antigen-1 (LFA-1), CD2, CDS, CD7, CD287, LIGHT, NKG2C, NKG2D, SLAMF7, NKp80, NKp30, NKp44, NKp46, CD160, B7-H3, and a ligand that specifically binds with CD83.

198. The fusion polypeptide of claim 197, wherein said one or more of said costimulatory signaling domains comprises the 4-1BB costimulatory domain.

199. The fusion polypeptide of claim 197 or 198, wherein said one or more of said costimulatory signaling domains comprises the CD28 costimulatory domain.

200. The fusion polypeptide of any one of claims 193-199, wherein said antigen binding domain is an scFv.

201. The fusion polypeptide of any one of claims 193-200, wherein said antigen binding domain binds an antigen selected from the group consisting of CD19; CD123; CD22; CD30; CD171; CS-1; C-type lectin-like molecule-1; CD33; epidermal growth factor receptor variant III (EGFRvIII); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member; B-cell maturation antigen; Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms-Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2; Mesothelin; Interleukin-11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease-Serine 21; vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha; Receptor tyrosine-protein kinase ERBB2 (Her2/neu); Mucin-1, cell surface associated (MUC1); epidermal growth factor receptor (EGFR); neural cell adhesion molecule (NCAM); Prostase; prostatic acid phosphatase (PAP); elongation factor 2 mutated (ELF2M); Ephrin B2; fibroblast activation protein alpha (FAP); insulin-like growth factor-1 receptor (IGF-1 receptor); carbonic anhydrase IX (CAIX); Proteasome (Prosome, Macropain) Subunit, Beta-Type, 9 (LMP2); glycoprotein 100 (gp100); oncogene polypeptide

consisting of breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type A receptor 2 (EphA2); Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high-molecular-weight-melanoma-associated antigen (HMWMAA); o-acetyl-GD2-ganglioside (OAcGD2); Folate receptor beta; tumor endothelial marker 1 (TEM1/CD248); tumor endothelial marker 7-related (TEM7R); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G-protein-coupled receptor class C group 5, member D (GPRC5D); chromosome X open reading frame 61 (CXORF61); CD97; CD179a; anaplastic lymphoma kinase (ALK); Polysialic acid; placenta-specific 1 (PLAC1); hexasaccharide portion of globoH glycosphingolipid (GloboH); mammary gland differentiation antigen (NY-BR-1); uroplakin 2 (UPK2); Hepatitis A virus cellular receptor 1 (HAVCR1); adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G-protein-coupled receptor 20 (GPR20); lymphocyte antigen 6 complex, locus K 9 (LY6K); Olfactory receptor 51E2 (OR51E2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ESO-1); Cancer/testis antigen 2 (LAGE-1a); Melanoma-associated antigen 1 (MAGE-A1); ETS translocation variant gene 6, located on chromosome 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1); angiopoietin-binding cell surface receptor 2 (Tie 2); melanoma cancer testis antigen 1 (MAD-CT-1); melanoma cancer testis antigen 2 (MAD-CT-2); Fos-related antigen 1; tumor protein p53 (p53); p53 mutant; prostein; surviving; telomerase; prostate carcinoma tumor antigen 1, melanoma antigen recognized by T cells 1; Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); sarcoma translocation breakpoints; melanoma-inhibitor of apoptosis (ML-IAP); ERG (transmembrane protease, serine 2 (TMPRSS2) ETS fusion gene); N-Acetyl glucosaminyl transferase V (NA17); paired box protein Pax 3 (PAX3); Androgen receptor; Cyclin B1; v-myc avian myelocytomatosis viral oncogene neuroblastoma-derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 1B1 (CYP1B1); CCCTC-Binding Factor (Zinc Finger Protein)-Like, Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax 5 (PAX5); proacrosin binding protein sp32 (OY-TES1); lymphocyte-specific protein tyrosine kinase (LCK); A-kinase anchor protein 4 (AKAP-4); synovial sarcoma, X breakpoint 2 (SSX2); Receptor for Advanced Glycation Endproducts (RAGE-1); renal ubiquitous 1 (RU1); renal ubiquitous 2 (RU2); legumain; human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); Fc fragment of IgA receptor (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75);

Glypican 3 (GPC3); Fc receptor like 5 (FCRL5); and immunoglobulin lambda-like polypeptide 1 (IGLL1).

~~202. The fusion polypeptide of any one of claims 193-200, wherein said antigen is chosen from CD19, CD22, BCMA, CD20, CD123, EGFRvIII, or mesothelin.~~

~~203. The fusion polypeptide of any one of claims 193-200, wherein said antigen is CD19.~~

~~204. The fusion polypeptide of any one of claims 193-200, wherein said antigen is CD22.~~

~~205. The fusion polypeptide of any one of claims 193-200, wherein said antigen is BCMA.~~

~~206. The fusion polypeptide of any one of claims 193-200, wherein said antigen is CD20.~~

~~207. The fusion polypeptide of any one of claims 193-200, wherein said antigen is CD123.~~

~~208. The fusion polypeptide of any one of claims 193-200, wherein said antigen is EGFRvIII.~~

~~209. A nucleic acid molecule encoding the fusion polypeptide of any one of claims 1-208.~~

~~210. A vector comprising the nucleic acid molecule of claim 209.~~

~~211. The vector of claim 210, wherein said vector is a viral vector.~~

~~212. The vector of claim 210, wherein said vector is a lentiviral vector.~~

~~213. A viral particle comprising the vector of any one of claims 210-212.~~

~~214. A cell, e.g., a host cell, comprising the fusion polypeptide of any one of claims 1-208, the nucleic acid molecule of claim 209, or the vector of any one of claims 210-212.~~

~~215. The cell of claim 214, wherein said cell, e.g., host cell, is a mammalian cell, e.g., a human cell, e.g., a human effector cell, e.g., a human T cell or a human NK cell.~~

~~216. The cell of claim 214 or 215, wherein said cell, e.g., host cell, is a CAR-expressing cell, e.g., a CAR-T cell.~~

~~217. The cell of claim 214 or 215, wherein said cell, e.g., host cell, comprises a component of a CRISPR/Cas system.~~

~~218. The cell of any one of claims 214-217, wherein said cell, e.g., host cell, is a human cancer cell, e.g., a human tumor cell.~~

~~219. The cell of any one of claims 214-218, wherein said cell, e.g., host cell, comprises a ubiquitin ligase complex, e.g., an E3 ubiquitin ligase complex, wherein the ubiquitin ligase complex comprises CRBN.~~

~~220. The cell of any one of claims 214-219, wherein the cell comprises the fusion polypeptide of any one of claims 1-79 or 188-208 or the cell comprises a nucleic acid molecule encoding the fusion polypeptide of any one of claims 1-79 or 188-208, wherein when the cell is contacted with COF1, e.g., an excess of COF1:~~

~~i) the association of the COF1/CRBN-binding polypeptide with CRBN is increased by at least, e.g., 10-, 50-, 100-, 1000-, or 10000-fold, compared to the association of the COF1/CRBN-binding polypeptide with CRBN when the cell is not contacted with COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;~~

~~ii) the association of the fusion polypeptide with CRBN is increased by at least, e.g., 10-, 50-, 100-, 1000-, or 10000-fold, compared to the association of the fusion polypeptide with CRBN when the cell is not contacted with COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;~~

~~iii) the ubiquitination of the heterologous polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the ubiquitination of the heterologous polypeptide when the cell is not contacted with COF1, e.g., as measured by an assay described herein;~~

~~iv) the ubiquitination of the fusion polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the ubiquitination of the fusion polypeptide when the cell is not contacted with COF1, e.g., as measured by an assay described herein;~~

~~v) the degradation of the fusion polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the degradation of the fusion polypeptide when the cell is not contacted with COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis; or~~

vi) the expression level of the fusion polypeptide is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the expression level of the fusion polypeptide when the cell is not contacted with COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

~~221. The cell of claim 214-220, wherein said cell further comprises COF1, e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof.~~

~~222. The cell of any one of claims 214-219, wherein the cell comprises the fusion polypeptide of any one of claims 80-82, 84-107, or 188-208 or the cell comprises a nucleic acid molecule encoding the fusion polypeptide of any one of claims 80-82, 84-107, or 188-208, wherein in the absence of a stabilization compound, the fusion polypeptide is degraded by a cellular degradation pathway, e.g., at least 50%, 60%, 70%, 80%, 90% or greater of the fusion polypeptide is degraded, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.~~

~~223. The cell of any one of claims 214-219, wherein the cell comprises the fusion polypeptide of any one of claims 83-208 or the cell comprises a nucleic acid molecule encoding the fusion polypeptide of any one of claims 83-208, wherein in the absence of a stabilization compound, the fusion polypeptide is degraded by a cellular degradation pathway, e.g., at least 50%, 60%, 70%, 80%, 90% or greater of the fusion polypeptide is degraded, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.~~

~~224. The cell of claim 222 or 223, further comprising a protease capable of cleaving said heterologous protease cleavage site.~~

~~225. The cell of any one of claims 222-224, when the cell is contacted with a stabilization compound, e.g., an excess of a stabilization compound:~~

- ~~i) the degradation domain assumes a conformation more resistant to cellular degradation relative to a conformation in the absence of the stabilization compound;~~
- ~~ii) the conformation of the fusion polypeptide is more permissive to cleavage at the heterologous protease cleavage site relative to a conformation in the absence of the stabilization compound; or~~
- ~~iii) the expression level of the fusion polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the expression level of the fusion polypeptide when the cell is not~~

contacted with the stabilization compound, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

226. The cell of any one of claims 222-225, further comprising a stabilization compound.

227. The cell of any one of claims 222-226, wherein the stabilization compound is bazedoxifene, or a pharmaceutically acceptable salt thereof, and optionally wherein the degradation domain comprises the amino acid sequence of SEQ ID NO: 46.

228. The cell of any one of claims 222 or 224-227, wherein when the cell is contacted with both a stabilization compound, e.g., an excess of a stabilization compound, and COF1, e.g., an excess of COF1:

i) the association of the COF1/CRBN binding polypeptide with CRBN is increased by at least, e.g., 10-, 50-, 100-, 1000-, or 10000-fold, compared to the association of the COF1/CRBN binding polypeptide with CRBN when the cell is only contacted with the stabilization compound but not COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

ii) the association of the fusion polypeptide with CRBN is increased by at least, e.g., 10-, 50-, 100-, 1000-, or 10000-fold, compared to the association of the fusion polypeptide with CRBN when the cell is only contacted with the stabilization compound but not COF1, e.g., as measured by an assay described herein, e.g., immunoprecipitation;

iii) the ubiquitination of the heterologous polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the ubiquitination of the heterologous polypeptide when the cell is only contacted with the stabilization compound but not COF1, e.g., as measured by an assay described herein;

iv) the ubiquitination of the fusion polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the ubiquitination of the fusion polypeptide when the cell is only contacted with the stabilization compound but not COF1, e.g., as measured by an assay described herein;

v) the degradation of the fusion polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the degradation of the fusion polypeptide when the cell is only contacted with the stabilization compound but not COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis; or

vi) the expression level of the fusion polypeptide is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the expression level of the fusion polypeptide when the cell is only contacted with the stabilization compound but not COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

229. The cell of any one of claims 222 or 224-228, further comprising COF1, e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof.

230. The cell of any one of claims 223-229, wherein when the cell is contacted with both a stabilization compound, e.g., an excess of a stabilization compound, and COF2, e.g., an excess of COF2:

- i) the association of the COF2/CRBN binding polypeptide with CRBN is increased by at least, e.g., 10-, 50-, 100-, 1000-, or 10000-fold, compared to the association of the COF2/CRBN binding polypeptide with CRBN when the cell is only contacted with the stabilization compound but not COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- ii) the association of the fusion polypeptide with CRBN is increased by at least, e.g., 10-, 50-, 100-, 1000-, or 10000-fold, compared to the association of the fusion polypeptide with CRBN when the cell is only contacted with the stabilization compound but not COF2, e.g., as measured by an assay described herein, e.g., immunoprecipitation;
- iii) the ubiquitination of the heterologous polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the ubiquitination of the heterologous polypeptide when the cell is only contacted with the stabilization compound but not COF2, e.g., as measured by an assay described herein;
- iv) the ubiquitination of the fusion polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the ubiquitination of the fusion polypeptide when the cell is only contacted with the stabilization compound but not COF2, e.g., as measured by an assay described herein;
- v) the degradation of the fusion polypeptide is increased by at least, e.g., 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, compared to the degradation of the fusion polypeptide when the cell is only contacted with the stabilization compound but not COF2, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis; or
- vi) the expression level of the fusion polypeptide is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the expression level of the fusion polypeptide when the cell is only contacted with the stabilization compound but not COF2, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

231. The cell of any one of claims 223-230, further comprising COF2, e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof.

~~232. The cell of any one of claims 214-231, wherein the heterologous polypeptide is a chimeric antigen receptor (CAR), optionally wherein the CAR comprises, in a N-terminal to C-terminal direction, an antigen binding domain, a transmembrane domain, and one or more intracellular signaling domains.~~

~~233. A pharmaceutical composition comprising the fusion polypeptide of any one of claims 1-208 or the cell of any one of claims 214-232, and a pharmaceutically acceptable carrier, excipient or stabilizer.~~

~~234. A method of making the cell of any one of claims 214-232, said method comprising providing a cell, e.g., an immune effector cell, with the nucleic acid molecule of claim 209, the vector of any one of claims 210-212, or the viral particle of claim 213.~~

~~235. A method of degrading a fusion polypeptide, comprising contacting the fusion polypeptide of any one of claims 1-79 or 188-208 or a cell comprising said fusion polypeptide with COF1 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof), optionally wherein in the presence of COF1 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof), the expression level of said fusion polypeptide is substantially decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of said fusion polypeptide in the absence of COF1 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof), e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.~~

~~236. The method of claim 235, wherein the fusion polypeptide or the cell is contacted with COF1 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof) *ex vivo*.~~

~~237. The method of claim 235, wherein the fusion polypeptide or the cell is contacted with COF1 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof) *in vivo*.~~

~~238. A method of regulating the expression of a fusion polypeptide, comprising:~~

~~i) contacting the fusion polypeptide of any one of claims 80-82, 84-107, or 188-208 or a cell comprising said fusion polypeptide with a stabilization compound, optionally wherein in the presence of the stabilization compound:~~

~~a) the degradation domain assumes a conformation more resistant to cellular degradation relative to a conformation in the absence of the stabilization compound;~~

~~b) the conformation of the fusion polypeptide is more permissive to cleavage at the heterologous protease cleavage site relative to a conformation in the absence of the stabilization compound; or~~

e) the expression level of the fusion polypeptide is increased by at least, e.g., 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50-fold, compared to the expression level of the fusion polypeptide in the absence of the stabilization compound, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

239. The method of claim 238, further comprising, after step i):

ii) contacting the fusion polypeptide of any one of claims 83-208 or a cell comprising said fusion polypeptide with COF1 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof), optionally wherein in the presence of COF1 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof), the expression level of the fusion polypeptide is substantially decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of the fusion polypeptide after step i) and before step ii), e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

240. The method of claim 238 or 239, wherein the stabilization compound is bazedoxifene, or a pharmaceutically acceptable salt thereof, and optionally wherein the degradation domain comprises the amino acid sequence of SEQ ID NO: 46.

241. The method of any one of claims 238-240, wherein the fusion polypeptide or the cell is contacted with COF1 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof) and/or the stabilization compound *ex vivo*.

242. The method of any one of claims 238-240, wherein the fusion polypeptide or the cell is contacted with COF1 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof) and/or the stabilization compound *in vivo*.

243. A method of regulating the expression of a fusion polypeptide, comprising:

i) contacting the fusion polypeptide of any one of claims 83-208 or a cell comprising said fusion polypeptide with a stabilization compound, optionally wherein in the presence of the stabilization compound:

a) the degradation domain assumes a conformation more resistant to cellular degradation relative to a conformation in the absence of the stabilization compound;

b) the conformation of the fusion polypeptide is more permissive to cleavage at the heterologous protease cleavage site relative to a conformation in the absence of the stabilization compound; or

e) the expression level of the fusion polypeptide is increased by at least, e.g., 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50-fold, compared to the expression level of the fusion polypeptide in the absence of the stabilization compound, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

244. The method of claim 243, further comprising, after step i):

ii) contacting the fusion polypeptide of any one of claims 83-208 or a cell comprising said fusion polypeptide with COF2 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof), optionally wherein in the presence of COF2 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof), the expression level of the fusion polypeptide is substantially decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of the fusion polypeptide after step i) and before step ii), e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

245. The method of claim 243 or 244, wherein the stabilization compound is bazedoxifene, or a pharmaceutically acceptable salt thereof, and optionally wherein the degradation domain comprises the amino acid sequence of SEQ ID NO: 46.

246. The method of any one of claims 243-245, wherein the fusion polypeptide or the cell is contacted with COF2 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof) and/or the stabilization compound *ex vivo*.

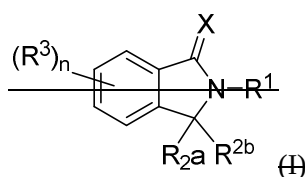
247. The method of any one of claims 243-245, wherein the fusion polypeptide or the cell is contacted with COF2 (e.g., lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof) and/or the stabilization compound *in vivo*.

248. The method of any one of claims 234-247, wherein the heterologous polypeptide is a chimeric antigen receptor (CAR), optionally wherein the CAR comprises, in a N-terminal to C-terminal direction, an antigen binding domain, a transmembrane domain, and one or more intracellular signaling domains.

249. A method of making a cell, comprising:

i) providing a cell comprising a nucleic acid molecule encoding a fusion polypeptide comprising a compound of formula 1 (COF1)/CRBN-binding polypeptide and a chimeric antigen receptor (CAR);

optionally wherein the CAR comprises, in a N-terminal to C-terminal direction, an antigen binding domain, a transmembrane domain, and one or more intracellular signaling domains; and
 ii) contacting the cell *ex vivo* with COF1, optionally wherein:
 in the presence of COF1, the expression level of the fusion polypeptide is substantially decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of the fusion polypeptide in the absence of COF1, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis, wherein the compound of Formula (I) is:



or a pharmaceutically acceptable salt, ester, hydrate, solvate, or tautomer thereof, wherein:

—— X is O or S;

—— R¹ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is independently and optionally substituted by one or more R⁴;

—— each of R^{2a} and R^{2b} is independently hydrogen or C₁-C₆ alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a carbonyl group or a thiocarbonyl group;

—— each of R³ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), or N(R^C)S(O)_xR^E, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R⁶;

—— each R⁴ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, halo, cyano, oxo, C(O)R^A, C(O)OR^B, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, S(O)_xR^E, S(O)_xN(R^C)(R^D), N(R^C)S(O)_xR^E, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R⁷;

each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C₁-C₆ alkyl;

each R⁶ is independently C₁-C₆ alkyl, oxo, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), N(R^C)C(O)R^A, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R⁸;

each R⁷ is independently halo, oxo, cyano, OR^B, N(R^C)(R^D), C(O)N(R^C)(R^D), or N(R^C)C(O)R^A;

each R^B is independently C_1 - C_6 alkyl, cyano, OR^B , $N(R^C)(R^D)$, $C(O)N(R^C)(R^D)$, or $N(R^C)C(O)R^A$;

n is 0, 1, 2, 3 or 4; and

—— x is 0, 1, or 2.

250. The method of claim 249, wherein after the cell is contacted with COF1 *ex vivo*, the proliferation of the cell is increased by at least, e.g., 1.2, 1.5, 2, 5, or 10 fold, relative to the proliferation of the cell prior to the contacting with COF1.

251. The method of claim 250, wherein COF1 is lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof.

252. The method of claim 249 or 250, wherein the COF1/CRBN binding polypeptide comprises or consists of an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-6, 11-15, 40, 41-43, 77, 78, 84-86, and 100 (e.g., the COF1/CRBN binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 3).

253. A method of treating a subject having a disease associated with expression of a tumor antigen, comprising:

i) contacting a cell comprising the fusion polypeptide of any one of claims 1-79 or 188-208 with COF1 *ex vivo*, optionally wherein:

in the presence of COF1, the expression level of the fusion polypeptide is decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of the fusion polypeptide before the cell is contacted with COF1 *ex vivo*, and

ii) administering to the subject an effective amount of the cell, optionally wherein the method further comprises after step i) and prior to step ii):

reducing the amount of COF1 contacting the cell, e.g., inside and/or surrounding the cell, thereby treating the disease.

254. The method of claim 253, further comprising after step ii):

iii) administering to the subject an effective amount of COF1, optionally wherein the administration of COF1 decreases, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step ii) and prior to step iii), optionally wherein:

- a) the subject has developed, is developing, or is anticipated to develop an adverse reaction,
- b) the administration of COF1 is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or
- c) the administration of COF1 reduces or prevents an adverse effect.

255. The method of claim 254, further comprising after step iii):

- iv) discontinuing the administration of COF1, optionally wherein discontinuing the administration of COF1 increases, e.g., by at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step iii) and prior to step iv) (e.g., wherein discontinuing the administration of COF1 restores the expression level of the fusion polypeptide to the expression level after step ii) and prior to step iii)), optionally wherein:
 - a) the subject has relapsed, is relapsing, or is anticipated to relapse,
 - b) the discontinuation of the administration of COF1 is in response to a tumor relapse in the subject, or in response to an anticipation of a relapse in the subject, and/or
 - c) the discontinuation of the administration of COF1 treats or prevents a tumor relapse.

256. The method of claim 255, further comprising after step iv):

- v) repeating step iii) and/or iv),
- thereby treating the disease.

257. A method of treating a subject having a disease associated with expression of a tumor antigen, comprising:

- i) administering to the subject an effective amount of a cell comprising the fusion polypeptide of any one of claims 1-79 or 188-208, optionally wherein the cell is contacted with COF1 *ex vivo* before administration, optionally wherein:
 - in the presence of COF1, the expression level of the fusion polypeptide is decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of the fusion polypeptide before the cell is contacted with COF1 *ex vivo*, optionally wherein after the cell is contacted with COF1 *ex vivo* and before the cell is administered to the subject, the amount of COF1 contacting the cell, e.g., inside and/or surrounding the cell, is reduced,
- thereby treating the disease.

258. The method of claim 257, wherein the cell is not contacted with COF1 *ex vivo* before administration.

259. The method of claim 257 or 258, further comprising after step i):

ii) administering to the subject an effective amount of COF1, optionally wherein the administration of COF1 decreases, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step i) and prior to step ii), optionally wherein:

- a) the subject has developed, is developing, or is anticipated to develop an adverse reaction,
- b) the administration of COF1 is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or
- c) the administration of COF1 reduces or prevents an adverse effect.

260. The method of claim 259, further comprising after step ii):

iii) discontinuing the administration of COF1, optionally wherein discontinuing the administration of COF1 increases, e.g., by at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step ii) and prior to step iii) (e.g., wherein discontinuing the administration of COF1 restores the expression level of the fusion polypeptide to the expression level after step i) and prior to step ii)), optionally wherein:

- a) the subject has relapsed, is relapsing, or is anticipated to relapse,
- b) the discontinuation of the administration of COF1 is in response to a tumor relapse in the subject, or in response to an anticipation of a relapse in the subject, and/or
- c) the discontinuation of the administration of COF1 treats or prevents a tumor relapse.

261. The method of claim 260, further comprising after step iii):

iv) repeating step ii) and/or iii);
thereby treating the disease.

262. A method of treating a subject having a disease associated with expression of a tumor antigen, comprising:

i) administering an effective amount of COF1 to the subject, wherein the subject comprises a cell comprising the fusion polypeptide of any one of claims 1-79 or 188-208, optionally wherein the administration of COF1 decreases, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide before the administration of COF1, optionally wherein:

- a) the subject has developed, is developing, or is anticipated to develop an adverse reaction,

- b) the administration of COF1 is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or
- c) the administration of COF1 reduces or prevents an adverse effect.

263. The method of claim 262, further comprising after step i):

- ii) discontinuing the administration of COF1, optionally wherein discontinuing the administration of COF1 increases, e.g., by at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step i) and prior to step ii) (e.g., wherein discontinuing the administration of COF1 restores the expression level of the fusion polypeptide to the expression level before the administration of COF1), optionally wherein:
 - a) the subject has relapsed, is relapsing, or is anticipated to relapse,
 - b) the discontinuation of the administration of COF1 is in response to a tumor relapse in the subject, or in response to an anticipation of a relapse in the subject, and/or
 - c) the discontinuation of the administration of COF1 treats or prevents a tumor relapse.

264. The method of claim 263, further comprising after step ii):

- iii) repeating step i) and/or ii),
- thereby treating the disease.

265. The method of any one of claims 253-264, wherein COF1 is lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof, optionally wherein the COF1/CRBN binding polypeptide comprises or consists of an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-6, 11-15, 40, 41-43, 77, 78, 84-86, and 100 (e.g., the COF1/CRBN binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 3).

266. The method of any one of claims 259-265, wherein COF1 is lenalidomide, or a pharmaceutically acceptable salt thereof, optionally wherein lenalidomide, or a pharmaceutically acceptable salt thereof, is administered at, e.g., 2.5 mg, 5 mg, 10 mg, 15 mg, or 25 mg per day.

267. A method of treating a subject having a disease associated with expression of a tumor antigen, comprising:

- i) administering to the subject:
 - (1) a stabilization compound, and

(2) an effective amount of a cell comprising the fusion polypeptide of any one of claims 80-82, 84-107, or 188-208, or an effective amount of a cell comprising the fusion polypeptide of any one of claims 83-208, optionally wherein:

the expression level of the fusion polypeptide in the presence of the stabilization compound is e.g., at least about 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, higher than the expression level of the fusion polypeptide in the absence of the stabilization compound, thereby treating the disease.

268. The method of claim 267, further comprising after step i):

ii) discontinuing the administration of the stabilization compound, optionally wherein discontinuing the administration of the stabilization compound reduces, e.g., at least about 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, the expression level of the fusion polypeptide relative to the expression of the fusion polypeptide after step i) and prior to step ii), optionally wherein:

a) the subject responded to the treatment of step i) (e.g., the subject has a complete response to the treatment of step i), the subject shows a shrinkage in tumor mass, the subject shows a decrease in tumor cells, or the treatment of step i) is effective in the subject), and/or

b) the discontinuation of the administration of the stabilization compound is in response to a response of the subject to the treatment of step i) (e.g., the subject has a complete response to the treatment of step i), the subject shows a shrinkage in tumor mass, the subject shows a decrease in tumor cells, or the treatment of step i) is effective in the subject).

269. The method of claim 267, further comprising after step i):

iii) discontinuing the administration of the stabilization compound, optionally wherein discontinuing the administration of the stabilization compound reduces, e.g., at least about 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, the expression level of the fusion polypeptide relative to the expression of the fusion polypeptide after step i) and prior to step ii), optionally wherein:

a) the subject has developed, is developing, or is anticipated to develop an adverse reaction,

b) the discontinuation of the administration of the stabilization compound is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or

c) the discontinuation of the administration of the stabilization compound reduces or prevents an adverse effect.

270. The method of claim 267, further comprising after step i):

~~iv) discontinuing the administration of the stabilization compound and administering to the subject an effective amount of COF1 or COF2, optionally wherein step iv) reduces, e.g., at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression of the fusion polypeptide after step i) and prior to step iv), optionally wherein:~~

- ~~a) the subject has developed, is developing, or is anticipated to develop an adverse reaction,~~
- ~~b) step iv) is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or~~
- ~~c) step iv) reduces or prevents an adverse effect.~~

~~271. The method of claim 270, wherein the adverse effect is an acute toxicity.~~

~~272. The method of claim 270 or 271, further comprising after step iv):~~

~~v) discontinuing the administration of COF1 or COF2, e.g., after the amount of cells expressing the fusion polypeptide on the surface is smaller than a pre-defined value, for, e.g., 1 day, 5 days, 10 days, or 15 days.~~

~~273. The method of any one of claims 268-272, further comprising after step ii), iii), iv), or v):~~

~~vi) administering an effective amount of a stabilization compound, optionally wherein the administration of the stabilization compound increases, e.g., by at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step ii), iii), iv), or v) and prior to step vi), optionally wherein:~~

- ~~a) the subject has relapsed, is relapsing, or is anticipated to relapse,~~
- ~~b) the administration of the stabilization compound is in response to a tumor relapse in the subject, or in response to an anticipation of a relapse in the subject, and/or~~
- ~~c) the administration of the stabilization compound treats or prevents a tumor relapse.~~

~~274. The method of claim 273, further comprising after step vi):~~

~~vii) repeating step iii), iv), v), or vi);~~
~~thereby treating the disease.~~

~~275. The method of any one of claims 267-274, further comprising prior to step i):~~

~~viii) contacting the cell with a stabilization compound ex vivo, optionally wherein the expression level of the fusion polypeptide in the presence of the stabilization compound is e.g., at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, higher than the expression level of the fusion polypeptide in the absence of the stabilization compound.~~

~~276. The method of any one of claims 267-274, wherein the cell is not contacted with the stabilization compound *ex vivo* before administration.~~

~~277. The method of claim 276, wherein the cell is not contacted with any of: the stabilization compound, COF1, or COF2 *ex vivo* before administration.~~

~~278. The method of any one of claims 267-277, wherein the stabilization compound is bazedoxifene, or a pharmaceutically acceptable salt thereof, and optionally wherein the degradation domain comprises the amino acid sequence of SEQ ID NO: 46.~~

~~279. The method of any one of claims 270-278, wherein COF1 is lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof, optionally wherein the COF1/CRBN binding polypeptide comprises or consists of an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-6, 11-15, 40, 41-43, 77, 78, 84-86, and 100 (e.g., the COF1/CRBN binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 3).~~

~~280. The method of any one of claims 270-278, wherein COF2 is lenalidomide or pomalidomide, or a pharmaceutically acceptable salt thereof, optionally wherein the COF2/CRBN binding polypeptide comprises or consists of an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-6, 11-15, 40, 41-43, 77, 78, 84-86, and 100 (e.g., the COF1/CRBN binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 3).~~

~~281. The method of any one of claims 270-280, wherein COF1 or COF2 is lenalidomide, or a pharmaceutically acceptable salt thereof, optionally wherein lenalidomide, or a pharmaceutically acceptable salt thereof, is administered at, e.g., 2.5 mg, 5 mg, 10 mg, 15 mg, or 25 mg per day.~~

~~282. The method of any one of claims 253-281, wherein the heterologous polypeptide of the fusion polypeptide is a chimeric antigen receptor (CAR), optionally wherein the CAR comprises, in a N-terminal to C-terminal direction, an antigen binding domain, a transmembrane domain, and one or more intracellular signaling domains.~~

~~283. The fusion polypeptide, nucleic acid molecule, vector, viral particle, cell, or pharmaceutical composition of any one of claims 1-233 for use as a medicament.~~

284. The fusion polypeptide, nucleic acid molecule, vector, viral particle, cell, or pharmaceutical composition of any one of claims 1-233 for use in the treatment of a subject having a disease associated with expression of a tumor antigen, e.g., for use in the method of any one of claims 253-282.

285. The method or composition for use of any one of claims 253-284, wherein the disease associated with expression of a tumor antigen is a cancer.

286. The method or composition for use of claim 285, wherein the cancer is mesothelioma (e.g., malignant pleural mesothelioma), e.g., in a subject who has progressed on at least one prior standard therapy; lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, squamous cell lung cancer, or large cell lung cancer); pancreatic cancer (e.g., pancreatic ductal adenocarcinoma, or metastatic pancreatic ductal adenocarcinoma (PDA), e.g., in a subject who has progressed on at least one prior standard therapy); esophageal adenocarcinoma, ovarian cancer (e.g., serous epithelial ovarian cancer, e.g., in a subject who has progressed after at least one prior regimen of standard therapy), breast cancer, colorectal cancer, bladder cancer or any combination thereof.

287. The method or composition for use of any one of claims 253-284, wherein the disease associated with expression of a tumor antigen is a hematological cancer, e.g., a hematological cancer chosen from a leukemia or lymphoma.

288. The method or composition for use of claim 287, wherein the cancer is chosen from: chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), multiple myeloma, acute lymphoid leukemia (ALL), Hodgkin lymphoma, B-cell acute lymphoid leukemia (BALL), T-cell acute lymphoid leukemia (TALL), small lymphocytic leukemia (SLL), B-cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B-cell lymphoma (DLBCL), DLBCL associated with chronic inflammation, chronic myeloid leukemia, myeloproliferative neoplasms, follicular lymphoma, pediatric follicular lymphoma, hairy cell leukemia, small cell- or a large cell- follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue), Marginal zone lymphoma, myelodysplasia, myelodysplastic syndrome, non-Hodgkin lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, splenic lymphoma/leukemia, splenic diffuse red pulp small B-cell lymphoma, hairy cell leukemia variant, lymphoplasmacytic lymphoma, a heavy chain disease, plasma cell myeloma, solitary plasmocytoma of

bone, extraosseous plasmocytoma, nodal marginal zone lymphoma, pediatric nodal marginal zone lymphoma, primary cutaneous follicle-center lymphoma, lymphomatoid granulomatosis, primary mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, ALK+ large B-cell lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, primary effusion lymphoma, B-cell lymphoma, acute myeloid leukemia (AML), or unclassifiable lymphoma.

289. The method or composition for use of claim 287, wherein the cancer is chosen from MCL, CLL, ALL, Hodgkin lymphoma, AML, or multiple myeloma.

290. The method or composition for use of any one of claims 253-289, wherein said cell is autologous to said subject.

291. The method or composition for use of any one of claims 253-289, wherein said cell is allogenic to said subject.

292. The method or composition for use of any one of claims 253-291, wherein said cell is a CAR-expressing cell, e.g., a CART cell.

293. The method or composition for use of any one of claims 253-292, wherein the subject was administered a cell expressing at least one fusion polypeptide of any one of claims 1-208, prior to administration of COF1 or COF2.

294. A method of identifying a genetic element associated with a specific biological phenotype, e.g., a genetic element associated with the development and/or progression of a cancer, the method comprising the steps of:

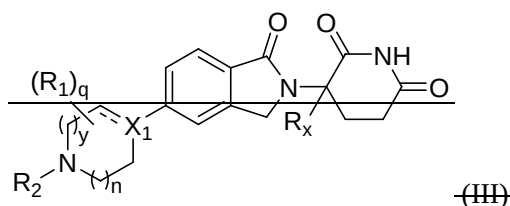
- i) modulating the expression of the fusion polypeptide of any one of claims 1-79 or 188-208 in cells by exposing said cell to COF1, e.g., lenalidomide, or a pharmaceutically acceptable salt thereof,
- (ii) selecting for cells with a phenotype of interest, e.g., a phenotype associated with the development and/or progression of a cancer, and
- (iii) identifying said fusion polypeptide that induces said phenotype of interest,

wherein exposure of said cell to COF1, e.g., lenalidomide, or a pharmaceutically acceptable salt thereof, decreases, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, the expression level of said fusion polypeptide relative to the expression level of said fusion polypeptide prior to exposure to COF1, e.g., lenalidomide, or a pharmaceutically acceptable salt thereof.

295. A method of identifying a genetic element associated with a specific biological phenotype, e.g., a genetic element associated with the development and/or progression of a cancer, the method comprising the steps of:

- i) modulating the expression of the fusion polypeptide of any one of claims 80-82, 84-107, or 188-208 or the expression of the fusion polypeptide of any one of claims 83-208, in cells by exposing said cell to a stabilization compound, e.g., bazedoxifene, or a pharmaceutically acceptable salt thereof, and then to COF1 or COF2, e.g., lenalidomide, or a pharmaceutically acceptable salt thereof;
 - (ii) selecting for cells with a phenotype of interest, e.g., a phenotype associated with the development and/or progression of a cancer, and
 - (iii) identifying said fusion polypeptide that induces said phenotype of interest,
- wherein exposure of said cell to the stabilization compound, e.g., bazedoxifene, or a pharmaceutically acceptable salt thereof, increases, e.g., by at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide prior to exposure to the stabilization compound, e.g., bazedoxifene, or a pharmaceutically acceptable salt thereof, and wherein exposure of said cell to COF1 or COF2, e.g., lenalidomide, or a pharmaceutically acceptable salt thereof, decreases, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, the expression level of said fusion polypeptide relative to the expression level of said fusion polypeptide after exposure to the stabilization compound and prior to exposure to COF1 or COF2, e.g., lenalidomide, or a pharmaceutically acceptable salt thereof.

296. A fusion polypeptide comprising a compound of Formula (III) (COF3)/CRBN (cereblon)-binding polypeptide and a heterologous polypeptide, e.g., a heterologous mammalian, bacterial, or viral polypeptide, wherein the compound of Formula (III) is:



or a pharmaceutically acceptable salt, ester, hydrate, solvate, or tautomer thereof, wherein:

X_1 is CR_3 ;

===== is optionally a double bond when X_1 is CR_3 and R_3 is absent;

each R_1 is independently C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, or halo, or

two R₁ together with the carbon atoms to which they are attached form a 5- or 6- membered heterocyclyl ring, or

two R₁, when on adjacent atoms, together with the atoms to which they are attached form a C₆-C₁₀-aryl or 5- or 6- membered heteroaryl ring comprising 1 to 3 heteroatoms selected from O, N, and S;

R₂ is hydrogen, C₁-C₆-alkyl, ~~C(O)C₁-C₆-alkyl, C(O)(CH₂)₀₋₃-C₆-C₁₀-aryl, C(O)O(CH₂)₀₋₃-C₆-C₁₀-aryl, C₆-C₁₀-aryl, or 5- or 6- membered heteroaryl comprising 1 to 3 heteroatoms selected from O, N, and S, C₃-C₈-carbocyclyl, or 5- to 7- membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein the alkyl is optionally substituted with one or more R₄; and the aryl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R₅; or~~

R₁ and R₂, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6- membered heterocyclyl ring;

R₃ is hydrogen, or R₃ is absent when ~~=====~~ is a double bond;

each R₄ is independently selected from ~~C(O)OR₆, C(O)NR₆R₆, NR₆C(O)R₆, halo, OH, NH₂, cyano, C₆-C₁₀-aryl, 5- or 6- membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, and S, C₃-C₈-carbocyclyl, and 5- to 7- membered heterocyclyl ring comprising 1 to 3 heteroatoms selected from O, N, and S, wherein the aryl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R₇;~~

each R₅ is independently selected from C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₆-alkoxy, C₁-C₆-haloalkyl, C₁-C₆-haloalkoxy, C₁-C₆-hydroxyalkyl, halo, OH, NH₂, cyano, C₃-C₇-carbocyclyl, 5- to 7- membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, C₆-C₁₀-aryl, and 5- or 6- membered heteroaryl comprising 1 to 3 heteroatoms selected from O, N, and S, or

~~two R₅, when on adjacent atoms, together with the atoms to which they are attached form a C₆-C₁₀-aryl or 5- or 6- membered heteroaryl comprising 1 to 3 heteroatoms selected from O, N, and S, optionally substituted with one or more R₁₀; or~~

two R₅, when on adjacent atoms, together with the atoms to which they are attached form a C₅-C₇-carbocyclyl or 5- to 7- membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S optionally substituted with one or more R₁₀;

R₆ and R₆ are each independently hydrogen, C₁-C₆-alkyl, or C₆-C₁₀-aryl;

each R₇ is independently selected from C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₆-alkoxy, C₁-C₆-haloalkyl, C₁-C₆-haloalkoxy, ~~C(O)R₈, (CH₂)₀₋₃C(O)OR₈, C(O)NR₈R₉, NR₈C(O)R₉, NR₈C(O)OR₉, S(O)_pNR₈R₉, S(O)_pR₁₂, (C₁-C₆)hydroxyalkyl, halo, OH, O(CH₂)₁₋₃CN, NH₂, cyano, O(CH₂)₀₋₃-C₆-C₁₀-aryl, adamantyl, O(CH₂)₀₋₃-5- or 6- membered heteroaryl comprising 1 to 3 heteroatoms selected from O, N, and S, C₆-C₁₀-aryl, monocyclic or bicyclic 5- to 10- membered heteroaryl comprising 1 to 3 heteroatoms selected from O, N, and S, C₃-C₇-carbocyclyl, and 5- to 7- membered~~

heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein the alkyl is optionally substituted with one or more R₁₁, and the aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents each independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy, or

two R₇ together with the carbon atom to which they are attached form a =O, or

two R₇, when on adjacent atoms, together with the atoms to which they are attached form a C₆-C₁₀ aryl or 5- or 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from O, N, and S, optionally substituted with one or more R₁₀, or

two R₇ together with the atoms to which they are attached form a C₅-C₇ carbocyclyl or a 5- to 7-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, optionally substituted with one or more R₁₀;

R₈ and R₉ are each independently hydrogen or C₁-C₆ alkyl;

each R₁₀ is independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, halo, OH, NH₂, and cyano, or

two R₁₀ together with the carbon atom to which they are attached form a =O;

each R₁₁ is independently selected from cyano, C₁-C₆ alkoxy, C₆-C₁₀ aryl, and 5- to 7-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein each aryl and heterocyclyl is optionally substituted with one or more substituents each independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, halo, OH, NH₂, and cyano;

R₁₂ is C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₆-C₁₀ aryl, or 5- to 7-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S;

R_x is hydrogen or deuterium;

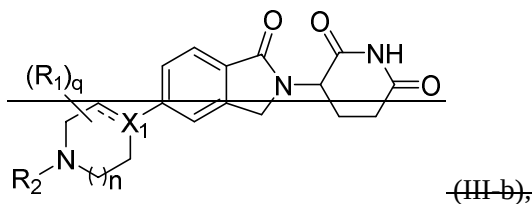
p is 0, 1, or 2;

n is 0, 1, or 2;

y is 1 or 2, wherein n + y ≤ 3; and

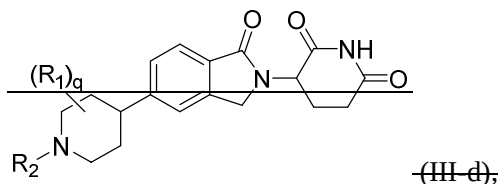
q is 0, 1, 2, 3, or 4.

297. The fusion polypeptide of claim 296, wherein the compound of Formula (III) is a compound of Formula (III-b):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof, wherein X_1 , R_1 , R_2 , n , q , and subvariables thereof are defined as described for Formula (III) in claim 296.

298. The fusion polypeptide of claim 296 or 297, wherein the compound of Formula (III) is a compound of Formula (III-d):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof, wherein R_1 , R_2 , q , and subvariables thereof are defined as described for Formula (III) in claim 296.

299. The fusion polypeptide of any one of claims 296-298, wherein:

- (i) the COF3/CRBN binding polypeptide is fused to the heterologous polypeptide,
- (ii) the COF3/CRBN binding polypeptide and the heterologous polypeptide are linked by a peptide bond,
- (iii) the COF3/CRBN binding polypeptide and the heterologous polypeptide are linked by a bond other than a peptide bond,
- (iv) the heterologous polypeptide is linked directly to the COF3/CRBN binding polypeptide,
- (v) the heterologous polypeptide is linked indirectly to the COF3/CRBN binding polypeptide,
- (vi) the COF3/CRBN binding polypeptide and the heterologous polypeptide are operatively linked via a linker, e.g., a glycine-serine linker, e.g., a linker comprising the amino acid sequence of SEQ ID NO: 28, or
- (vii) the COF3/CRBN binding polypeptide is linked to the C-terminus or N-terminus of the heterologous polypeptide.

300. The fusion polypeptide of any one of claims 296-299, wherein:

- (i) the association of the fusion polypeptide with CRBN in the absence of COF3 is no more than, e.g., 0.01%, 0.1%, 1%, 5%, 10%, 15%, or 20%, of the association of the fusion polypeptide with CRBN in the presence of COF3, e.g., an excess of COF3, e.g., as measured by an assay described herein, e.g., immunoprecipitation, optionally wherein the fusion polypeptide does not bind to CRBN in the absence of COF3;
- (ii) the ubiquitination of the fusion polypeptide in the absence of COF3 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70%, of the ubiquitination of the fusion polypeptide in the presence of COF3, e.g., an excess of COF3, e.g., as measured by an assay described herein, optionally

wherein the fusion polypeptide is ubiquitinated at one or more lysine or methionine residues in the presence of COF3; or

(iii) the degradation of the fusion polypeptide in the absence of COF3 is no more than, e.g., 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, or 70% of the degradation of the fusion polypeptide in the presence of COF3, e.g., an excess of COF3, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis, optionally wherein the degradation of the fusion polypeptide is mediated by ubiquitination in the presence of COF3; optionally wherein the association, ubiquitination, and/or degradation is as measured in a mammalian cell, e.g., a human cell.

301. The fusion polypeptide of any one of claims 296-300, wherein the COF3/CRBN binding polypeptide is between 10 and 95 amino acid residues in length, between 15 and 90 amino acid residues in length, between 20 and 85 amino acid residues in length, between 25 and 80 amino acid residues in length, between 30 and 75 amino acid residues in length, between 35 and 70 amino acid residues in length, between 40 and 65 amino acid residues in length, between 45 and 65 amino acid residues in length, between 50 and 65 amino acid residues in length, or between 55 and 65 amino acid residues in length.

302. The fusion polypeptide of any one of claims 296-301, wherein the COF3/CRBN binding polypeptide comprises a beta turn, a beta hairpin, a beta strand, or an alpha helix, optionally wherein the COF3/CRBN binding polypeptide comprises, from N-terminus to C-terminus, a first beta strand, a beta hairpin, a second beta strand, and a first alpha helix, optionally wherein the COF3/CRBN binding polypeptide comprises, from N-terminus to C-terminus, a first beta strand, a beta hairpin, a second beta strand, a first alpha helix, and a second alpha helix, optionally wherein the beta hairpin and the second alpha helix are separated by no more than 60, 50, 40, or 30 amino acid residues.

303. The fusion polypeptide of any one of claims 296-302, wherein the COF3/CRBN binding polypeptide comprises a COF3/CRBN binding sequence from a naturally occurring polypeptide or a COF3/CRBN binding variant thereof, e.g., a naturally occurring IKZF polypeptide or a COF3/CRBN binding variant thereof, e.g., a naturally occurring IKZF2, or a COF3/CRBN binding variant thereof, optionally wherein the COF3/CRBN binding polypeptide comprises two or more discontinuous sequences from a naturally occurring IKZF polypeptide, e.g., a naturally occurring IKZF2.

304. The fusion polypeptide of any one of claims 296-303, wherein the COF3/CRBN binding polypeptide comprises amino acid residues 130-174 of IKZF2 (numbered according to SEQ ID NO: 21) (e.g., the

COF3/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 113) or a sequence that differs from amino acid residues 130-174 of IKZF2 (numbered according to SEQ ID NO: 21) by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues (e.g., a sequence that differs from amino acid residues 130-174 of SEQ ID NO: 21 by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid residues) (e.g., a sequence having no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, or 40 amino acid substitutions from amino acid residues 130-174 of SEQ ID NO: 21).

305. The fusion polypeptide of any one of claims 296-304, wherein the COF3/CRBN-binding polypeptide comprises amino acid residues 230-243 of IKZF2 (numbered according to SEQ ID NO: 21) (e.g., the COF3/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 114) or a sequence that differs from amino acid residues 230-243 of IKZF2 (numbered according to SEQ ID NO: 21) by no more than 1, 2, 3, 4, 5, or 10 amino acid residues (e.g., a sequence that differs from amino acid residues 230-243 of SEQ ID NO: 21 by no more than 1, 2, 3, 4, 5, or 10 amino acid residues) (e.g., a sequence having no more than 1, 2, 3, 4, 5, or 10 amino acid substitutions from amino acid residues 230-243 of SEQ ID NO: 21).

306. The fusion polypeptide of claim 304 or 305, wherein histidine at position 141 remains unaltered, numbered according to SEQ ID NO: 21.

307. The fusion polypeptide of any one of claims 296-306, wherein:

(i) the COF3/CRBN-binding polypeptide comprises amino acid residues 130-174 of IKZF2 (numbered according to SEQ ID NO: 21), e.g., the COF3/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 113; and/or

(ii) the COF3/CRBN-binding polypeptide comprises amino acid residues 230-243 of IKZF2 (numbered according to SEQ ID NO: 21), e.g., the COF3/CRBN-binding polypeptide comprises the amino acid sequence of SEQ ID NO: 114.

308. The fusion polypeptide of any one of claims 296-307, wherein the COF3/CRBN-binding polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 109.

309. The fusion polypeptide of any one of claims 296-308, wherein the heterologous polypeptide is chosen from a cytoplasmic and/or nuclear polypeptide, or a transmembrane polypeptide, e.g., a heterologous polypeptide in Table 2.

310. The fusion polypeptide of claim 309, wherein the cytoplasmic and/or nuclear polypeptide is selected from the group consisting of a component of the apoptosis pathway (e.g., Caspase 9), a component of a CRISPR/Cas system (e.g., Cas9), a transcription factor (e.g., MITF, c-Myc, STAT3, STAT5, NF-kappaB, beta-catenin, Notch, GLI, or c-JUN), Tet methylcytosine dioxygenase 2 (TET2), FKBP, and Tau.

311. The fusion polypeptide of claim 309, wherein the transmembrane polypeptide is selected from the group consisting of CD62L, CCR1, CCR2, CCR5, CCR7, CCR10, CXCR2, CXCR3, CXCR4, CXCR6, CTLA4, PD1, BTLA, VISTA, CD137L, CD80, CD86, TIGIT, CD3, CD8, CD19, CD22, CD20, BCMA, and a chimeric antigen receptor (CAR).

312. The fusion polypeptide of claim 309, wherein the heterologous polypeptide is selected from the group consisting of a chimeric antigen receptor (CAR), a component of a CRISPR/Cas system (e.g., Cas9), CD8, CD19, and CD22, optionally wherein the heterologous polypeptide is a chimeric antigen receptor (CAR).

313. The fusion polypeptide of claim 312, wherein the CAR comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain (e.g., a primary signaling domain or a costimulatory signaling domain), optionally wherein the primary signaling domain comprises a CD3-zeta stimulatory domain and/or the costimulatory signaling domain comprises an intracellular domain from a costimulatory protein selected from the group consisting of CD27, CD28, 4-1BB (CD137), OX40, GITR, CD30, CD40, ICOS, BAFTR, HVEM, ICAM-1, lymphocyte function-associated antigen-1 (LFA-1), CD2, CDS, CD7, CD287, LIGHT, NKG2C, NKG2D, SLAMF7, NKp80, NKp30, NKp44, NKp46, CD160, B7-H3, and a ligand that specifically binds with CD83.

314. The fusion polypeptide of claim 312, wherein the antigen binding domain binds an antigen selected from the group consisting of CD19; CD123; CD22; CD30; CD171; CS-1; C-type lectin-like molecule-1, CD33; epidermal growth factor receptor variant III (EGFRvIII); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member; B-cell maturation antigen; Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor associated glycoprotein 72 (TAG72); CD38; CD44v6; Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2; Mesothelin; Interleukin-11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21; vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha; Receptor tyrosine-protein kinase ERBB2 (Her2/neu); Mucin-1, cell surface associated (MUC1); epidermal growth factor receptor

(EGFR); neural cell adhesion molecule (NCAM); Prostate; prostatic acid phosphatase (PAP); elongation factor 2 mutated (ELF2M); Ephrin B2; fibroblast activation protein alpha (FAP); insulin-like growth factor 1 receptor (IGF-1 receptor); carbonic anhydrase IX (CAIX); Proteasome (Prosome, Macropain) Subunit, Beta Type, 9 (LMP2); glycoprotein 100 (gp100); oncogene polypeptide consisting of breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type A receptor 2 (EphA2); Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma-associated antigen (HMWMAA); o-acetyl-GD2 ganglioside (OAcGD2); Folate receptor beta; tumor endothelial marker 1 (TEM1/CD248); tumor endothelial marker 7 related (TEM7R); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G-protein-coupled receptor class C group 5, member D (GPRC5D); chromosome X open reading frame 61 (CXORF61); CD97; CD179a; anaplastic lymphoma kinase (ALK); Polysialic acid; placenta-specific 1 (PLAC1); hexasaccharide portion of globoH glycosphingolipid (GloboH); mammary gland differentiation antigen (NY-BR-1); uroplakin 2 (UPK2); Hepatitis A virus cellular receptor 1 (HAVCR1); adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G-protein-coupled receptor 20 (GPR20); lymphocyte antigen 6 complex, locus K 9 (LY6K); Olfactory receptor 51E2 (OR51E2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ESO-1); Cancer/testis antigen 2 (LAGE-1a); Melanoma-associated antigen 1 (MAGE-A1); ETS translocation variant gene 6, located on chromosome 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1); angiopoietin-binding cell surface receptor 2 (Tie-2); melanoma-cancer testis antigen 1 (MAD-CT-1); melanoma-cancer testis antigen 2 (MAD-CT-2); Fos-related antigen 1; tumor protein p53 (p53); p53 mutant; prostatein; surviving; telomerase; prostate carcinoma tumor antigen-1, melanoma antigen recognized by T cells 1; Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); sarcoma translocation breakpoints; melanoma-inhibitor of apoptosis (ML-IAP); ERG (transmembrane protease, serine 2 (TMPRSS2) ETS fusion-gene); N-Acetyl-glucosaminyl-transferase V (NA17); paired box protein Pax-3 (PAX3); Androgen receptor; Cyclin B1; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 1B1 (CYP1B1); CCCTC-Binding Factor (Zinc Finger Protein) Like, Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin-binding protein sp32 (OY-TES1); lymphocyte-specific protein tyrosine kinase (LCK); A kinase anchor protein 4 (AKAP-4); synovial sarcoma, X-breakpoint 2 (SSX2); Receptor for Advanced Glycation Endproducts (RAGE-1); renal ubiquitous 1 (RU1); renal ubiquitous 2 (RU2); legumain; human papilloma-virus E6 (HPV E6); human papilloma-virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); Fc fragment of IgA receptor (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module containing mucin-like hormone receptor like 2 (EMR2); lymphocyte antigen 75 (LY75); Glypican 3 (GPC3); Fc receptor like 5 (FCRL5); and immunoglobulin lambda-like polypeptide 1 (IGLL1), optionally wherein the antigen-binding domain binds an antigen chosen from CD19, CD22, BCMA, CD20, CD123, EGFRvIII, or mesothelin.

315. The fusion polypeptide of any one of claims 296-314, wherein the fusion polypeptide further comprises a degradation domain, wherein the degradation domain is separated from the COF3/CRBN binding polypeptide and the heterologous polypeptide by a heterologous protease cleavage site.

316. The fusion polypeptide of claim 315, wherein the fusion polypeptide comprises, from N terminus to C-terminus:

- i) the degradation domain, the heterologous protease cleavage site, the heterologous polypeptide, and the COF3/CRBN binding polypeptide;
- ii) the degradation domain, the heterologous protease cleavage site, the COF3/CRBN binding polypeptide, and the heterologous polypeptide;
- iii) the COF3/CRBN binding polypeptide, the heterologous polypeptide, the heterologous protease cleavage site, and the degradation domain; or
- iv) the heterologous polypeptide, and the COF3/CRBN binding polypeptide, the heterologous protease cleavage site, and the degradation domain.

317. The fusion polypeptide of claim 315 or 316, wherein the degradation domain has a first state associated with a first level of expression of the fusion polypeptide and a second state associated with a second level of expression of the fusion polypeptide, wherein the second level is increased, e.g., by at least 2-, 3-, 4-, 5-, 10-, 20- or 30-fold over the first level in the presence of a stabilization compound, optionally wherein:

in the absence of the stabilization compound, the fusion polypeptide is degraded by a cellular degradation pathway, e.g., at least 50%, 60%, 70%, 80%, 90% or greater of the fusion polypeptide is degraded, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis; or

in the presence of the stabilization compound:

- i) the degradation domain assumes a conformation more resistant to cellular degradation relative to a conformation in the absence of the stabilization compound; or
- ii) the conformation of the fusion polypeptide is more permissive to cleavage at the heterologous protease cleavage site relative to a conformation in the absence of the stabilization compound.

318. The fusion polypeptide of any one of claims 315-317, wherein the degradation domain is chosen from an estrogen receptor (ER) domain, an FKB protein (FKBP) domain, or a dihydrofolate reductase (DHFR) domain.

319. The fusion polypeptide of any one of claims 315-318, wherein the heterologous protease cleavage site is cleaved by a mammalian intracellular protease selected from the group consisting of furin, PCSK1, PCSK5, PCSK6, PCSK7, cathepsin B, Granzyme B, Factor XA, Enterokinase, genenase, sortase, precision protease, thrombin, TEV protease, and elastase 1.

320. The fusion polypeptide of any one of claims 315-318, wherein the heterologous protease cleavage site is cleaved by a mammalian extracellular protease selected from the group consisting of Factor XA, Enterokinase, genenase, sortase, precession protease, thrombin, TEV protease, and elastase 1.

321. A nucleic acid molecule encoding the fusion polypeptide of any one of claims 296-320.

322. A vector comprising the nucleic acid molecule of claim 321, optionally wherein the vector is a viral vector, e.g., a lentiviral vector, a retroviral vector, or an adenoviral vector.

323. A cell, e.g., a host cell, comprising the fusion polypeptide of any one of claims 296-320, the nucleic acid molecule of claim 321, or the vector of claim 322, optionally wherein the cell is a T cell, a NK cell, or a tumor cell.

324. A pharmaceutical composition comprising the fusion polypeptide of any one of claims 296-320 or the cell of claim 323, and a pharmaceutically acceptable carrier, excipient or stabilizer.

325. A method of making the cell of claim 323, said method comprising providing a cell, e.g., an immune effector cell, with the nucleic acid molecule of claim 321 or the vector of claim 322.

326. A method of degrading a fusion polypeptide, comprising contacting the fusion polypeptide of any one of claims 296-320 or a cell comprising said fusion polypeptide with COF3, optionally wherein in the presence of COF3, the expression level of said fusion polypeptide is substantially decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of said fusion polypeptide in the absence of COF3, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis, optionally wherein:

the fusion polypeptide or the cell is contacted with COF3 *ex vivo*, or

the fusion polypeptide or the cell is contacted with COF3 *in vivo*.

327. A method of regulating the expression of a fusion polypeptide, comprising:

i) contacting the fusion polypeptide of any one of claims 315-320 or a cell comprising said fusion polypeptide with a stabilization compound, optionally wherein in the presence of the stabilization compound:

a) the degradation domain assumes a conformation more resistant to cellular degradation relative to a conformation in the absence of the stabilization compound;

b) the conformation of the fusion polypeptide is more permissive to cleavage at the heterologous protease cleavage site relative to a conformation in the absence of the stabilization compound; or

c) the expression level of the fusion polypeptide is increased by at least, e.g., 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, compared to the expression level of the fusion polypeptide in the absence of the stabilization compound, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis,

optionally wherein the fusion polypeptide or the cell is contacted with the stabilization compound *ex vivo* or *in vivo*.

328. The method of claim 327, further comprising, after step i):

ii) contacting the fusion polypeptide of any one of claims 315-320 or a cell comprising said fusion polypeptide with COF3, optionally wherein in the presence of COF3, the expression level of the fusion polypeptide is substantially decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of the fusion polypeptide after step i) and before step ii), e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis, optionally wherein the fusion polypeptide or the cell is contacted with COF3 *ex vivo* or *in vivo*.

329. A method of making a cell, comprising:

i) providing a cell, e.g., an immune effector cell, with a nucleic acid molecule encoding the fusion polypeptide of any one of claims 296-320; and

ii) contacting the cell *ex vivo* with COF3, optionally wherein:

in the presence of COF3, the expression level of the fusion polypeptide is substantially decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of the fusion polypeptide in the absence of COF3, e.g., as measured by an assay described herein, e.g., a Western blot analysis or a flow cytometry analysis.

330. A method of treating a subject having a disease associated with expression of a tumor antigen, comprising:

i) contacting a cell comprising the fusion polypeptide of any one of claims 296-314 with COF3 *ex vivo*, optionally wherein:

in the presence of COF3, the expression level of the fusion polypeptide is decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of the fusion polypeptide before the cell is contacted with COF3 *ex vivo*, and

ii) administering to the subject an effective amount of the cell, optionally wherein the method further comprises after step i) and prior to step ii):

reducing the amount of COF3 contacting the cell, e.g., inside and/or surrounding the cell, thereby treating the disease.

331. The method of claim 330, further comprising after step ii):

iii) administering to the subject an effective amount of COF3, optionally wherein the administration of COF3 decreases, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step ii) and prior to step iii), optionally wherein:

a) the subject has developed, is developing, or is anticipated to develop an adverse reaction,

- b) the administration of COF3 is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or
- c) the administration of COF3 reduces or prevents an adverse effect.

332. The method of claim 331, further comprising after step iii):

- iv) discontinuing the administration of COF3, optionally wherein discontinuing the administration of COF3 increases, e.g., by at least about 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step iii) and prior to step iv) (e.g., wherein discontinuing the administration of COF3 restores the expression level of the fusion polypeptide to the expression level after step ii) and prior to step iii)), optionally wherein:
 - a) the subject has relapsed, is relapsing, or is anticipated to relapse,
 - b) the discontinuation of the administration of COF3 is in response to a tumor relapse in the subject, or in response to an anticipation of a relapse in the subject, and/or
 - c) the discontinuation of the administration of COF3 treats or prevents a tumor relapse.

333. The method of claim 332, further comprising after step iv):

- v) repeating step iii) and/or iv),
- thereby treating the disease.

334. A method of treating a subject having a disease associated with expression of a tumor antigen, comprising:

- i) administering to the subject an effective amount of a cell comprising the fusion polypeptide of any one of claims 296-314, optionally wherein the cell is contacted with COF3 *ex vivo* before administration, optionally wherein: in the presence of COF3, the expression level of the fusion polypeptide is decreased, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, relative to the expression level of the fusion polypeptide before the cell is contacted with COF3 *ex vivo*, optionally wherein after the cell is contacted with COF3 *ex vivo* and before the cell is administered to the subject, the amount of COF3 contacting the cell, e.g., inside and/or surrounding the cell, is reduced,
- thereby treating the disease.

335. The method of claim 334, wherein the cell is not contacted with COF3 *ex vivo* before administration.

336. The method of claim 334 or 335, further comprising after step i):

- ii) administering to the subject an effective amount of COF3, optionally wherein the administration of COF3 decreases, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step i) and prior to step ii), optionally wherein:
 - a) the subject has developed, is developing, or is anticipated to develop an adverse reaction,

- b) the administration of COF3 is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or
- c) the administration of COF3 reduces or prevents an adverse effect.

337. The method of claim 336, further comprising after step ii):

- iii) discontinuing the administration of COF3, optionally wherein discontinuing the administration of COF3 increases, e.g., by at least about 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step ii) and prior to step iii) (e.g., wherein discontinuing the administration of COF3 restores the expression level of the fusion polypeptide to the expression level after step i) and prior to step ii)), optionally wherein:
 - a) the subject has relapsed, is relapsing, or is anticipated to relapse,
 - b) the discontinuation of the administration of COF3 is in response to a tumor relapse in the subject, or in response to an anticipation of a relapse in the subject, and/or
 - c) the discontinuation of the administration of COF3 treats or prevents a tumor relapse.

338. The method of claim 337, further comprising after step iii):

- iv) repeating step ii) and/or iii),
- thereby treating the disease.

339. A method of treating a subject having a disease associated with expression of a tumor antigen, comprising:

- i) administering an effective amount of COF3 to the subject, wherein the subject comprises a cell comprising the fusion polypeptide of any one of claims 296-314, optionally wherein the administration of COF3 decreases, e.g., by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 percent, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide before the administration of COF3, optionally wherein:
 - a) the subject has developed, is developing, or is anticipated to develop an adverse reaction,
 - b) the administration of COF3 is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or
 - c) the administration of COF3 reduces or prevents an adverse effect.

340. The method of claim 339, further comprising after step i):

- ii) discontinuing the administration of COF3, optionally wherein discontinuing the administration of COF3 increases, e.g., by at least about 1.5-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, or 50-fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step i) and prior to step ii) (e.g., wherein discontinuing the administration of COF3 restores the expression level of the fusion polypeptide to the expression level before the administration of COF3), optionally wherein:
 - a) the subject has relapsed, is relapsing, or is anticipated to relapse,

- b) the discontinuation of the administration of COF3 is in response to a tumor relapse in the subject, or in response to an anticipation of a relapse in the subject, and/or
- c) the discontinuation of the administration of COF3 treats or prevents a tumor relapse.

341. The method of claim 340, further comprising after step ii):

- iii) repeating step i) and/or ii),
- thereby treating the disease.

342. A method of treating a subject having a disease associated with expression of a tumor antigen, comprising:

- i) administering to the subject:

- (1) a stabilization compound, and

- (2) an effective amount of a cell comprising the fusion polypeptide of any one of claims 315-320, or an effective amount of a cell comprising the fusion polypeptide of any one of claims 315-320, optionally wherein:

the expression level of the fusion polypeptide in the presence of the stabilization compound is e.g., at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, higher than the expression level of the fusion polypeptide in the absence of the stabilization compound,

thereby treating the disease.

343. The method of claim 342, further comprising after step i):

- ii) discontinuing the administration of the stabilization compound, optionally wherein discontinuing the administration of the stabilization compound reduces, e.g., at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression of the fusion polypeptide after step i) and prior to step ii), optionally wherein:

- a) the subject responded to the treatment of step i) (e.g., the subject has a complete response to the treatment of step i), the subject shows a shrinkage in tumor mass, the subject shows a decrease in tumor cells, or the treatment of step i) is effective in the subject), and/or

- b) the discontinuation of the administration of the stabilization compound is in response to a response of the subject to the treatment of step i) (e.g., the subject has a complete response to the treatment of step i), the subject shows a shrinkage in tumor mass, the subject shows a decrease in tumor cells, or the treatment of step i) is effective in the subject).

344. The method of claim 342, further comprising after step i):

- iii) discontinuing the administration of the stabilization compound, optionally wherein discontinuing the administration of the stabilization compound reduces, e.g., at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression of the fusion polypeptide after step i) and prior to step ii), optionally wherein:

- a) the subject has developed, is developing, or is anticipated to develop an adverse reaction,

b) the discontinuation of the administration of the stabilization compound is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or

c) the discontinuation of the administration of the stabilization compound reduces or prevents an adverse effect.

345. The method of claim 342, further comprising after step i):

iv) discontinuing the administration of the stabilization compound and administering to the subject an effective amount of COF3, optionally wherein step iv) reduces, e.g., at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression of the fusion polypeptide after step i) and prior to step iv), optionally wherein:

a) the subject has developed, is developing, or is anticipated to develop an adverse reaction;

b) step iv) is in response to an occurrence of an adverse reaction in the subject, or in response to an anticipation of an occurrence of an adverse reaction in the subject, and/or

c) step iv) reduces or prevents an adverse effect;

optionally wherein the adverse effect is an acute toxicity.

346. The method of claim 345, further comprising after step iv):

v) discontinuing the administration of COF3, e.g., after the amount of cells expressing the fusion polypeptide on the surface is smaller than a pre-defined value, for, e.g., 1 day, 5 days, 10 days, or 15 days.

347. The method of any one of claims 343-346, further comprising after step ii), iii), iv), or v):

vi) administering an effective amount of a stabilization compound, optionally wherein the administration of the stabilization compound increases, e.g., by at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, the expression level of the fusion polypeptide relative to the expression level of the fusion polypeptide after step ii), iii), iv), or v) and prior to step vi), optionally wherein:

a) the subject has relapsed, is relapsing, or is anticipated to relapse;

b) the administration of the stabilization compound is in response to a tumor relapse in the subject, or in response to an anticipation of a relapse in the subject, and/or

c) the administration of the stabilization compound treats or prevents a tumor relapse.

348. The method of claim 347, further comprising after step vi):

vii) repeating step iii), iv), v), or vi);

thereby treating the disease.

349. The method of any one of claims 342-348, further comprising prior to step i):

viii) contacting the cell with a stabilization compound *ex vivo*, optionally wherein the expression level of the fusion polypeptide in the presence of the stabilization compound is e.g., at least about 1.5, 2, 3, 4, 5, 10, 20, 30, 40, or 50 fold, higher than the expression level of the fusion polypeptide in the absence of the stabilization compound.

350. The method of any one of claims 342-348, wherein the cell is not contacted with the stabilization compound *ex vivo* before administration.

351. The method of any one of claims 330-350, wherein the disease associated with expression of a tumor antigen is a cancer.

352. The method of claim 351, wherein the cancer is mesothelioma (e.g., malignant pleural mesothelioma), e.g., in a subject who has progressed on at least one prior standard therapy; lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, squamous cell lung cancer, or large cell lung cancer); pancreatic cancer (e.g., pancreatic ductal adenocarcinoma, or metastatic pancreatic ductal adenocarcinoma (PDA), e.g., in a subject who has progressed on at least one prior standard therapy); esophageal adenocarcinoma, ovarian cancer (e.g., serous epithelial ovarian cancer, e.g., in a subject who has progressed after at least one prior regimen of standard therapy); breast cancer, colorectal cancer, bladder cancer or any combination thereof.

353. The method of claim 351, wherein the cancer is a hematological cancer chosen from: chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), multiple myeloma, acute lymphoid leukemia (ALL), Hodgkin lymphoma, B-cell acute lymphoid leukemia (BALL), T-cell acute lymphoid leukemia (TALL), small lymphocytic leukemia (SLL), B-cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B-cell lymphoma (DLBCL), DLBCL associated with chronic inflammation, chronic myeloid leukemia, myeloproliferative neoplasms, follicular lymphoma, pediatric follicular lymphoma, hairy cell leukemia, small cell- or a large cell follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma (extranodal marginal zone lymphoma of mucosa associated lymphoid tissue), Marginal zone lymphoma, myelodysplasia, myelodysplastic syndrome, non-Hodgkin lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, splenic lymphoma/leukemia, splenic diffuse red pulp small B-cell lymphoma, hairy cell leukemia variant, lymphoplasmacytic lymphoma, a heavy chain disease, plasma cell myeloma, solitary plasmocytoma of bone, extraosseous plasmocytoma, nodal marginal zone lymphoma, pediatric nodal marginal zone lymphoma, primary cutaneous follicle center lymphoma, lymphomatoid granulomatosis, primary mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, ALK+ large B-cell lymphoma, large B-cell lymphoma arising in HHV8 associated multicentric Castleman disease, primary effusion lymphoma, B-cell lymphoma, acute myeloid leukemia (AML), or unclassifiable lymphoma.