believed to play a role in the disease. Environmental components may include alterations in flora of the gut which are affected by exposure to ingested foods and medications.

[0009] IBD is associated with abdominal pain, vomiting, diarrhea, rectal bleeding, severe cramps, muscle spasms, weight loss, malnutrition, fever, and anemia. Patients with IBD may also suffer from skin lesions, joint pain, eye inflammation, and liver disorders, and children suffering from ulcerative colitis may suffer from growth defects. Although rarely fatal, these symptoms decrease quality of life for patients.

[0010] Thus, there is a pressing need to develop reliable methods of treating bowel diseases such as CRC and IBD. There is a further need to identify methods of treatment that provide effective and permanent relief from symptoms across a broad spectrum of patients and which are not associated with negative side effects or cycles of remission and/or inflammation.

SUMMARY

[0011] Described herein are antisense oligonucleotides that inhibit the expression of fragile X mental retardation protein (FMRP), and methods of using the same. In one aspect, the present disclosure provides an oligonucleotide for inhibiting the expression of fragile X mental retardation protein (FMRP), comprising a sequence selected from the group consisting of:

5′-CCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 1),
5′-CTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 2),
5′-TCCACCACCAGCTCCTCC-3′ (SEQ ID NO: 3),
5′-CTTCCACCACCAGCTCC-3′ (SEQ ID NO: 4),
~~5′-TCACCCTTTATCATCCTC-3′ (SEQ ID NO: 5),~~
5′-TCCACCACCAGCTCCTCCAT-3′ (SEQ ID NO: 6),
5′-ACTTCCACCACCAGCTCCTC-3′ (SEQ ID NO: 7),
5′-TTCCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 8), and
5′-ACTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 9), ~~and~~
~~5′-CTCACCCTTTATCATCCTCA-3′ (SEQ ID NO: 10)~~, or a complement thereof.

[0011a] In another aspect, the present disclosure provides a pharmaceutically acceptable composition for inhibiting the expression of FMRP, comprising: (a) an oligonucleotide as described herein and (b) a pharmaceutically acceptable carrier. In another aspect, the present disclosure provides use of an oligonucleotide as described herein in the

manufacture of a medicament for treating colorectal cancer~~a bowel disease or treating or preventing a solid tumor, tumor invasion, or tumor metastasis~~. In another aspect, the present disclosure provides use of an antisense oligonucleotide ~~or siRNA~~ that inhibits the expression of fragile X mental retardation protein (FMRP) in the manufacture of a medicament for treating colorectal cancer, wherein the antisense oligonucleotide comprises a sequence selected from the group consisting of:~~a bowel disease or treating or preventing a solid tumor, tumor invasion, or tumor metastasis~~

5′-CCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 1),
5′-CTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 2),
5′-TCCACCACCAGCTCCTCC-3′ (SEQ ID NO: 3),
5′-CTTCCACCACCAGCTCC-3′ (SEQ ID NO: 4),
5′-TCCACCACCAGCTCCTCCAT-3′ (SEQ ID NO: 6),
5′-ACTTCCACCACCAGCTCCTC-3′ (SEQ ID NO: 7),
5′-TTCCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 8), and
5’-ACTTCCACCACCAGCTCCT-3 (SEQ ID NO: 9).

[0011b] In some examples, the present disclosure provides a method of treating a bowel disease in a patient in need thereof comprising administering to the patient an effective amount of an antisense oligonucleotide that inhibits the expression of FMRP. In some examples, the bowel disease may be colorectal cancer or an inflammatory bowel disease such as Crohn’s disease or ulcerative colitis. In some examples, the antisense oligonucleotide induces necroptosis.

[0012] In some examples, the present disclosure provides a method of treating a solid tumor, tumor invasion, or tumor metastasis in a patient in need thereof comprising administering to the patient an effective amount of an antisense oligonucleotide that inhibits the expression of FMRP. In some examples, the present disclosure provides a method of preventing or ameliorating tumor invasion or tumor metastasis. In certain examples, the present disclosure provides a method of preventing or ameliorating colorectal cancer tumor invasion or colorectal cancer tumor metastasis.

[0013] In some examples, the antisense oligonucleotide that inhibits the expression of FMRP comprises a sequence selected from the group consisting of:
5′-CCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 1),

5′-CTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 2),

5′-TCCACCACCAGCTCCTCC-3′ (SEQ ID NO: 3),

5′-CTTCCACCACCAGCTCC-3′ (SEQ ID NO: 4), and

5′-TCACCCTTTATCATCCTC-3′ (SEQ ID NO: 5), or a complement thereof.

[0014] In further examples, the antisense oligonucleotide that inhibits the expression of FMRP comprises a sequence selected from the group consisting of:

5′-TCCACCACCAGCTCCTCCAT-3′ (SEQ ID NO: 6),

5′-ACTTCCACCACCAGCTCCTC-3′ (SEQ ID NO: 7),

5′-TTCCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 8),

5′-ACTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 9), and

5′-CTCACCCTTTATCATCCTCA-3′ (SEQ ID NO: 10), or a complement thereof.

WHAT IS CLAIMED IS:

1. An oligonucleotide for inhibiting the expression of fragile X mental retardation protein (FMRP), comprising a sequence selected from the group consisting of:

5′-CCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 1),
5′-CTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 2),
5′-TCCACCACCAGCTCCTCC-3′ (SEQ ID NO: 3),
5′-CTTCCACCACCAGCTCC-3′ (SEQ ID NO: 4),
~~5′-TCACCCTTTATCATCCTC-3′ (SEQ ID NO: 5),~~
5′-TCCACCACCAGCTCCTCCAT-3′ (SEQ ID NO: 6),
5′-ACTTCCACCACCAGCTCCTC-3′ (SEQ ID NO: 7),
5′-TTCCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 8), and
5′-ACTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 9), ~~and~~
~~5′-CTCACCCTTTATCATCCTCA-3′ (SEQ ID NO: 10)~~, or a complement thereof.

2. The oligonucleotide of claim 1, wherein the oligonucleotide comprises ribonucleotides, deoxyribonucleotides, or a combination of ribonucleotides and deoxyribonucleotides.

3. The oligonucleotide of claim 1 or 2, wherein the oligonucleotide comprises one or more modified nucleoside selected from the group consisting of 5-methylcytidine, 5-methyl-2′-deoxycytidine, deoxycytidine, 5-methyl-2′-deoxycytidine 5′-monophosphate, and 5-methyl-2′-deoxycytidine-5′-monophosphorothioate, 2′-*O*-methylcytidine, 2′-*O*-methylguanosine, 2′-*O*-methylthymidine, 2′-*O*-methyluridine, and 2′-*O*-methyladenosine, 5-methyl cytosine and 5-methylguanine, 2′-*O*-(2-methoxyethyl) nucleosides, 2′-deoxy-2′-fluoro nucleosides, and 2′-fluoro-β-D-arabinonucleosides.

4. The oligonucleotide of any one of claims 1 to 3, wherein the oligonucleotide comprises one or more modified nucleotide selected from the group consisting of bridged nucleic acids, locked nucleic acids (LNA), constrained ethyl (cET) nucleic acids, tricyclo-DNAs (tcDNA), 2′-*O*,4′-C-ethylene linked nucleic acids (ENA), and peptide nucleic acids (PNA).

5. The oligonucleotide of any one of claims 1 to 4, wherein the oligonucleotide comprises at least one internucleoside linkage selected from the group consisting of a

phosphorothioate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoromorpholidate linkage, a phosphoropiperazidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

6. The oligonucleotide of claim 5, wherein the oligonucleotide comprises at least one phosphorothioate linkage.

7. The oligonucleotide of claim 5, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

8. The oligonucleotide of any one of claims 1 to 7, wherein the oligonucleotide is capable of inducing necroptosis.

9. The oligonucleotide of any one of claims 1 to 8, wherein the oligonucleotide is capable of increasing activation of one or more kinases selected from the group consisting of: receptor interacting protein kinase 1 (RIPK1), receptor interacting protein kinase 3 (RIPK3), and mixed lineage kinase domain-like protein (MLKL).

10. The oligonucleotide of any one of claims 1 to 9, wherein the oligonucleotide is an antisense oligonucleotide ~~or part of an siRNA~~, or a pharmaceutically acceptable salt thereof.

11. The oligonucleotide of claim 10, ~~wherein the oligonucleotide is part of an siRNA, and~~ wherein at least one cytidine of the oligonucleotide is 5-methylcytidine.

12. A pharmaceutically acceptable composition for inhibiting the expression of FMRP, comprising: (a) an oligonucleotide of any one of claims 1-11 and (b) a pharmaceutically acceptable carrier.

13. Use of an oligonucleotide of any one of claims 1-12 in the manufacture of a medicament for treating colorectal cancer ~~a bowel disease preventing a solid tumor, tumor invasion, or tumor metastasis~~.

14. Use of an antisense oligonucleotide ~~or siRNA~~ that inhibits the expression of fragile X mental retardation protein (FMRP) in the manufacture of a medicament for treating colorectal cancer ~~a bowel preventing a solid tumor, tumor invasion, or tumor metastasis~~, wherein the antisense oligonucleotide comprises a sequence selected from the group consisting of:
5′-CCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 1),
5′-CTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 2),
5′-TCCACCACCAGCTCCTCC-3′ (SEQ ID NO: 3),
5′-CTTCCACCACCAGCTCC-3′ (SEQ ID NO: 4),
5′-TCCACCACCAGCTCCTCCAT-3′ (SEQ ID NO: 6),
5′-ACTTCCACCACCAGCTCCTC-3′ (SEQ ID NO: 7),
5′-TTCCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 8), and
5’-ACTTCCACCACCAGCTCCT-3 (SEQ ID NO: 9).

~~15. The use of claim 14, wherein the antisense oligonucleotide or siRNA comprises a sequence selected from the group consisting of:~~
~~5′-CCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 1),~~
~~5′-CTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 2),~~
~~5′-TCCACCACCAGCTCCTCC-3′ (SEQ ID NO: 3),~~
~~5′-CTTCCACCACCAGCTCC-3′ (SEQ ID NO: 4),~~
~~5′-TCACCCTTTATCATCCTC-3′ (SEQ ID NO: 5),~~
~~5′-TCCACCACCAGCTCCTCCAT-3′ (SEQ ID NO: 6),~~
~~5′-ACTTCCACCACCAGCTCCTC-3′ (SEQ ID NO: 7),~~
~~5′-TTCCACCACCAGCTCCTCCA-3′ (SEQ ID NO: 8),~~
~~5′-ACTTCCACCACCAGCTCCT-3′ (SEQ ID NO: 9), and~~
~~5′-CTCACCCTTTATCATCCTCA-3′ (SEQ ID NO: 10), or a complement thereof.~~

~~16. The use of any one of claims 13-15, wherein the bowel disease is colorectal cancer or an inflammatory bowel disease; the inflammatory bowel disease is Crohn’s disease or ulcerative colitis; and/or the tumor is a colorectal cancer tumor.~~

~~17.~~15. The use of any one of claims ~~13-16~~13-14, wherein the medicament is to be administered to a patient enterally or parenterally.

~~18.~~16. The use of claim ~~17~~15, wherein the enteral administration is oral, sublingual, gastric, or rectal administration.

~~19.~~17. The use of claim ~~17~~15, wherein the parenteral administration is intravenous, intratumoral, intrajejunal, intraileal, intracolonic, or intrarectal administration.

~~20.~~18. The use of any one of claims ~~13-19~~13-17, wherein the medicament is for use in a human.