[0008] There is an urgent need for methods to select subjects who would benefit from use of mTOR inhibitor agents and therapies. What is needed are methods using biomarkers to identify those who would benefit from mTOR therapy.

BRIEF SUMMARY

[0009] This disclosure relates to methods, agents and uses of mTOR therapy treating cancer.

[0010] This disclosure includes new agents and methods for inhibiting mTOR. The novel structures and compositions of this disclosure for inhibiting mTOR can provide novel therapeutic methods.

[0011] In some examples, new therapies can be supplied by a combination of novel mTOR-suppressing agents of this disclosure with additional mTOR inhibitor agents.

[0012] This disclosure includes methods to select subjects who would benefit from use of mTOR agents and mTOR therapies. A range of specific biomarkers can be used to identify those who would benefit from mTOR therapy.

[0013] Examples of this disclosure include the following:

[0014] A method for treating or ameliorating a symptom of cancer in a human or animal subject in need, the method comprising administering a therapeutically sufficient amount of a pharmaceutical composition comprising an agent for suppressing mTOR to the subject.

[0015] An agent for suppressing mTOR for treating or ameliorating a symptom of cancer in a human or animal subject in need.

[0015a] In an aspect of the present disclosure, there is provided a composition comprising an antisense oligonucleotide agent for suppressing mTOR having any one of the sequences in the following table, wherein the sequence is modified with at least one phosphorothioate internucleoside linkage:

SEQ ID NO:	Ref.	ANTISENSE SEQUENCE 5' -> 3"
1	719-738	TTCGGCTCACGCTGGGTTGT
2	974-993	CGAGGTTTTGTTCCGAAGCC
3	985-1004	GGGTAATGTGACGAGGTTTT
4	986-1005	GGGGTAATGTGACGAGGTTT
5	1163-1182	CACACCTGATCAAATTTCTC
6	1164-1183	GCACACCTGATCAAATTTCT
7	2670-2689	CTGCTCAGTCTTCAGAAAAT
8	2671-2690	TCTGCTCAGTCTTCAGAAAA
9	4121-4140	AAGTTTAAGAGGGTCTGTGT
10	5115-5134	TGTTGGCAGAGGATGGTCAA
11	5117-5136	ACTGTTGGCAGAGGATGGTC
12	5355-5374	TTTGGGGATTGTGCTCTCAT
13	5467-5486	GGTTCTGATGTTTGTAGTGT
14	5468-5487	TGGTTCTGATGTTTGTAGTG
15	5473-5492	GGGCTTGGTTCTGATGTTTG
16	5474-5493	CGGGCTTGGTTCTGATGTTT
17	6481-6500	TGGGGTCATATGTTCCTGGC
18	6482-6501	TTGGGGTCATATGTTCCTGG
19	7769-7788	GGTTTCAGTTTAGTGGAAGC
20	8297-8316	TGAATTGAAGCGTGTGAGTC

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[0015b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising an mTOR-specific antisense oligonucleotide in combination with an agent for inhibiting mTOR.

[0015c] In a further aspect of the present disclosure, there is provided a composition as disclosed herein for use in therapy.

[0015d] In another aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein for use in therapy.

[0016] Use of a composition comprising an agent for suppressing mTOR in the preparation of a medicament for treating or ameliorating a symptom of cancer in a human or animal subject in need.

[0016a] In a further aspect of the present disclosure, there is provided a use of a composition as disclosed herein in the preparation of a medicament for treating or ameliorating a symptom of cancer in a human or animal subject in need.

[0016b] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the preparation of a medicament for treating or ameliorating a symptom of cancer in a human or animal subject.

[0017] The method, agent or use above, wherein the cancer is a sarcoma, a lung cancer, an ovarian cancer, or a pancreatic cancer.

[0018] The method, agent or use above, comprising using one or more biomarkers to select subjects who benefit from the method, agent or use.

[0019] The method, agent or use above, wherein the one or more biomarkers are a level of a tumor mutation burden (TMB), a tumor neoantigen, a tumor-associated immune cell, or a combination thereof.

WHAT IS CLAIMED IS:

1. A composition comprising an antisense oligonucleotide agent for suppressing mTOR having any one of the sequences in the following table, wherein the sequence is modified with at least one phosphorothioate internucleoside linkage:

SEQ ID NO:	Ref.	ANTISENSE SEQUENCE 5' -> 3"
1	719-738	TTCGGCTCACGCTGGGTTGT
2	974-993	CGAGGTTTTGTTCCGAAGCC
3	985-1004	GGGTAATGTGACGAGGTTTT
4	986-1005	GGGGTAATGTGACGAGGTTT
5	1163-1182	CACACCTGATCAAATTTCTC
6	1164-1183	GCACACCTGATCAAATTTCT
7	2670-2689	CTGCTCAGTCTTCAGAAAAT
8	2671-2690	TCTGCTCAGTCTTCAGAAAA
9	4121-4140	AAGTTTAAGAGGGTCTGTGT
10	5115-5134	TGTTGGCAGAGGATGGTCAA
11	5117-5136	ACTGTTGGCAGAGGATGGTC
12	5355-5374	TTTGGGGATTGTGCTCTCAT
13	5467-5486	GGTTCTGATGTTTGTAGTGT
14	5468-5487	TGGTTCTGATGTTTGTAGTG
15	5473-5492	GGGCTTGGTTCTGATGTTTG
16	5474-5493	CGGGCTTGGTTCTGATGTTT
17	6481-6500	TGGGGTCATATGTTCCTGGC
18	6482-6501	TTGGGGTCATATGTTCCTGG
19	7769-7788	GGTTTCAGTTTAGTGGAAGC
20	8297-8316	TGAATTGAAGCGTGTGAGTC

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2. A composition of claim 1 for use in therapy.

3. Use of a composition of claim 1 in the preparation of a medicament for treating or ameliorating a symptom of cancer in a human or animal subject in need.

4. The use of claim 3, wherein the cancer is a sarcoma, a lung cancer, an ovarian cancer, or a pancreatic cancer.

5. The use of claim 3 or 4, wherein subjects who benefit from the use are selected using one or more biomarkers.

6. The use of claim 5, wherein the one or more biomarkers are a level of a tumor mutation burden (TMB), a tumor neoantigen, a tumor-associated immune cell, or a combination thereof.

7. The use of claim 5, wherein the one or more biomarkers are a level of a basophil cell, a B-cell, a T-cell, a T-helper cell (Th), an eosinophil cell, a macrophage cell, a mesenchymal stem cell, or a combination thereof, as determined in a tumor microenvironment.

8. The use of claim 5, wherein the one or more biomarkers are a level of a CD4+ cell, a memory T-cell, a CD8+ cell, a natural killer T-cell, a regulatory T-cell, a type 1 T-helper cell (Th1), a type 2 T-helper cell (Th2), or a combination thereof, as determined in a tumor microenvironment.

9. The use of claim 5, wherein the cancer is a sarcoma and the one or more biomarkers are a level of a tumor mutation burden (TMB), a tumor neoantigen level, a mesenchymal stem cell determined in a tumor microenvironment, a type 1 T-helper cell (Th) determined in a tumor microenvironment, or a combination thereof.

10. The use of claim 5, wherein the cancer is a lung squamous cell carcinoma and the one or more biomarkers are a level of a CD4+ cell determined in a tumor microenvironment, a memory T-cell determined in a tumor microenvironment, an eosinophil cell determined in a tumor microenvironment, or a combination thereof.

11. The use of claim 5, wherein the cancer is a pancreatic cancer and the one or more biomarkers are a level of a CD8+ cell determined in a tumor microenvironment, a tumor mutation burden (TMB), or a combination thereof.

12. The use of claim 5, wherein the cancer is an ovarian cancer and the one or more biomarkers are a level of a natural killer T-cell determined in a tumor microenvironment, a tumor neoantigen determined in a tumor microenvironment, or a combination thereof.

13. The use of any of claims 3-12, wherein the agent for suppressing mTOR is an mTOR-specific antisense oligonucleotide complementary to a mTOR transcript and 15-30 nucleotides in length, or complementary to a mTOR pre-RNA, pre-mRNA or mRNA and 18-21 nucleotides in length.

14. The use of any of claims 3-13, wherein the agent for suppressing mTOR is an mTOR-specific antisense oligonucleotide comprising any of the 20 nucleotide length sequences in the following table:

SEQ ID NO:	Ref.	ANTISENSE SEQUENCE 5’ -> 3”
21	719-738	TTCGGCTCACGCTGGGTTGT
22	974-993	CGAGGTTTTGTTCCGAAGCC
23	985-1004	GGGTAATGTGACGAGGTTTT
24	986-1005	GGGGTAATGTGACGAGGTTT
25	1163-1182	CACACCTGATCAAATTTCTC
26	1164-1183	GCACACCTGATCAAATTTCT
27	2670-2689	CTGCTCAGTCTTCAGAAAAT
28	2671-2690	TCTGCTCAGTCTTCAGAAAA
29	4121-4140	AAGTTTAAGAGGGTCTGTGT
30	5115-5134	TGTTGGCAGAGGATGGTCAA
31	5117-5136	ACTGTTGGCAGAGGATGGTC
32	5355-5374	TTTGGGGATTGTGCTCTCAT
33	5467-5486	GGTTCTGATGTTTGTAGTGT
34	5468-5487	TGGTTCTGATGTTTGTAGTG
35	5473-5492	GGGCTTGGTTCTGATGTTTG
36	5474-5493	CGGGCTTGGTTCTGATGTTT
37	6481-6500	TGGGGTCATATGTTCCTGGC
38	6482-6501	TTGGGGTCATATGTTCCTGG
39	7769-7788	GGTTTCAGTTTAGTGGAAGC
40	8297-8316	TGAATTGAAGCGTGTGAGTC

and chemically-modified variants thereof, LNA variants thereof, gapmer variants thereof, and pooling and combinations thereof.

15. The use of claim 14, wherein the mTOR-specific antisense oligonucleotides have no more than one or two mismatches as compared to a target human mTOR.

16. The use of claim 14, wherein the mTOR-specific antisense oligonucleotides reduce a mTOR transcript level by at least 60%, or at least 70%, or at least 80%, or at least 90%.

17. The use of claim 14, wherein the mTOR-specific antisense oligonucleotides have one or more nucleotides chemically modified as a phosphorothioate internucleoside linkage, a methoxypropylphosphonate internucleoside linkage, an aminophosphoro linkage to a morpholino group, a 2’-OMe ribose group, a 2’-MOE methoxyethyl ribose group, a 2’-4’ constrained methoxyethyl bicyclic ribose group, a 2’-4’ constrained ethyl bicyclic ribose group, an LNA ribose group, a 2’-F ribose group, or a 5-methylcytodine base.

18. The use of claim 14, wherein the antisense oligonucleotide is conjugated to a polyethylene glycol, a lipid, or a triantenarry N-acteyl-galactosamine.

19. The use of any of claims 15-18, comprising antisense oligonucleotide in a carrier of sterile water for injection, saline, isotonic saline, or a combination thereof.

20. The use of any of claims 15-19, wherein the antisense oligonucleotides are substantially free of excipients.

21. The use of any of claims 15-20, wherein the antisense oligonucleotides are stable for at least 14 days in carrier at 37°C.

22. The use of any of claims 3-21, wherein the medicament is combined with a standard of care treatment for the cancer, wherein the standard of care treatment comprises chemotherapy or radiation therapy, and wherein the medicament is to be administered to the subject in the absence of immune checkpoint inhibitors.

23. The use of any of claims 3-22, wherein the medicament decreases mortality rate at month 6, 12, 18, 24, 30, or 36.

24. The use of any of claims 3-22, wherein the medicament increases survival rate at month 6, 12, 18, 24, 30, or 36.

25. A pharmaceutical composition comprising an mTOR-specific antisense oligonucleotide in combination with an agent for inhibiting mTOR.

26. A pharmaceutical composition of claim 25 for use in therapy.

27. Use of a pharmaceutical composition of claim 25 in the manufacture of a medicament for treating or ameliorating a symptom of cancer in a human or animal subject.

28. The use of claim 27, wherein the cancer is a sarcoma, a lung cancer, an ovarian cancer, or a pancreatic cancer.

29. The use of claim 27 or claim 28, wherein subjects who benefit from the use are selected using one or more biomarkers.

30. The use of claim 29, wherein the one or more biomarkers are a level of a tumor mutation burden (TMB), a tumor neoantigen, a tumor-associated immune cell, or a combination thereof.

31. The use of claim 29, wherein the one or more biomarkers are a level of a basophil cell determined in a tumor microenvironment, a B-cell determined in a tumor microenvironment, a T-cell determined in a tumor microenvironment, a T-helper cell (Th) determined in a tumor microenvironment, an eosinophil cell determined in a tumor microenvironment, a macrophage

cell determined in a tumor microenvironment, a mesenchymal stem cell determined in a tumor microenvironment, or a combination thereof.

32. The use of claim 29, wherein the one or more biomarkers are a level of a CD4+ cell determined in a tumor microenvironment, a memory T-cell determined in a tumor microenvironment, a CD8+ cell determined in a tumor microenvironment, a natural killer T-cell determined in a tumor microenvironment, a regulatory T-cell determined in a tumor microenvironment, a type 1 T-helper cell (Th1) determined in a tumor microenvironment, a type 2 T-helper cell (Th2) determined in a tumor microenvironment, or a combination thereof.

33. The use of claim 29, wherein the cancer is a sarcoma and the one or more biomarkers are a level of a tumor mutation burden (TMB), a tumor neoantigen level, a mesenchymal stem cell determined in a tumor microenvironment, a type 1 T-helper cell (Th) determined in a tumor microenvironment, or a combination thereof.

34. The use of claim 29, wherein the cancer is a lung squamous cell carcinoma and the one or more biomarkers are a level of a CD4+ cell determined in a tumor microenvironment, a memory T-cell determined in a tumor microenvironment, an eosinophil cell determined in a tumor microenvironment, or a combination thereof.

35. The use of claim 29, wherein the cancer is a pancreatic cancer and the one or more biomarkers are a level of a CD8+ cell determined in a tumor microenvironment, a tumor mutation burden (TMB), or a combination thereof.

36. The use of claim 29, wherein the cancer is an ovarian cancer and the one or more biomarkers are a level of a natural killer T-cell determined in a tumor microenvironment, a tumor neoantigen determined in a tumor microenvironment, or a combination thereof.

37. The use of any of claims 27-36, wherein the mTOR-specific antisense oligonucleotide is complementary to a mTOR transcript and 15-30 nucleotides in length, or complementary to a mTOR pre-RNA, pre-mRNA or mRNA and 18-21 nucleotides in length.

38. The use of any of claims 27-36, wherein the mTOR-specific antisense oligonucleotide comprises any of the 20 nucleotide length sequences in the following table:

SEQ ID NO:	Ref.	ANTISENSE SEQUENCE 5’ -> 3”
1	719-738	TTCGGCTCACGCTGGGTTGT
2	974-993	CGAGGTTTTGTTCCGAAGCC
3	985-1004	GGGTAATGTGACGAGGTTTT
4	986-1005	GGGGTAATGTGACGAGGTTT
5	1163-1182	CACACCTGATCAAATTTCTC
6	1164-1183	GCACACCTGATCAAATTTCT
7	2670-2689	CTGCTCAGTCTTCAGAAAAT
8	2671-2690	TCTGCTCAGTCTTCAGAAAA
9	4121-4140	AAGTTTAAGAGGGTCTGTGT
10	5115-5134	TGTTGGCAGAGGATGGTCAA
11	5117-5136	ACTGTTGGCAGAGGATGGTC
12	5355-5374	TTTGGGGATTGTGCTCTCAT
13	5467-5486	GGTTCTGATGTTTGTAGTGT
14	5468-5487	TGGTTCTGATGTTTGTAGTG
15	5473-5492	GGGCTTGGTTCTGATGTTTG
16	5474-5493	CGGGCTTGGTTCTGATGTTT
17	6481-6500	TGGGGTCATATGTTCCTGGC
18	6482-6501	TTGGGGTCATATGTTCCTGG
19	7769-7788	GGTTTCAGTTTAGTGGAAGC
20	8297-8316	TGAATTGAAGCGTGTGAGTC

and chemically-modified variants thereof, LNA variants thereof, gapmer variants thereof, and pooling and combinations thereof.

39. The use of claim 37 or claim 38, wherein the mTOR-specific antisense oligonucleotides have no more than one or two mismatches as compared to a target human mTOR.

40. The use of claim 37 or claim 38, wherein the mTOR-specific antisense oligonucleotides reduce a mTOR transcript level by at least 60%, or at least 70%, or at least 80%, or at least 90%.

41. The use of claim 37 or claim 38, wherein the mTOR-specific antisense oligonucleotides have one or more nucleotides chemically modified as a phosphorothioate internucleoside linkage, a methoxypropylphosphonate internucleoside linkage, an aminophosphoro linkage to a morpholino group, a 2’-OMe ribose group, a 2’-MOE methoxyethyl ribose group, a 2’-4’ constrained methoxyethyl bicyclic ribose group, a 2’-4’ constrained ethyl bicyclic ribose group, an LNA ribose group, a 2’-F ribose group, or a 5-methylcytodine base.

42. The use of claim 37 or claim 38, wherein the antisense oligonucleotide is conjugated to a polyethylene glycol, a lipid, or a triantenarry N-acteyl-galactosamine.

43. The use of claim 37 or claim 38, comprising antisense oligonucleotides in a carrier of sterile water for injection, saline, isotonic saline, or a combination thereof, and wherein the antisense oligonucleotide is stable for at least 14 days in carrier at 37°C.

44. The use of claim 37 or claim 38, comprising antisense oligonucleotides substantially free of excipients.

45. The use of any of claims 27-44, wherein the agent for inhibiting mTOR is rapamycin, everolimus, temsirolimus, sirolimus, deforolimus, ridaforolimus, zotarolimus, torkinib, samotolisib, omipalisib, apitolisib, vistusertib, dactolisib, gedatolisib, voxtalisib, chrysophanic, or a combination thereof.

46. The use of any of claims 27-44, wherein the agent for inhibiting mTOR is 1-[4-[4-(1-Oxopropyl)-1-piperazinyl]-3-(trifluoromethyl)phenyl]-9-(3-quinolinyl)-benzo[h]-1,6-naphthyridin-2(1H)-one, 3-[4-(4-Morpholinylpyrido[3',2':4,5]furo[3,2-d]pyrimidin-2-yl]phenol hydrochloride, N-[4-[4-(4-Morpholinyl)-1-[1-(3-pyridinylmethyl)-4-piperidinyl]-1H-pyrazolo[3,4-d]pyrimidin-6-yl]phenyl]-carbamic acid methyl ester dihydrochloride, 2,4-Difluoro-N-[2-methoxy-5-[4-(4-pyridazinyl)-6-quinolinyl]-3-pyridinyl]benzenesulfonamide (omipalisib), 5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide (niclosamide), or a combination thereof.

47. The use of any of claims 27-46, wherein the medicament is combined with a standard of care treatment for the cancer, wherein the standard of care treatment comprises chemotherapy or radiation therapy, and wherein the medicament is to be administered to the subject in the absence of immune checkpoint inhibitors.

48. The use of any of claims 27-47, wherein the mTOR-specific antisense oligonucleotide and agent for inhibiting mTOR are each to be administered to the subject concurrently, simultaneously, sequentially, or separately in time.

49. The use of any of claims 27-48, wherein the medicament decreases mortality rate at month 6, 12, 18, 24, 30, or 36.

50. The use of any of claims 27-49, wherein the medicament increases survival rate at month 6, 12, 18, 24, 30, or 36.