COMPOUNDS INCLUDING A MUTANT KRAS SEQUENCE AND A LIPID AND USES THEREOF

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on _____ is named _____ and is _____ bytes in size.

BACKGROUND OF THE INVENTION

RAS proteins are essential components of cell signaling pathways. Oncogenic activation of RAS proteins by mutation is frequently detected in several types of cancer, including pancreatic cancer. There continues to be a need for further and more effective cancer treatments.

SUMMARY

The disclosure provides compounds that can be used in therapeutic methods.

Accordingly, in one example, the disclosure features a compound including a mutant KRAS sequence and a lipid, where the mutant KRAS sequence is conjugated to the lipid by a linker, and (i) the linker includes one or more polyethylene glycol blocks, (ii) the lipid is 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine (DSPE), and (iii) the mutant KRAS sequence comprises or consists of an amino acid sequence selected from the group consisting of YKLVVVGADGVGKSALTI (SEQ ID NO:23), YKLVVVGAVGVGKSALTI (SEQ ID NO:24), YKLVVVGARGVGKSALTI (SEQ ID NO:25), YKLVVVGAAGVGKSALTI (SEQ ID NO:26), YKLVVVGASGVGKSALTI (SEQ ID NO:27), YKLVVVGACGVGKSALTI (SEQ ID NO:28), YKLVVVGATGVGKSALTI (SEQ ID NO:29), and YKLVVVGAGDVGKSALTI (SEQ ID NO:30).

In another example, the disclosure features a compound including a mutant KRAS sequence and a lipid, where the mutant KRAS sequence is conjugated to the lipid by a linker, and (i) the linker includes one or more polyethylene glycol blocks, (ii) the lipid is 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine (DSPE), and (iii) the mutant KRAS sequence comprises or consists of an amino acid sequence selected from the group consisting of CYKLVVVGADGVGKSALTI (SEQ ID NO:1), CYKLVVVGAVGVGKSALTI (SEQ ID NO:2), CYKLVVVGARGVGKSALTI (SEQ ID NO:3), CYKLVVVGAAGVGKSALTI (SEQ ID NO:4), CYKLVVVGASGVGKSALTI (SEQ ID NO:5), CYKLVVVGACGVGKSALTI (SEQ ID NO:6), CYKLVVVGATGVGKSALTI (SEQ ID NO:22), and CYKLVVVGAGDVGKSALTI (SEQ ID NO:7). In one aspect, the present disclosure refers to a compound comprising a mutant KRAS sequence and a lipid, wherein the mutant KRAS sequence is conjugated to the lipid by a linker, and (i) the linker comprises one or more polyethylene glycol blocks, (ii) the lipid is 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine (DSPE), and (iii) the mutant KRAS sequence consists of an amino acid sequence selected from the group consisting of CYKLVVVGADGVGKSALTI (SEQ ID NO:1), CYKLVVVGAVGVGKSALTI (SEQ ID NO:2), CYKLVVVGARGVGKSALTI (SEQ ID NO:3), CYKLVVVGAAGVGKSALTI (SEQ ID NO:4), CYKLVVVGASGVGKSALTI (SEQ ID NO:5), CYKLVVVGACGVGKSALTI (SEQ ID NO:6), CYKLVVVGATGVGKSALTI (SEQ ID NO:22), ~~and~~ CYKLVVVGAGDVGKSALTI (SEQ ID NO:7), YKLVVVGADGVGKSALTI (SEQ ID NO:23), YKLVVVGAVGVGKSALTI (SEQ ID NO:24), YKLVVVGARGVGKSALTI (SEQ ID NO:25), YKLVVVGAAGVGKSALTI (SEQ ID NO:26), YKLVVVGASGVGKSALTI (SEQ ID NO:27), YKLVVVGACGVGKSALTI (SEQ ID NO:28), YKLVVVGATGVGKSALTI (SEQ ID NO:29), and YKLVVVGAGDVGKSALTI (SEQ ID NO:30).

In one example, the mutant KRAS sequence, at its N-terminus, is conjugated to the linker through a cysteine-maleimide linkage.

In another example the linker includes 48 repeat units of polyethylene glycol.

CLAIMS

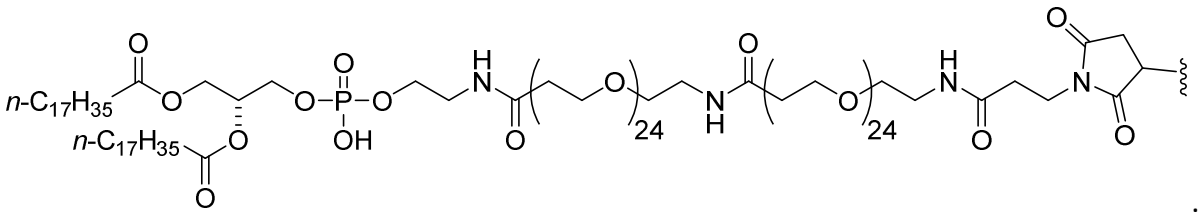
1. A compound comprising a mutant KRAS sequence and a lipid, wherein the mutant KRAS sequence is conjugated to the lipid by a linker, and (i) the linker comprises one or more polyethylene glycol blocks, (ii) the lipid is 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine (DSPE), and (iii) the mutant KRAS sequence consists of an amino acid sequence selected from the group consisting of CYKLVVVGADGVGKSALTI (SEQ ID NO:1), CYKLVVVGAVGVGKSALTI (SEQ ID NO:2), CYKLVVVGARGVGKSALTI (SEQ ID NO:3), CYKLVVVGAAGVGKSALTI (SEQ ID NO:4), CYKLVVVGASGVGKSALTI (SEQ ID NO:5), CYKLVVVGACGVGKSALTI (SEQ ID NO:6), CYKLVVVGATGVGKSALTI (SEQ ID NO:22), ~~and~~ CYKLVVVGAGDVGKSALTI (SEQ ID NO:7), YKLVVVGADGVGKSALTI (SEQ ID NO:23), YKLVVVGAVGVGKSALTI (SEQ ID NO:24), YKLVVVGARGVGKSALTI (SEQ ID NO:25), YKLVVVGAAGVGKSALTI (SEQ ID NO:26), YKLVVVGASGVGKSALTI (SEQ ID NO:27), YKLVVVGACGVGKSALTI (SEQ ID NO:28), YKLVVVGATGVGKSALTI (SEQ ID NO:29), and YKLVVVGAGDVGKSALTI (SEQ ID NO:30).

~~2. The compound of claim 1, wherein the mutant KRAS sequence consists of an amino acid sequence selected from the group consisting of YKLVVVGADGVGKSALTI (SEQ ID NO:23), YKLVVVGAVGVGKSALTI (SEQ ID NO:24), YKLVVVGARGVGKSALTI (SEQ ID NO:25), YKLVVVGAAGVGKSALTI (SEQ ID NO:26), YKLVVVGASGVGKSALTI (SEQ ID NO:27), YKLVVVGACGVGKSALTI (SEQ ID NO:28), YKLVVVGATGVGKSALTI (SEQ ID NO:29), and YKLVVVGAGDVGKSALTI (SEQ ID NO:30).~~

~~3~~2. The compound of claim 1 ~~or 2~~, wherein the mutant KRAS sequence, at its N-terminus, is conjugated to the linker through a cysteine-maleimide linkage.

~~4~~3. The compound of claim 1 ~~or 2~~, wherein linker comprises 48 repeat units of polyethylene glycol.

~~5~~4. The compound of claim 1 ~~or 2~~, wherein the mutant KRAS sequence, at its N-terminus, is conjugated to the following structure:



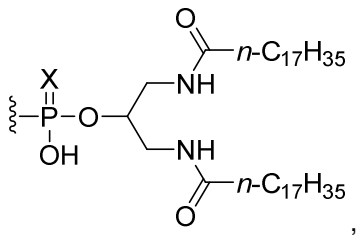
.

~~6~~5. A composition comprising one or more compounds of claim 1 ~~or 2~~, and a pharmaceutically acceptable carrier.

~~7~~6. The composition of claim ~~6~~5, wherein the composition comprises (1) a compound comprising the amino acid sequence YKLVVVGADGVGKSALTI (SEQ ID NO:23), (2) a compound comprising the amino acid sequence YKLVVVGAVGVGKSALTI (SEQ ID NO:24), (3) a compound comprising the amino acid sequence YKLVVVGARGVGKSALTI (SEQ ID NO:25), (4) a compound comprising the amino acid sequence YKLVVVGAAGVGKSALTI (SEQ ID NO:26), (5) a compound comprising the amino acid sequence YKLVVVGASGVGKSALTI (SEQ ID NO:27), (6) a compound comprising the amino acid sequence YKLVVVGACGVGKSALTI (SEQ ID NO:28) or a compound comprising the amino acid sequence YKLVVVGATGVGKSALTI (SEQ ID NO:29), and (7) a compound comprising the amino acid sequence YKLVVVGAGDVGKSALTI (SEQ ID NO:30).

~~8~~7. The composition of claim ~~6~~5, wherein the composition comprises (1) a compound comprising the amino acid sequence CYKLVVVGADGVGKSALTI (SEQ ID NO:1), (2) a compound comprising the amino acid sequence CYKLVVVGAVGVGKSALTI (SEQ ID NO:2), (3) a compound comprising the amino acid sequence CYKLVVVGARGVGKSALTI (SEQ ID NO:3), (4) a compound comprising the amino acid sequence CYKLVVVGAAGVGKSALTI (SEQ ID NO:4), (5) a compound comprising the amino acid sequence CYKLVVVGASGVGKSALTI (SEQ ID NO:5), (6) a compound comprising the amino acid sequence CYKLVVVGACGVGKSALTI (SEQ ID NO:6) or a compound comprising the amino acid sequence CYKLVVVGATGVGKSALTI (SEQ ID NO:22), and (7) a compound comprising the amino acid sequence CYKLVVVGAGDVGKSALTI (SEQ ID NO:7).

~~9~~8. The composition of claim ~~6~~5, wherein the composition further comprises a compound consisting of the nucleotide sequence 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO:8), which, at its 5' end, is bonded or linked by a linker to the following lipid:



,

or a salt thereof,
wherein X is O or S.

~~10~~9. The composition of claim ~~6~~5, wherein the composition comprises 700 µg of each compound.

~~11~~10. The composition of claim ~~9~~8, wherein the nucleotide sequence is bonded to the lipid.

~~12~~11. Use of the composition of claim ~~6~~ 5 in the manufacture of a medicament for treating a cancer in a human patient.

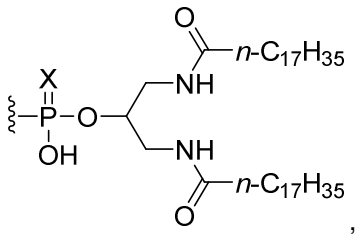
~~13~~12. The use of claim ~~12~~11, wherein the medicament is to be administered with an adjuvant.

~~14~~13. The use of claim ~~13~~12, wherein the adjuvant comprises a CpG nucleotide sequence.

~~15~~14. The use of claim ~~14~~13, wherein the CpG nucleotide sequence comprises 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO: 8).

~~16~~15. The use of claim ~~12~~11, wherein 0.1 mg, 0.5 mg, or 2.5 mg of the adjuvant is to be administered.

~~17~~16. The use of claim ~~12~~11, wherein the medicament is to be administered to the patient with a compound consisting of the nucleotide sequence 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO:8), which, at its 5' end, is bonded or linked by a linker to the following lipid:



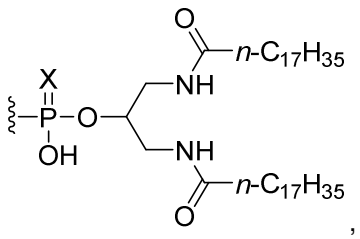
,

or a salt thereof,

wherein X is O or S.

~~18~~17. The use of claim ~~17~~16, wherein the nucleotide sequence is bonded to the lipid.

~~19~~18. The use of claim ~~17~~16, wherein 0.1 mg, 0.5 mg, or 2.5 mg of the compound consisting of the nucleotide sequence 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO:8), which, at its 5' end, is bonded or linked by a linker to the following lipid:



,

or a salt thereof,

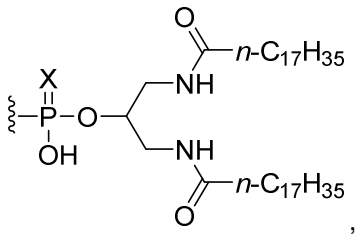
wherein X is O or S,

is to be administered.

~~20~~19. The use of claim ~~12~~11, wherein the cancer is a pancreatic cancer, a lung cancer, or a colorectal cancer.

~~21~~20. The use of claim ~~12~~11, wherein all internucleoside groups connecting the nucleosides in 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO:8) are phosphorothioates.

~~22~~21. A kit comprising (i) a compound of claim 1 ~~or 2~~, and (ii) a compound consisting of the nucleotide sequence 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO:8), which, at its 5' end, is bonded or linked by a linker to the following lipid:



,

or a salt thereof,

wherein X is O or S.