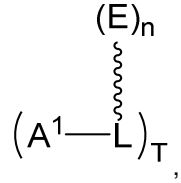
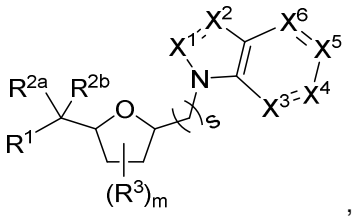
compositions including such conjugates and uses of such conjugates in the treatment of disorders associated with dysregulation or overexpression of CD73 (e.g., cancer, fibrosis, or a viral infection).

In one aspect, the disclosure provides a conjugate, or a pharmaceutically acceptable salt thereof, described by formula (M-I):



(M-I)

wherein A^1 has the structure of formula (A):

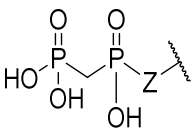
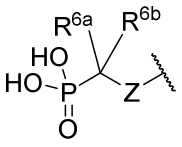


(A)

m is 0, 1, 2, 3, 4, 5, or 6;

s is 0 or 1;

each of X^1, X^2, X^3, X^4, X^5, and X^6 is, independently, N, CR^4, or C-Y-R^5, wherein at least one of X^1, X^2, X^3, X^4, X^5, and X^6 is C-Y-R^5 and R^5 is a bond to L;

R^1 is  or ;

Z is O, S, or sulfonyl;

each of R^{2a} and R^{2b} is, independently, H, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl;

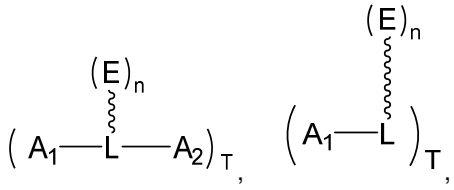
each R^3 is, independently, OH, SH, halogen, optionally substituted amino, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl;

R^4 is H, halogen, OH, SH, optionally substituted amino, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl;

each of R^{6a} and R^{6b} is, independently, H, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl;

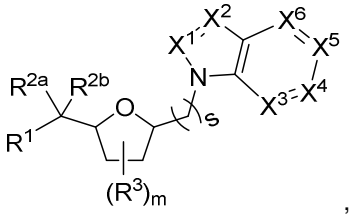
Y is a first linker;
L is a second linker;
n is 1 or 2;
each E comprises an Fc domain monomer;
T is an integer from 1 to 20; and
the squiggly line indicates that L is covalently attached to E.

In an example, the disclosure features a conjugate, or a pharmaceutically acceptable salt thereof, described by formula (D-I) or (M-I):



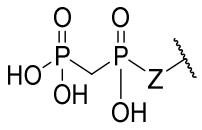
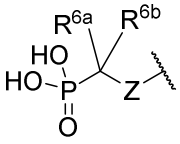
(D-I) (M-I)

wherein each of A^1 and A^2, independently, has the structure of formula (A):



(A)

m is 0, 1, 2, 3, 4, 5, or 6;
s is 0 or 1;
each of X^1, X^2, X^3, X^4, X^5, and X^6 is, independently, N, CR^4, or C-Y-R^5, wherein at least one of X^1, X^2, X^3, X^4, X^5, and X^6 is C-Y-R^5 and R^5 is a bond to L;

R^1 is  or ;

Z is O, S, or sulfonyl;
each of R^{2a} and R^{2b} is, independently, H, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl;
each R^3 is, independently, OH, SH, halogen, optionally substituted amino, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl;

R^4 is H, halogen, OH, SH, optionally substituted amino, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl;

each of R^{6a} and R^{6b} is, independently, H, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl;

Y is a first linker;

L is a second linker;

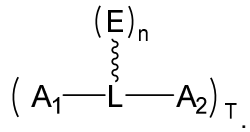
n is 1 or 2;

each E includes an Fc domain monomer;

T is an integer from 1 to 20; and

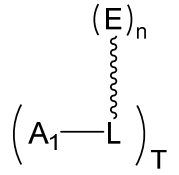
the squiggly line indicates that L is covalently attached to E.

In some examples, the conjugate is described by formula (D-I):



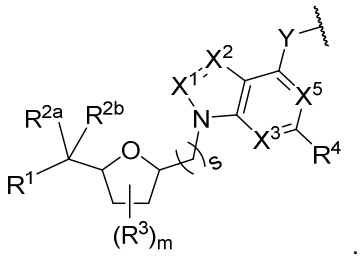
(D-I)

In some examples, the conjugate is described by formula (M-I):



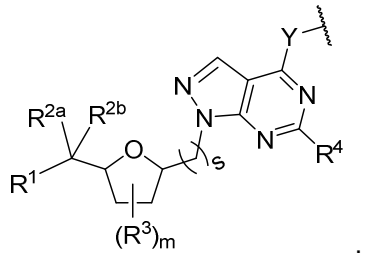
(M-I)

In some examples, A^1 and A^2 have the structure of formula (A-I):



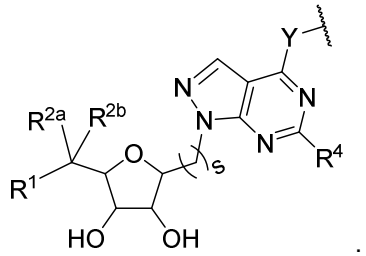
(A-I)

In some examples, A^1 and A^2 each have the structure of formula (A-Ia):



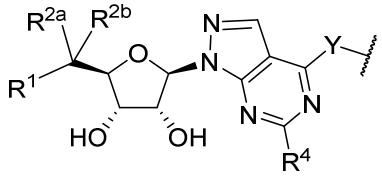
(A-Ia)

In some examples, A^1 and A^2 each have the structure of formula (A-Ib):



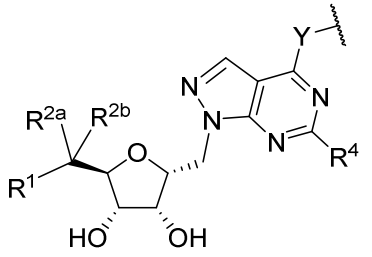
(A-Ib)

In some examples, A^1 and A^2 each have the structure of formula (A-Ib-1):



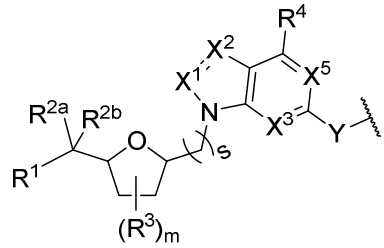
(A-Ib-1)

In some examples, A^1 and A^2 each have the structure of formula (A-Ib-2):



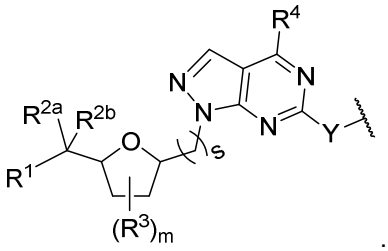
(A-Ib-2)

In some examples, A^1 and A^2 each have the structure of formula (A-II):



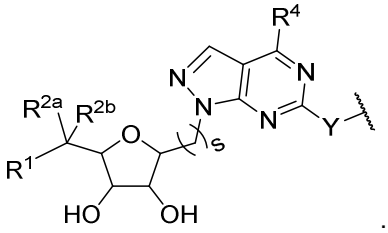
(A-II)

In some examples, A^1 and A^2 each have the structure of formula (A-IIa):



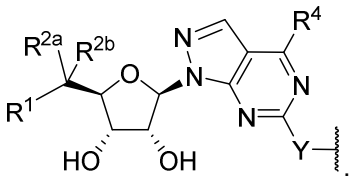
(A-IIa)

In some examples, A^1 and A^2 each have the structure of formula (A-IIb):



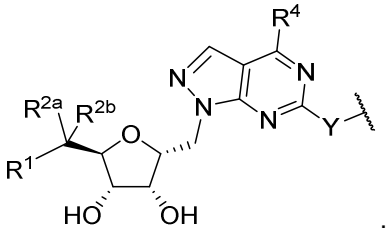
(A-IIb)

In some examples, A^1 and A^2 each have the structure of formula (A-IIb-1):



(A-IIb-1)

In some examples, A^1 and A^2 each have the structure of formula (A-IIb-2):

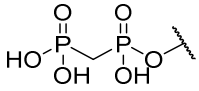


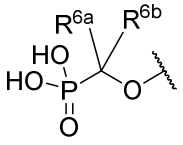
(A-IIb-2)

In some examples, s is 0. In some examples, s is 1.

In some examples, each of R^{2a} and R^{2b} is, independently, H, optionally substituted C_1-C_{20} alkyl, or optionally substituted C_1-C_{20} heteroalkyl. In some examples, each of R^{2a} and R^{2b} is H.

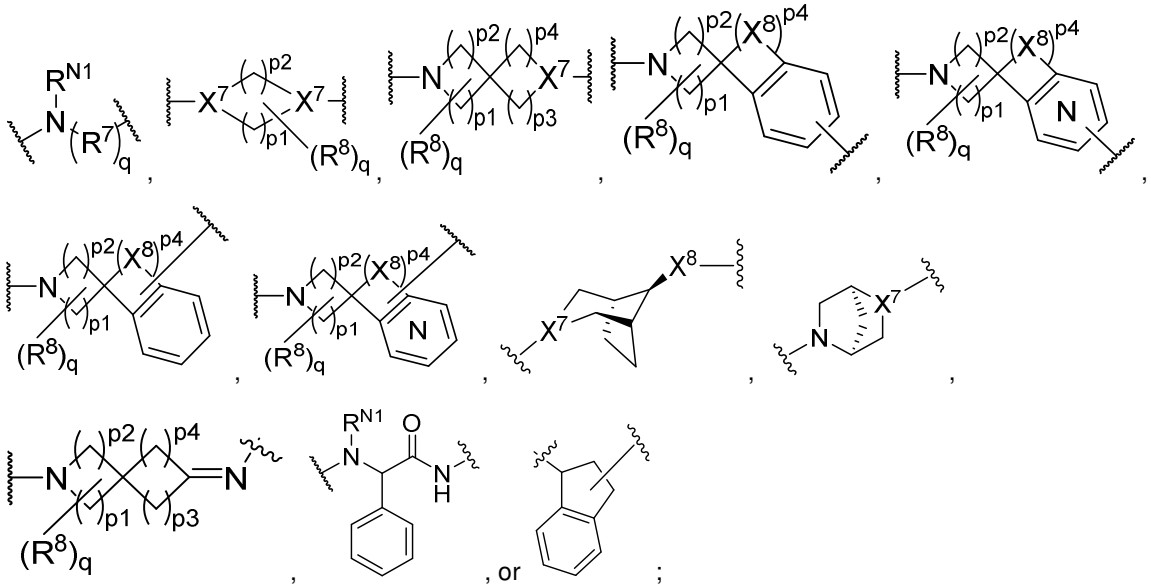
In some examples, R^4 is H, halogen, OH, SH, optionally substituted amino, optionally substituted C_1-C_{20} alkyl, or optionally substituted C_1-C_{20} heteroalkyl. In some examples, R^4 is halogen. In some examples, R^4 is Cl.

In some examples, R^1 is .

In some examples, R^1 is .

In some examples, each of R^{6a} and R^{6b} is, independently, H, optionally substituted C_1-C_{20} alkyl, or optionally substituted C_1-C_{20} heteroalkyl. In some examples, each of R^{6a} and R^{6b} is, independently, H, -CH_3, -CH_2CH_3, -CH_2OH, -CH_2OCH_3 -CH_2CH_2OH, or -$CH_2CH_2OCH_3$. In some examples, each of R^{6a} and R^{6b} is H.

In some examples Y is:



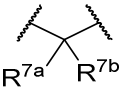
each of p1, p2, p3, and p4 is, independently, 0, 1, 2, 3, or 4;

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

each X^7 is, independently, N or CH;

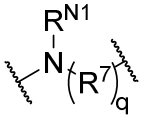
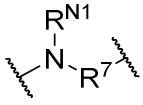
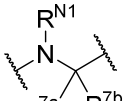
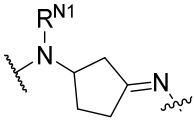
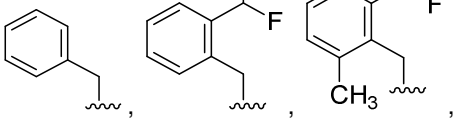
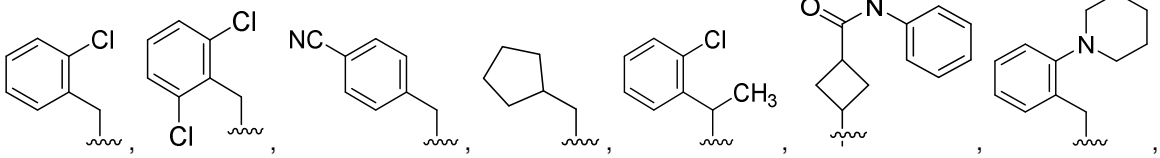
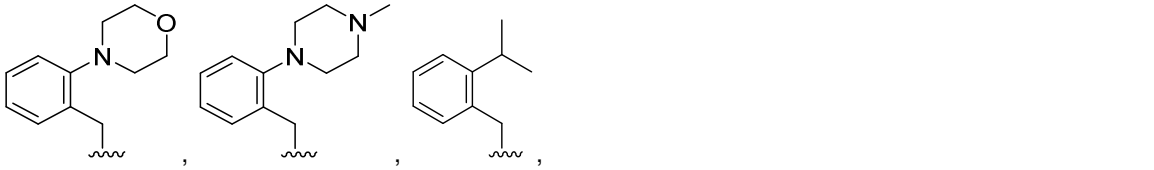
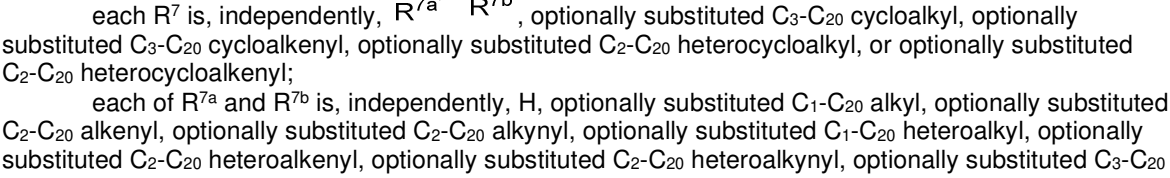
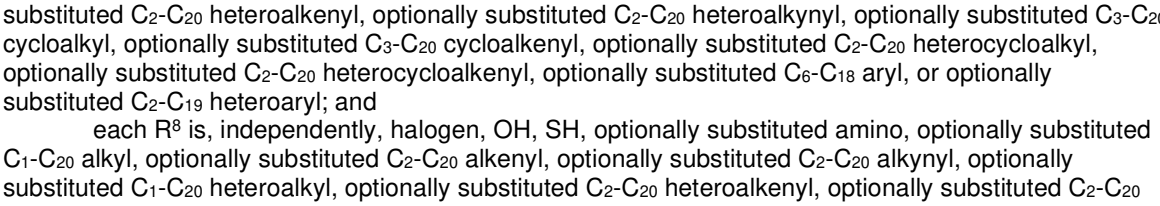
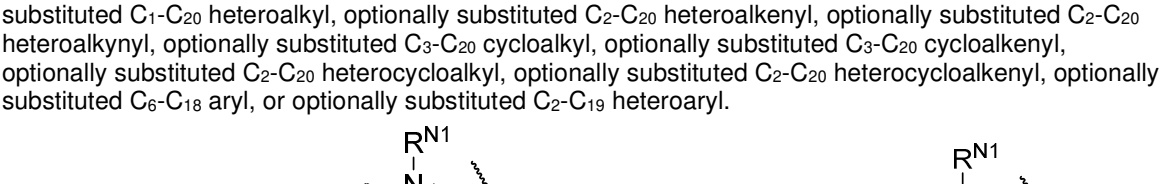
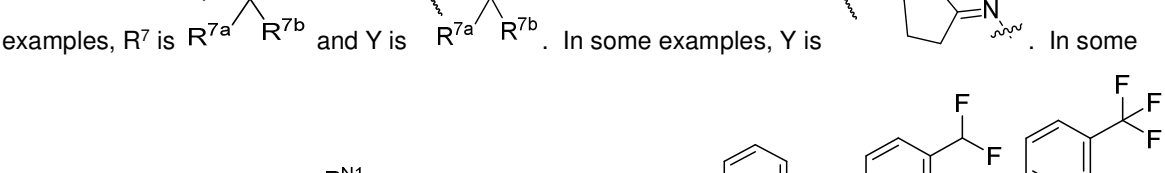
each X^8 is, independently, O, NH, CH_2, or C(=O);

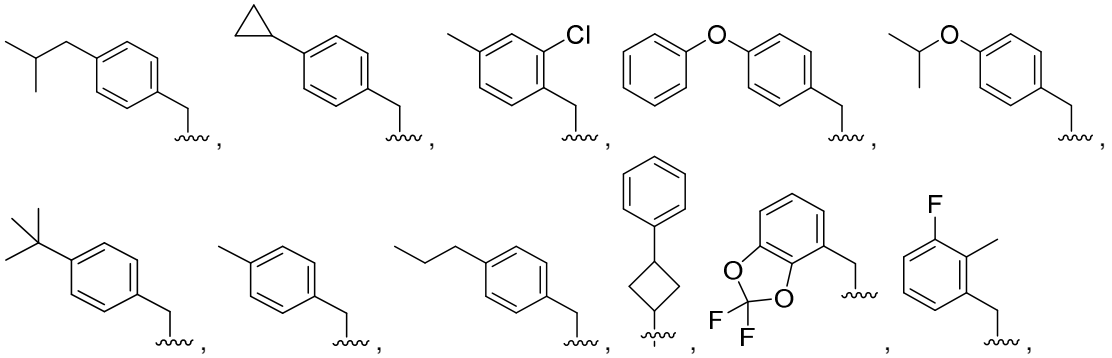
R^{N1} is H, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, optionally substituted C_2-C_{19} heteroaryl, optionally substituted C_1-C_{20} alkaryl, or optionally substituted C_1-C_{20} alkylcycloalkyl;

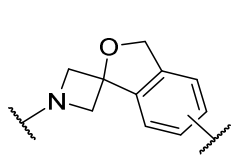
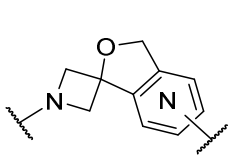
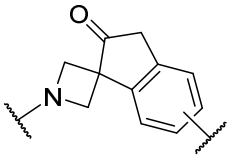
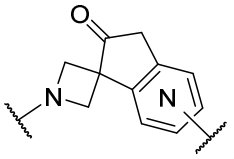
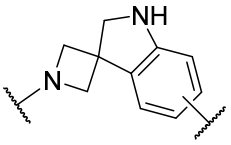
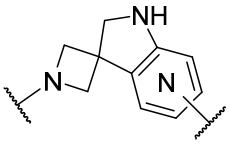
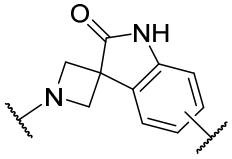
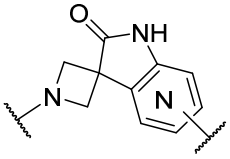
each R^7 is, independently, , optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, or optionally substituted C_2-C_{20} heterocycloalkenyl;

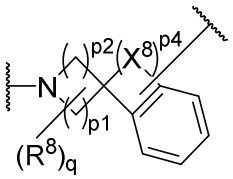
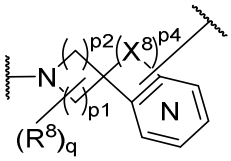
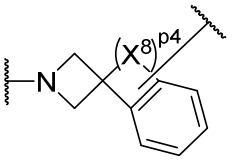
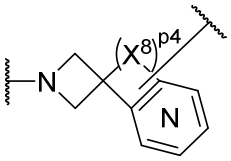
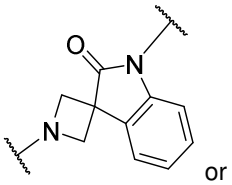
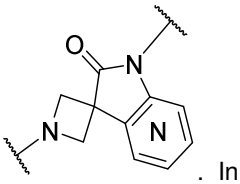
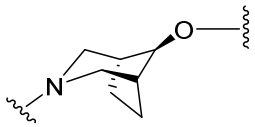
each of R^{7a} and R^{7b} is, independently, H, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl; and

each R^8 is, independently, halogen, OH, SH, optionally substituted amino, optionally substituted C_1-C_{20} alkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_3-C_{20} cycloalkenyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_2-C_{20} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, or optionally substituted C_2-C_{19} heteroaryl.

In some examples, Y is . In some examples, q is 1 and Y is . In some examples, R^7 is  and Y is . In some examples, Y is . In some examples, q is 0 and Y is . In some examples, R^{N1} is H, , , , , , , , , , , , , , ,



In some examples, Y is  or . In some examples, Y is  or . In some examples, Y is  or . In some examples, Y is .

In some examples, L includes one or more optionally substituted C_1-C_{40} alkylene, optionally substituted C_1-C_{40} heteroalkylene, optionally substituted C_1-C_{40} alkoxylene, optionally substituted C_2-C_{20} alkenylene, optionally substituted C_2-C_{20} heteroalkenylene, optionally substituted C_2-C_{20} alkynylene, optionally substituted C_2-C_{20} heteroalkynylene, optionally substituted C_3-C_{20} cycloalkylene, optionally substituted C_2-C_{20} heterocycloalkylene, optionally substituted C_4-C_{20} cycloalkenylene, optionally substituted C_4-C_{20} heterocycloalkenylene, optionally substituted C_8-C_{20} cycloalkynylene, optionally substituted C_8-C_{20} heterocycloalkynylene, optionally substituted C_5-C_{15} arylene, optionally substituted C_2-C_{15} heteroarylene, O, S, NR^i, P, carbonyl, thiocarbonyl, sulfonyl, phosphate, phosphoryl, or imino,

wherein R^i is H, optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_2-C_{20} alkenyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} alkynyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_3-C_{20} cycloalkyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C_4-C_{20} cycloalkenyl, optionally substituted C_4-C20 heterocycloalkenyl, optionally substituted C_8-C_{20} cycloalkynyl, optionally substituted C_8-C_{20} heterocycloalkynyl, optionally substituted C_5-C_{15} aryl, or optionally substituted C_2-C_{15} heteroaryl.

In some examples, L is oxo substituted. In some examples, L includes between 1 and 250 atoms. In some examples, L is capable of forming an amide, a carbamate, a sulfonyl, or a urea linkage.

In some examples, L is described by the formula:

$$J^1\text{-}(Q^1)_g\text{-}(T^1)_h\text{-}(Q^2)_i\text{-}(T^2)_j\text{-}(Q^3)_k\text{-}(T^3)_l\text{-}(Q^4)_m\text{-}(T^4)_n\text{-}(Q^5)_o\text{-}J^2$$

wherein J^1 is a bond attached to A_1;

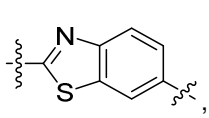
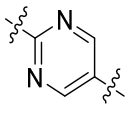
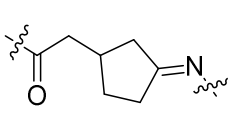
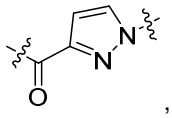
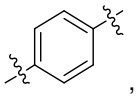
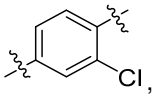
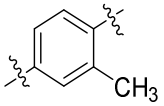
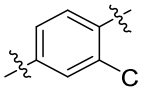
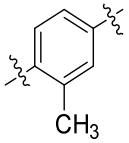
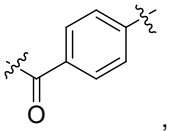
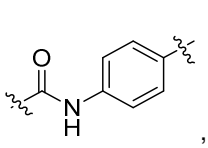
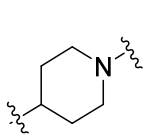
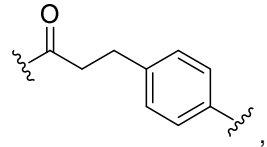
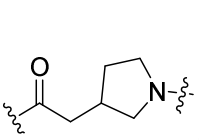
J^2 is a bond attached to E or is a functional group capable of reacting with a functional group conjugated to E;

each of Q^1, Q^2, Q^3, Q^4, and Q^5 is, independently, optionally substituted C1-C40 alkylene, optionally substituted C1-C40 heteroalkylene, optionally substituted C1-C40 alkoxylene, optionally substituted C2-C20 alkenylene, optionally substituted C2-C20 heteroalkenylene, optionally substituted C2-C20 alkynylene, optionally substituted C2-C20 heteroalkynylene, optionally substituted C3-C20 cycloalkylene, optionally substituted C_2-C_{20} heterocycloalkylene, optionally substituted C4-C20 cycloalkenylene, optionally substituted C4-C20 heterocycloalkenylene, optionally substituted C8-C20 cycloalkynylene, optionally substituted C8-C20 heterocycloalkynylene, optionally substituted C5-C15 arylene, or optionally substituted C2-C15 heteroarylene;

each of T^1, T^2, T^3, T^4 is, independently, O, S, NR^i, P, carbonyl, thiocarbonyl, sulfonyl, phosphate, phosphoryl, imino, or oximo;

R^i is H, optionally substituted C1-C20 alkyl, optionally substituted C1-C20 heteroalkyl, optionally substituted C2-C20 alkenyl, optionally substituted C2-C20 heteroalkenyl, optionally substituted C2-C20 alkynyl, optionally substituted C2-C20 heteroalkynyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C_2-C_{20} heterocycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C5-C15 aryl, or optionally substituted C2-C15 heteroaryl; and

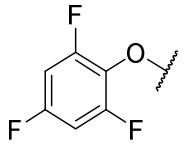
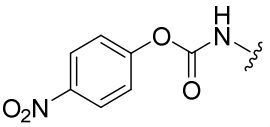
each of g, h, i, j, k, l, m, n, and o is, independently, 0, 1, or 2.

In some examples, Q^1 is , , , , , , , , , , , , , or .

In some examples, Q^2 is optionally substituted C_1-C_{40} alkylene, optionally substituted C_1-C_{40} heteroalkylene, optionally substituted C_1-C_{40} alkoxylene, or optionally substituted C_2-C_{15} heteroarylene.

In some examples, Q^3 is optionally substituted C_2-C_{15} heteroarylene.

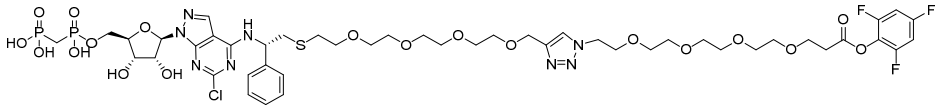
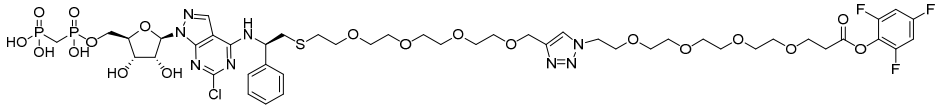
In some examples, Q^4 is optionally substituted C_1-C_{40} alkylene, optionally substituted C_1-C_{40} heteroalkylene, or optionally substituted C_1-C_{40} alkoxylene.

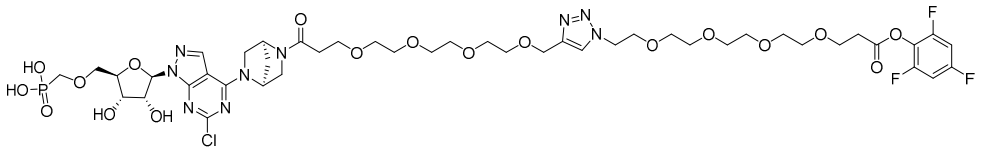
In some examples, J^2 is  or .

The disclosure features an intermediate (Int) of Table 1. These intermediates include one or more inhibitors of CD73 and a linker and may be used in the synthesis of a conjugate described herein. Intermediates of Table 1 may be conjugated to, for example, an Fc domain or Fc domain monomer (e.g., by way of a linker) by any suitable methods known to those of skill in the art, including any of the methods described or exemplified herein. In some examples, the conjugate includes E, wherein E is an Fc domain monomer or an Fc domain. In preferred examples, one or more nitrogen atoms of one or more surface exposed lysine residues of E or one or more sulfur atoms of one or more surface exposed cysteines in E is covalently conjugated to a linker (e.g., a PEG_2-PEG_{20} linker). The linker conjugated to E may be functionalized such that it may react to form a covalent bond with any of the Ints described herein (e.g., an Int of Table 1). In preferred examples, E is conjugated to a linker functionalized with an azido group and the Int (e.g., an Int of Table 1) is functionalized with an alkyne group. Conjugation (e.g., by click chemistry) of the linker-azido of E and linker-alkyne of the Int forms a conjugate of the disclosure. In yet other examples, E is conjugated to a linker functionalized with an alkyne group and the Int (e.g., an Int of Table 1) is functionalized with an azido group. Conjugation (e.g., by click chemistry) of the linker-alkyne of E and the linker-azido of the Int forms a conjugate of the disclosure. In yet other examples, the Int (e.g., an Int of Table 2) is functionalized with a phenyl ester group (e.g., a trifluorophenyl ester group or a tetrafluorophenyl ester group). Conjugation (e.g., by acylation) of E and the linker-phenyl ester (e.g., trifluorophenyl ester or tetrafluorophenyl ester) of the Int forms a conjugate of the disclosure. Conjugation (e.g., by acylation) of E and the linker-phenyl ester (e.g., trifluorophenyl ester or tetrafluorophenyl ester) of the Int is conducted by methods described herein or known in the art.

The disclosure further features a composition (e.g., a pre-conjugation intermediate) having the structure of an Int of Table 1 .

Table 1. Intermediates

Intermediate	Structure
Int-1	
Int-2	

Intermediate	Structure
Int-335	

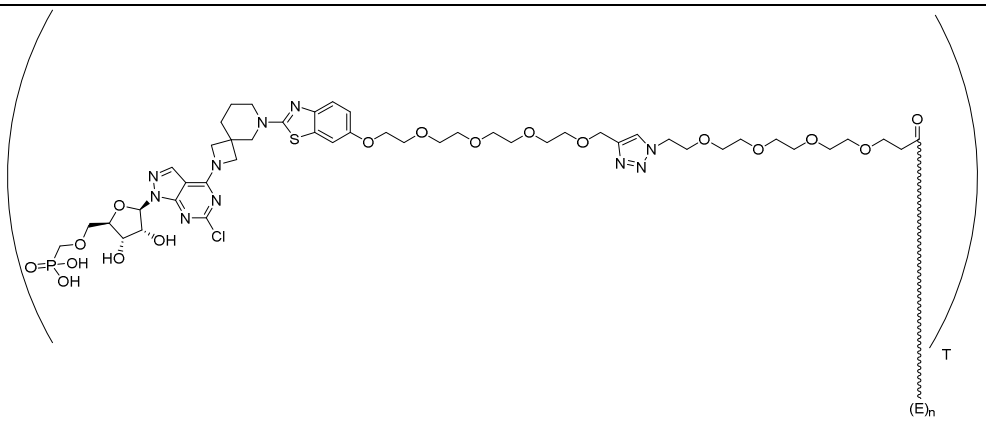
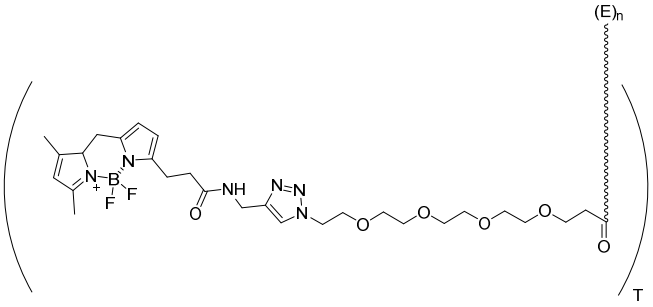
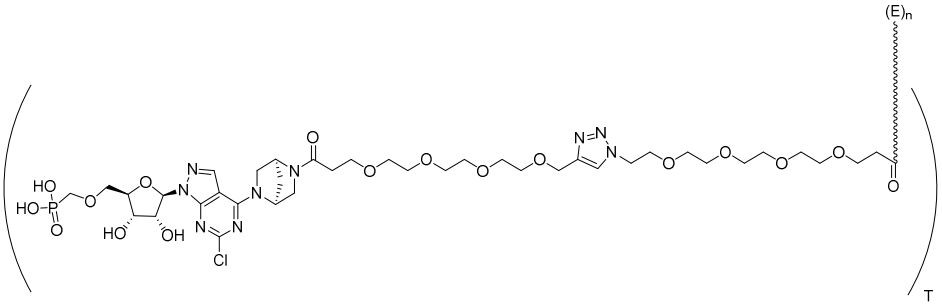
The disclosure also features a conjugate of Table 2. Each conjugate of Table 2 corresponds to a conjugate of formula (D-I) or (M-I). Conjugates of Table 2 include conjugates formed by the covalent reaction of an Int of Table 1 with E. Conjugates of table 2 further include conjugates formed by the covalent reaction of an Int of Table 1 with a linker which is in turn conjugated to E. In some examples, the reactive moiety of the Int (e.g., the alkyne or azido group) reacts with a corresponding reactive group (e.g., an alkyne or azido group) of a linker covalently attached to E, such that an Int of Table 1 is covalently attached to E. In some examples, the reactive moiety of the Int (e.g., the phenyl ester group, e.g., tetrafluorophenyl ester or trifluorophenyl ester group) reacts with a corresponding reactive group (e.g., nitrogen or sulfur atom) of an amino acid side chain of E, such that an Int of Table 1 is covalently attached to E.

In some examples in any conjugate of Table 2, n is 1 or 2. When n is 1, E includes an Fc domain monomer (e.g., an Fc domain monomer having the sequence of any one of SEQ ID NOs: 1-112 and 115-120. When n is 2, each E includes an Fc domain monomer (e.g., an Fc domain monomer having the sequence of any one of SEQ ID NOs: 1-112 and 115-120), and the Fc domain monomers dimerize to form and Fc domain.

In some examples in any conjugate of Table 2, T is an integer from 1 to 20 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20). The disclosure also provides a population of any of the conjugates of Table 2 wherein the average value of T is 1 to 20 (e.g., the average value of T is 1 to 2, 1 to 3, 1 to 4, 1 to 5, 5 to 10, 10 to 15, or 15 to 20). In some examples, the average value of T is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

The squiggly line in the conjugates of Table 2 indicates that each Int is covalently attached to an amino acid side chain in E (e.g., the nitrogen atom of a surface exposed lysine or the sulfur atom of a surface exposed cysteine in E), or a pharmaceutically acceptable salt thereof.

The disclosure also provides a conjugate of Table 2, wherein the conjugate is produced by conjugation (e.g., via a linker) of an Int of Table 1 to an Fc domain or an Fc domain monomer. In one aspect, the disclosure provides a conjugate, or a pharmaceutically acceptable salt thereof, described by a formula of Table 2.

Int	Conjugate Structure
Int-333	
Int-334	
Int-335	

The disclosure further features a method of making an Fc conjugate by conjugating (e.g., via a linker) an Int of Table 1 to an Fc domain monomer or an Fc domain. In some examples, the disclosure provides a conjugate, wherein the conjugate includes a small molecule targeting agent, wherein the targeting agent is described by an Int of Table 1, which is conjugated to an Fc (e.g., via a linker).

In some examples, the squiggly line connected to E indicates that the L of each A_1-L or each A_1-L-A_2 is covalently attached to a nitrogen atom of a solvent-exposed lysine of E. In some examples, the squiggly line connected to E indicates that the L of each A_1-L or each A_1-L-A_2 is covalently attached to the sulfur atom of a solvent-exposed cysteine of E.

In some examples, n is 2, and each E dimerizes to form an Fc domain.

In some examples, each E is a human IgG1 Fc domain monomer. In some examples, each E includes a substitution mutation at N297 selected from N297A, N297G, or N297Q, wherein the amino acid numbering of each Fc domain monomer is according to the Kabat EU index. In some examples, each E includes a C220S substitution mutation, wherein the amino acid numbering of each Fc domain monomer is according to the Kabat EU index. In some examples, each E includes a M252Y, a S254T, and a T256E substitution mutation, wherein the amino acid numbering of each Fc domain monomer is according to the Kabat EU index.

In some examples, each E includes an amino acid sequence having at least 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 1-112 and 115-120. In some examples, each E includes the amino acid sequence of any one of SEQ ID NOs: 1-112 and 115-120.

In some examples, each E includes an amino acid sequence having at least 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence of any one of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 17, or SEQ ID NO: 18. In some examples, each E includes the amino acid sequence of any one of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 17, or SEQ ID NO: 18. In some examples, each E includes the amino acid sequence of SEQ ID NO: 13. In some examples, each E includes the amino acid sequence of SEQ ID NO: 14. In some examples, each E includes the amino acid sequence of SEQ ID NO: 17. In some examples, each E includes the amino acid sequence of SEQ ID NO: 18.

In some examples, each E includes an amino acid sequence having at least 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence of any one of SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, or SEQ ID NO: 83. In some examples, each E includes the amino acid sequence of any one of SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, or SEQ ID NO: 83. In some examples, each E includes the amino acid sequence of SEQ ID NO: 80. In some examples, each E includes the amino acid sequence of SEQ ID NO: 81. In some examples, each E includes the amino acid sequence of SEQ ID NO: 82. In some examples, each E includes the amino acid sequence of SEQ ID NO: 83.

In some examples, each E includes an amino acid sequence having at least 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 115. In some examples, each E includes the amino acid sequence of SEQ ID NO: 115. In some examples, each E includes an amino acid sequence having at least 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 116. In some examples, each E includes the amino acid sequence of SEQ ID NO: 116. In some examples, each E includes an amino acid sequence having at least 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 117. In some examples, each E includes the amino acid sequence of SEQ ID NO: 117. In some examples, each E includes an amino acid sequence having at least 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 118. In some examples, each E includes the amino acid sequence of SEQ ID NO: 118. In some examples, each E includes an amino acid sequence having at least 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 119.

In some examples, each E includes the amino acid sequence of SEQ ID NO: 119. In some examples, each E includes an amino acid sequence having at least 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 120. In some examples, each E includes the amino acid sequence of SEQ ID NO: 120.

In some examples, n is 1 and T represents the number of A_1-L or A_1-L-A_2 moieties bound to each E. In some examples, n is 2 and the two Es dimerize to form a Fc domain and T represents the number of A_1-L or A_1-L-A_2 moieties bound to the Fc domain. In some examples, T is an integer from 1 to 20 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20).

The disclosure also provides a population of conjugates described herein wherein the average value of T is 1 to 20 (e.g., the average value of T is 1 to 2, 1 to 3, 1 to 4, 1 to 5, 5 to 10, 10 to 15, or 15 to 20). In one aspect, the disclosure provides a population of conjugates as disclosed herein, or a pharmaceutically acceptable salt thereof, wherein the average value of T is 1 to 10. In some examples, the average value of T is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

In another example, the disclosure provides a pharmaceutical composition including a conjugate or a population of conjugates, or a pharmaceutically acceptable salt thereof, described herein and a pharmaceutically acceptable excipient. In one aspect, the disclosure provides a pharmaceutical composition comprising a conjugate or a population of conjugates as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another example, the disclosure provides a cancer in a subject, the method including administering to the subject a conjugate, population of conjugates, or pharmaceutical composition described herein. In one aspect, the disclosure provides use of a conjugate, population of conjugates, or pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject having cancer.

In some examples, the cancer is selected from lung cancer, optionally non-small cell lung cancer or small-cell lung cancer; head and neck cancer, optionally squamous cell carcinoma; renal cell carcinoma; breast cancer; ovarian cancer; pancreatic cancer; colorectal cancer; urothelial cancer; bile duct cancer; endometrial cancer; melanoma; or esophageal cancer. In some examples, the cancer is a solid tumor. In some examples, the cancer overexpresses or is known to overexpress CD73 relative to a non-cancerous cell of the same tissue type.

In some examples, the method further includes administering to the subject an immune checkpoint inhibitor. In some examples, the immune checkpoint inhibitor is a PD-1 inhibitor. In some examples, the PD-1 inhibitor is an anti-PD-1 monoclonal antibody.

In another example, the disclosure provides a method of treating or preventing a viral infection in a subject, the method including administering to the subject a conjugate, population of conjugates, or pharmaceutical composition described herein. In some examples, the viral infection is a betacoronavirus infection. In some examples, the betacoronavirus is SARS-CoV-2. In some examples, the SARS-CoV-2 is an Alpha, Delta, or Omicron variant. In some examples, the SARS-CoV-2 is an Omicron variant. In some examples, the Omicron variant is a BA.1, BA.2, BA.3, BA.4, or BA.5 lineage. In some examples, the method further includes administering to the subject an antiviral agent or an antiviral vaccine.

In another example, the disclosure provides a method of treating or preventing fibrosis in a subject, the method including administering to the subject a conjugate, population of conjugates, or pharmaceutical composition described herein. In some examples, the fibrosis is pulmonary fibrosis, dermal fibrosis, renal fibrosis, hepatic fibrosis, cardiac fibrosis, or systemic sclerosis. In some

examples, the fibrosis is pulmonary fibrosis. In some examples, the pulmonary fibrosis associated with a viral infection (e.g., associated with a SARS-CoV-2 infection), drug-induced pulmonary fibrosis, radiation-induced pulmonary fibrosis, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, pneumoconiosis, interstitial lung disease, sarcoidosis, silicosis, or systemic sclerosis.

In some examples of any of the methods of treatment described herein, the conjugate, population of conjugates, or pharmaceutical composition is administered intramuscularly, intravenously, intradermally, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subcutaneously, subconjunctival, intravesicularlly, mucosally, intrapericardially, intraumbilically, intraocularally, orally, locally, by inhalation, by injection, or by infusion.

Definitions

To facilitate the understanding of this invention, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the areas relevant to the present invention. Terms such as "a", "an," and "the" are not intended to refer to only a singular entity but include the general class of which a specific example may be used for illustration. The terminology herein is used to describe specific embodiments of the invention, but their usage does not delimit the invention, except as outlined in the claims.

As used herein, the term “Fc domain monomer” refers to a polypeptide chain that includes at least a hinge domain and second and third antibody constant domains (C_H2 and C_H3) or functional fragments thereof (e.g., fragments that that capable of (i) dimerizing with another Fc domain monomer to form an Fc domain, and (ii) binding to an Fc receptor. The Fc domain monomer can be any immunoglobulin antibody isotype, including IgG, IgE, IgM, IgA, or IgD (e.g., IgG). Additionally, the Fc domain monomer can be an IgG subtype (e.g., IgG1, IgG2a, IgG2b, IgG3, or IgG4) (e.g., IgG1). In some embodiments, an Fc domain monomer does not include any portion of an immunoglobulin that is capable of acting as an antigen-recognition region, e.g., a variable domain or a complementarity determining region (CDR). Fc domain monomers in the compositions as described herein can contain one or more changes from a wild-type Fc domain monomer sequence (e.g., 1-10, 1-8, 1-6, 1-4 amino acid substitutions, additions, or deletions) that alter the interaction between an Fc domain and an Fc receptor. Examples of suitable changes are known in the art. In certain embodiments, a human Fc domain monomer (e.g., an IgG heavy chain, such as IgG1) includes a region that extends from any of Asn208, Glu216, Asp221, Lys222, or Cys226 to the carboxyl-terminus of the heavy chain at Lys447. C-terminal Lys447 of the Fc region may or may not be present, without affecting the structure or stability of the Fc region. C-terminal Lys 447 may be proteolytically cleaved upon expression of the polypeptide. In some embodiments of any of the Fc domain monomers described herein, C-terminal Lys 447 is optionally present or absent. The N-terminal N (e.g., Asn 201) of the Fc region may or may not be present, without affecting the structure of stability of the Fc region. N-terminal Asn may be deamidated upon expression of the polypeptide. In some embodiments of any of the Fc domain monomers described herein, N-terminal Asn is optionally present or absent. Unless otherwise specified herein, numbering of amino acid