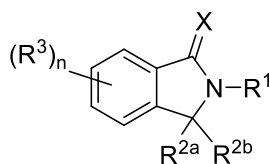


What is claimed is:

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;

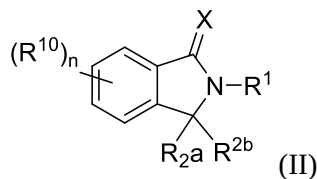
each R⁷ is independently halo, oxo, cyano, -OR^B, -N(R^C)(R^D), -C(O)N(R^C)(R^D), or -N(R^C)C(O)R^A;

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.