

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
27 May 2022 (27.05.2022)



(10) International Publication Number
WO 2022/109376 A3

(51) International Patent Classification:

A61K 31/712 (2006.01) C12N 15/113 (2010.01)
A61K 31/713 (2006.01)

(21) International Application Number:

PCT/US2021/060279

(22) International Filing Date:

22 November 2021 (22.11.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/117,213 23 November 2020 (23.11.2020) US

(71) Applicant: UNITED STATES GOVERNMENT AS
REPRESENTED BY THE DEPARTMENT OF VET-
ERANS AFFAIRS [US/US]; 810 Vermont Avenue NW,
Washington, DC 20420 (US).

(72) Inventors: KRAEMER, Brian; 26247 39th Pl S., Kent,
WA 98108 (US). WHEELER, Jeanna M.; 2037 S.
Washington St., Seattle, WA 98144 (US). MCMILLAN,
Pamela; 2351 26th Ave West, Seattle, WA 98199 (US).
STROVAS, Timothy J.; 421 Iron Avenue, Algona, WA
98001 (US). BAKER, Jeremy; 804 James Street, Apt.
C301, Seattle, WA 98104 (US).

(74) Agent: KLIEM, Michele A. et al.; Ballard Spahr LLP, 999
Peachtree Street, Suite 1600, Atlanta, GA 30309 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN,
KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO,
NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,
SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))

Published:

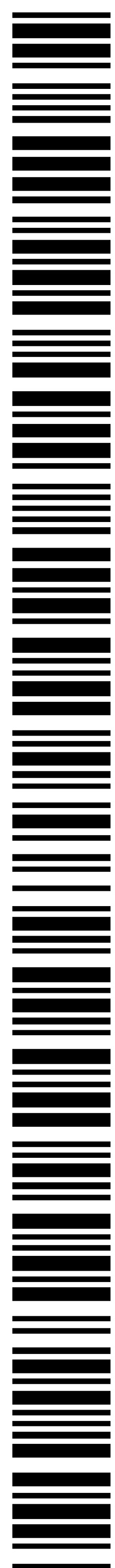
— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))
— with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:

14 July 2022 (14.07.2022)

(54) Title: COMPOSITIONS AND METHODS FOR SUPPRESSING MSUT2

(57) Abstract: Described herein are small interfering RNA (siRNA) molecules and their use in methods and pharmaceutical composi-
tions for inhibiting the expression of mammalian suppressor of taupathy 2. Also, described herein are the use of said siRNA molecules
in the treatment of Alzheimer's disease or dementia, and reducing accumulation of phosphorylated and aggregated human tau.



WO 2022/109376 A3

COMPOSITIONS AND METHODS FOR SUPPRESSING MSUT2

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/117,213,
5 filed November 23, 2020. The content of this earlier filed application is hereby incorporated
by reference herein in its entirety.

STATEMENT REGARDING FEDERALLY FUNDED RESEARCH

This invention was made with government support under grant number
10 RF1AG055474 awarded by National Institutes of Health. The government has certain rights
in the invention.

INCORPORATION OF THE SEQUENCE LISTING

The present application contains a sequence listing that is submitted via EFS-Web
15 concurrent with the filing of this application, containing the file name
“37759_0352P1_SL.txt” which is 45,056 bytes in size, created on November 19, 2021, and is
herein incorporated by reference in its entirety.

BACKGROUND

20 The molecular mechanisms underpinning neurodegenerative diseases include the
cellular disruption of proteostasis. In Alzheimer’s disease (AD), this disruption manifests as
the deposition of amyloid plaques and neurofibrillary tangles (NFTs), the diagnostic
pathological lesions of the disorder. While the mechanistic relationship between plaques and
tangles remains unclear, abnormal tau and A β synergize to drive neurodegeneration in AD.
25 A large body of evidence supports the idea of A β amyloid pathology initiating the disease
process in AD. However, the discovery of tau mutations in frontotemporal lobar
degeneration with tau inclusions (FTLD-tau) (P. Poorkaj, et al., *Ann. Neurol.* **43**, 815-825
(1998); M. G. Spillantini, et al., *Proc. Natl. Acad. Sci. U.S.A.* **95**, 7737-7741 (1998); L. N.
Clark, et al., *Proc. Natl. Acad. Sci. U.S.A.* **95**, 13103-13107 (1998); and M. Hutton, et al.,
30 *Nature* **393**, 702-705 (1998)) demonstrates that tau pathology can cause neurodegeneration
independent of amyloid plaques. Furthermore, tau pathology, not amyloid deposition,
correlates with the severity of dementia in AD (L. M. Bierer, et al., *Arch Neurol* **52**, 81-88
(1995). Thus, findings to date justify active investigation of the mechanistic underpinnings of

both amyloid- and tau-mediated neurodegeneration in AD. Despite a diverse array of highly powered AD clinical trials targeting amyloid production, clearance, or deposition, none have been successful. Altogether, these observations suggest that tau-targeted therapies in conjunction with removal of amyloid may be required to achieve cognitive preservation when
 5 treating AD (M. R. Khanna, et al., *Alzheimers Dement* **12**, 1051-1065 (2016); and C. Ballatore, et al., *Nat Rev Neurosci* **8**, 663-672 (2007)).

SUMMARY

Disclosed herein are compositions comprising a nucleic acid sequence or molecule wherein the nucleic acid comprises or consists of a sequence having the sequence set forth in:

10 UUUUCUGGUUUCUGUGCCACACUCAGU (SEQ ID NO: 7),
 UUUUUCUGGUUUCUGUGCCACACUCAG (SEQ ID NO: 9),
 GUUUUUCUGGUUUCUGUGCCACACUCA (SEQ ID NO: 11),
 AGUUUUUCUGGUUUCUGUGCCACACUC (SEQ ID NO: 13),
 AAGUUUUUCUGGUUUCUGUGCCACACU (SEQ ID NO: 15),
 15 GCAGGCCAGUACUUGCAGCGCUCCAAA (SEQ ID NO: 17),
 AAGCAGGGAAGUAACGGCAGAGCUGAC (SEQ ID NO: 19).
 CAAGCAGGGAAGUAACGGCAGAGCUGA (SEQ ID NO: 21),
 ACAAGCAGGGAAGUAACGGCAGAGCUG (SEQ ID NO: 23),
 UACAAGCAGGGAAGUAACGGCAGAGCU (SEQ ID NO: 25)
 20 UUACAAGCAGGGAAGUAACGGCAGAGC (SEQ ID NO: 27),
 CUUACAAGCAGGGAAGUAACGGCAGAG (SEQ ID NO: 29),
 UCUUACAAGCAGGGAAGUAACGGCAGA (SEQ ID NO: 31),
 UUCUACAAGCAGGGAAGUAACGGCAG (SEQ ID NO: 33),
 CACUCAUCUCAGCGUUAGAAAAGCUACC (SEQ ID NO: 35),
 25 UCUGGUUUCUGUGCCACACUCAGUUCAC (SEQ ID NO: 37),
 UACUUGCAGCGCUCCAAAAGUUUUUCUG (SEQ ID NO: 39),
 UCCCCAUUUUUACAAGCAGGCCAGUACU (SEQ ID NO: 41),
 GAUGGGGUGAUGGUAGGCACACUCAUCC (SEQ ID NO: 43),
 UUGGGGAAGGCUUUGCAGGGUGAGAUGG (SEQ ID NO: 45),
 30 AAACAUUUUUCAGCAAAUUUACAAUUGG (SEQ ID NO: 47),
 UAUUUACAAUUUGGGUGAACAAACAAAC (SEQ ID NO: 49),
 UCUGGUUUAGUACACUUUGCAUCAUAUU (SEQ ID NO: 51),
 UACUCACAUGAGUGAAGGGACAAUCUGG (SEQ ID NO: 53),

UUGGAGACAGUACUGGAAUUCUUCUACU (SEQ ID NO: 55),
 GUGGUGCUGGUGGUGCAACUGGUUUUGG (SEQ ID NO: 57),
 ACGGCAGAGCUGACUACUGGAAGGUGGU (SEQ ID NO: 59),
 CCAUCUUCUUACAAGCAGGGAAGUAACGG (SEQ ID NO: 61),
 5 GUUUUGGAUGAUAGAAGGGACAUCCAUC (SEQ ID NO: 63),
 UACAUUGAGUGUUAAACCUACAAUGUUU (SEQ ID NO: 65),
 GUAGAAUGUGCAGUCCGGUCUUGUACAUC (SEQ ID NO: 67),
 UGGUGGGACAUAUAAUGGUGGGAUGGUAG (SEQ ID NO: 69),
 UCGAAUCCAUAUUAAGGCAUGUCGUGGU (SEQ ID NO: 71), or
 10 UUAUUCGCUGGUUUGAGGUCGAAUCCAUC (SEQ ID NO: 73).

Disclosed herein are compositions comprising a nucleic acid sequence or molecule wherein the nucleic acid comprises or consists of a sequence having at least 90% identity to the sequence set forth in:

UUUUCUGGUUUCUGUGCCACACUCAGU (SEQ ID NO: 7),
 15 UUUUUCUGGUUUCUGUGCCACACUCAG (SEQ ID NO: 9),
 GUUUUUCUGGUUUCUGUGCCACACUCA (SEQ ID NO: 11),
 AGUUUUUCUGGUUUCUGUGCCACACUC (SEQ ID NO: 13),
 AAGUUUUUCUGGUUUCUGUGCCACACU (SEQ ID NO: 15),
 GCAGGCCAGUACUUGCAGCGCUCCAAA (SEQ ID NO: 17),
 20 AAGCAGGGAAGUAACGGCAGAGCUGAC (SEQ ID NO: 19).
 CAAGCAGGGAAGUAACGGCAGAGCUGA (SEQ ID NO: 21),
 ACAAGCAGGGAAGUAACGGCAGAGCUG (SEQ ID NO: 23),
 UACAAGCAGGGAAGUAACGGCAGAGCU (SEQ ID NO: 25)
 UUACAAGCAGGGAAGUAACGGCAGAGC (SEQ ID NO: 27),
 25 CUUACAAGCAGGGAAGUAACGGCAGAG (SEQ ID NO: 29),
 UCUUACAAGCAGGGAAGUAACGGCAGA (SEQ ID NO: 31),
 UUCUACAAGCAGGGAAGUAACGGCAG (SEQ ID NO: 33),
 CACUCAUCUCAGCGUUAGAAAAGCUACC (SEQ ID NO: 35),
 UCUGGUUUCUGUGCCACACUCAGUUCAC (SEQ ID NO: 37),
 30 UACUUGCAGCGCUCCAAAAGUUUUUCUG (SEQ ID NO: 39),
 UCCCCAUUUUUACAAGCAGGCCAGUACU (SEQ ID NO: 41),
 GAUGGGGUGAUGGUAGGCACACUCAUCC (SEQ ID NO: 43),

UUGGGGAAGGCUUUGCAGGGUGAGAUGG (SEQ ID NO: 45),
 AAACAUUUUUCAGCAAAUUUACAAUUGG (SEQ ID NO: 47),
 UAUUUACAAUUUGGGUGAACAAACAAAC (SEQ ID NO: 49),
 UCUGGUUUAGUACACUUUGCAUCAUAUU (SEQ ID NO: 51),
 5 UACUCACAUGAGUGAAGGGACAAUCUGG (SEQ ID NO: 53),
 UUGGAGACAGUACUGGAAUUCUUCUACU (SEQ ID NO: 55),
 GUGGUGCUGGUGGUGCAACUGGUUUUGG (SEQ ID NO: 57),
 ACGGCAGAGCUGACUACUGGAAGGUGGU (SEQ ID NO: 59),
 CCAUCUUCUUACAAGCAGGGAAGUAACGG (SEQ ID NO: 61),
 10 GUUUUGGAUGAUAGAAGGGACAUUCCAUC (SEQ ID NO: 63),
 UACAUUGAGUGUUAAACCUACAAUGUUU (SEQ ID NO: 65),
 GUAGAAUGUGCAGUCCGGUCUUGUACAUC (SEQ ID NO: 67),
 UGGUGGGACAUUAAUGGUGGGAUGGUAG (SEQ ID NO: 69),
 UCGAAUCCAUUUCAAGGCAUGUCGUGGU (SEQ ID NO: 71), or
 15 UUAUUCGCUGGUUUGAGGUCGAAUCCAUC (SEQ ID NO: 73).

Disclosed herein are siRNA molecules wherein the siRNA molecule specifically
 targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID
 NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78 and reduces expression of mammalian
 suppressor of tauopathy 2 (MSUT2) gene in a cell, wherein the siRNA molecule comprises a
 20 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule
 comprises at least one sequence having at least 90% sequence identity to a sequence selected
 from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of treating Alzheimer's disease or dementia, the
 methods comprising: administering to a subject with Alzheimer's disease or dementia a
 25 therapeutically effective amount of a small interfering RNA (siRNA) molecule or a
 composition comprising the siRNA molecule that specifically targets at least one sequence
 selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and
 SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended
 double-stranded structure, wherein the siRNA molecule comprises at least one sequence
 30 selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, and wherein the
 therapeutically effective amount reduces accumulation of phosphorylated and aggregated
 human tau.

Disclosed herein are methods of treating Alzheimer's disease or dementia, the methods comprising: administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, and wherein the therapeutically effective amount reduces accumulation of phosphorylated and aggregated human tau.

Disclosed herein are methods of inhibiting expression of a MSUT2 polynucleotide in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of inhibiting expression of a MSUT2 polynucleotide in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of reducing phosphorylated and aggregated human tau protein in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide

blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of reducing phosphorylated and aggregated human tau protein in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of suppressing expression of a MSUT2 polynucleotide in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of suppressing expression of a MSUT2 polynucleotide in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of potentiating a neuroinflammatory response to a pathological tau protein in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID

NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

5 Disclosed herein are methods of potentiating a neuroinflammatory response to a pathological tau protein in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID
10 NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of decreasing astrogliosis or microgliosis in a subject,
15 the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended
20 double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of decreasing astrogliosis or microgliosis in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a
25 composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of
30 SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of reducing neuroinflammation in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a

composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence
5 selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of reducing neuroinflammation in a subject, the methods comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence
10 selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

Disclosed herein are methods of inhibiting expression of a MSUT2 polynucleotide, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA
20 molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of inhibiting expression of a MSUT2 polynucleotide, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA
30 molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of suppressing expression of a MSUT2 polynucleotide, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID

NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of suppressing expression of a MSUT2 polynucleotide, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of potentiating a neuroinflammatory response to a pathological tau protein, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of potentiating a neuroinflammatory response to a pathological tau protein, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of decreasing astrogliosis or microgliosis, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID

NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of decreasing astrogliosis or microgliosis, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of reducing neuroinflammation, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of reducing neuroinflammation, the methods comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Other features and advantages of the present compositions and methods are illustrated in the description below, the drawings, and the claims.

DETAILED DESCRIPTION

Many modifications and other embodiments of the present disclosure set forth herein will come to mind to one skilled in the art to which this disclosure pertains having the benefit of the teachings presented in the foregoing descriptions and the associated drawings.

5 Therefore, it is to be understood that the present disclosure is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

10 Before the present compositions and methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar
15 or equivalent to those described herein can be used in the practice or testing of the present disclosure, example methods and materials are now described.

Moreover, it is to be understood that unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be
20 followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is in no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, and the number or type of
25 aspects described in the specification.

All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the
30 present disclosure is not entitled to antedate such publication by virtue of prior disclosures. Further, the dates of publication provided herein can be different from the actual publication dates, which can require independent confirmation.

Definitions

As used in the specification and in the claims, the term “comprising” can include the aspects “consisting of” and “consisting essentially of.” “Comprising” can also mean “including but not limited to.”

5 As used in the specification and the appended claims, the singular forms “a,” “an” and “the” can include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a compound” includes mixtures of compounds; reference to “a pharmaceutical carrier” includes mixtures of two or more such carriers, and the like.

10 The word “or” as used herein means any one member of a particular list and also includes any combination of members of that list.

As used herein, the terms “optional” or “optionally” mean that the subsequently described event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances where it does not.

15 As used herein, the term “sample” is meant a tissue or organ from a subject; a cell (either within a subject, taken directly from a subject, or a cell maintained in culture or from a cultured cell line); a cell lysate (or lysate fraction) or cell extract; or a solution containing one or more molecules derived from a cell or cellular material (e.g. a polypeptide or nucleic acid), which is assayed as described herein. A sample may also be any body fluid or excretion (for example, but not limited to, blood, urine, stool, saliva, tears, bile) that contains cells or cell
20 components.

As used herein, the term “subject” refers to the target of administration, e.g., a human. The subject of the disclosed methods can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. The term “subject” also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals
25 (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.). In one aspect, a subject is a mammal. In another aspect, a subject is a human. The term does not denote a particular age or sex. Thus, adult, child, adolescent and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

30 As used herein, the term “patient” refers to a subject afflicted with a disease or disorder. The term “patient” includes human and veterinary subjects. In some aspects of the disclosed methods, the “patient” has been diagnosed with a need for treatment for Alzheimer’s disease or dementia, such as, for example, prior to the administering step.

Ranges can be expressed herein as from “about” or “approximately” one particular value, and/or to “about” or “approximately” another particular value. When such a range is expressed, a further aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” or “approximately,” it will be understood that the particular value forms a further aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint and independently of the other endpoint. It is also understood that there are a number of values disclosed herein and that each value is also herein disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. It is also understood that each unit between two particular units is also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

“Inhibit,” “inhibiting” and “inhibition” mean to diminish or decrease an activity, response, condition, disease, or other biological parameter. This can include, but is not limited to, the complete ablation of the activity, response, condition, or disease. This may also include, for example, a 10% inhibition or reduction in the activity, response, condition, or disease as compared to the native or control level. Thus, in an aspect, the inhibition or reduction can be a 10, 20, 30, 40, 50, 60, 70, 80, 90, 100%, or any amount of reduction in between as compared to native or control levels. In an aspect, the inhibition or reduction is 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, or 90-100% as compared to native or control levels. In an aspect, the inhibition or reduction is 0-25, 25-50, 50-75, or 75-100% as compared to native or control levels.

“Modulate”, “modulating” and “modulation” as used herein mean a change in activity or function or number. The change may be an increase or a decrease, an enhancement or an inhibition of the activity, function or number.

As used herein, the term “treating” refers to partially or completely alleviating, ameliorating, relieving, delaying onset of, inhibiting or slowing progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular disease, disorder, and/or condition. Treatment can be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition. Treatment can also be administered to a subject to ameliorate one more signs of symptoms of a disease,

disorder, and/or condition. For example, the disease, disorder, and/or condition can be relating to Alzheimer's disease, Alzheimer's disease-related dementia or dementia.

The phrase "nucleic acid" as used herein refers to a naturally occurring or synthetic oligonucleotide or polynucleotide, whether DNA or RNA or a DNA-RNA hybrid, single-
5 stranded or double-stranded, sense or antisense, which is capable of hybridization to a complementary nucleic acid by Watson-Crick base-pairing. Nucleic acids as disclosed herein can also include nucleotide analogs (e.g., BrdU), and non-phosphodiester internucleoside linkages (e.g., peptide nucleic acid or thiodiester linkages). In particular, nucleic acids can include, without limitation, DNA, RNA, cDNA, gDNA, ssDNA, dsDNA or any combination
10 thereof.

Nucleic acid sequences recited herein are written in a 5' to 3' direction unless otherwise indicated. The term "nucleic acid" refers to either DNA or RNA or a modified form thereof comprising the purine or pyrimidine bases present in DNA (adenine "A", cytosine "C", guanine "G", thymine "T") or in RNA (adenine "A", cytosine "C", guanine "G", uracil
15 "U"). Interfering RNAs provided herein may comprise "T" bases, for example at 3' ends, even though "T" bases do not naturally occur in RNA. In some cases these bases may appear as "dT" to differentiate deoxyribonucleotides present in a chain of ribonucleotides.

As used herein, the term "complementary" refers to the ability of a nucleic acid to form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. A percent complementary indicates the percentage of residues
20 in a nucleic acid molecule which can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, 10 out of 10 being 50%, 60%, 70%, 80%, 90%, and 100% complementary).

As used herein, the term "vector" or "construct" refers to a nucleic acid sequence
25 capable of transporting into a cell another nucleic acid to which the vector sequence has been linked. The term "expression vector" includes any vector, (e.g., a plasmid, cosmid or phage chromosome) containing a gene construct in a form suitable for expression by a cell (e.g., linked to a transcriptional control element or regulatory element). The terms "plasmid" and "vector" can be used interchangeably, as a plasmid is a commonly used form of vector.
30 Moreover, this disclosure is intended to include other vectors which serve equivalent functions.

All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains. All publications and

patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, certain changes and modifications may be practiced within the scope of the appended claims.

Tauopathies are a heterogeneous group of neurodegenerative diseases characterized by abnormal metabolism of misfolded τ (tau) proteins leading to intracellular accumulation and formation of neurofibrillary tangles (NFT). In Alzheimer's disease (AD), tau neuropathology correlates with severity of dementia. However, interventions for AD and related dementias are limited to treatment of symptoms that do not directly alter tau pathology or the resultant neurodegeneration. This underscores the need for tau-targeted disease-modifying therapeutics. Furthermore, the results from amyloid-targeted clinical trials in AD patients suggest that achieving cognitive preservation in AD may require tau-targeted therapy in conjunction with the removal of amyloid. MSUT2 controls neuronal susceptibility to tau toxicity in the mammalian brain. The mechanism of MSUT2 modulation of tauopathy appears to involve MSUT2 binding to poly(A) RNA and its modulation of RNA polyadenylation. Described herein are siRNAs that inhibit MSUT2 from binding to poly(A) RNA providing a pharmacological means of intervening against tauopathy.

It has been shown that targeted reduction of the MSUT2 protein reverses the toxic consequences of pathological tau in animal models and human cells. Described herein are nucleotide sequences facilitating gene silencing approaches targeting MSUT2 such as RNA mediated interference and/or antisense oligonucleotides.

RNA interference (RNAi) is a naturally occurring post-transcriptional regulatory mechanism present in most eukaryotic cells that uses small double stranded RNA (dsRNA) molecules to direct homology-dependent gene silencing. Shortly after its first description, RNAi was also shown to occur in mammalian cells by means of double-stranded small interfering RNAs (siRNAs) 21 nucleotides long.

The process of RNA interference is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes and is commonly shared by diverse phyla and flora, where it is called post-transcriptional gene silencing.

The mechanism of RNAi is initiated when long double stranded RNAs are processed by an RNase III-like protein known as Dicer. The protein Dicer typically contains an N-

terminal RNA helicase domain, an RNA-binding so-called Piwi/Argonaute/Zwille (PAZ) domain, two RNase III domains and a double-stranded RNA binding domain (dsRBD) (Collins et al. FEBS Letters, 2005, Vol. 579, Issue 26, pp. 5841-5849) and its activity leads to the processing of the long double stranded RNAs into 21-24 nucleotide double stranded

5 siRNAs with 2 base 3' overhangs and a 5' phosphate and 3' hydroxyl group. The resulting siRNA duplexes are then incorporated into the effector complex known as RNA-induced silencing complex (RISC), where the antisense or guide strand of the siRNA guides RISC to recognize and cleave target mRNA sequences (Elbashir et al. 2001, Nature, 411(6836):494-8) upon ATP-dependent unwinding of the double-stranded siRNA molecule through an RNA

10 helicase activity (Nykanen et al. 2001, Cell, 107(3):309-21). The catalytic activity of RISC, which leads to mRNA degradation, is mediated by the endonuclease Argonaute 2 (AGO2) (Liu et al. 2004, Science, 305(5689):1437-41; and Song et al. 2004, Science, 305:1434-37). AGO2 belongs to the highly conserved Argonaute family of proteins. Argonaute proteins are about 100 KDa highly basic proteins that contain two common domains, namely PIWI and

15 PAZ domains (Cerutti et al 2000, Trends Biochem. Sci, 25(10): 481-482). The PIWI domain is important for the interaction with Dicer and contains the nuclease activity responsible for the cleavage of mRNAs. AGO2 uses one strand of the siRNA duplex as a guide to find messenger RNAs containing complementary sequences and cleaves the phosphodiester backbone between bases 10 and 11 relative to the guide strand's 5' end (Elbashir et al 2001,

20 Nature, 411(6836):494-8). An important step during the activation of RISC is the cleavage of the sense or passenger strand by AGO2, removing this strand from the complex (Rand et al. 2005, Cell, 123(4): 621-9). Crystallography studies analyzing the interaction between the siRNA guide strand and the PIWI domain reveal that it is about 2 to 8 nucleotides that constitute a "seed sequence" that directs target mRNA recognition by RISC, and that a

25 mismatch of a single nucleotide in this sequence may drastically affect silencing capability of the molecule (Ma et al. 2005, Nature 429, pp. 318-322; Doench et al. 2004, Genes Dev., 18(5): 504-11; and Lewis et al. 2003, Cell 115, pp. 787-798). Once the mRNA has been cleaved, due to the presence of unprotected RNA ends in the fragments the mRNA is further cleaved and degraded by intracellular nucleases and will no longer be translated into proteins

30 (Orban et al. 2005, RNA, 11(4): 459-469) while RISC will be recycled for subsequent rounds (Hutvagner et al 2002, Science, 297(5589):2056-60). This constitutes a catalytic process leading to the selective reduction of specific mRNA molecules and the corresponding proteins. It is possible to exploit this native mechanism for gene silencing with the purpose of

regulating any gene(s) of choice by directly delivering siRNA effectors into the cells or tissues, where they will activate RISC and produce a potent and specific silencing of the targeted mRNA.

Compositions

5 Disclosed herein are target sequences and nucleic acids useful in the methods described herein. In some aspects, the target sequence(s) can be selected from one or more of the sequences listed in Table 1. In some aspects, the target can be MSUT2 gene (also known as ZC3H14). The mouse MSUT2 gene ID is 75553. The human MSUT2 gene ID is 79882. In some aspects, the target sequence can encompass a fragment of the mRNA MSUT2
10 sequence. In some aspects, the target sequence can encompass a fragment of the mRNA MSUT2 sequence, wherein the mRNA MSUT2 sequence comprises the ZF domain. In some aspects, the target sequence can be SEQ ID NO: 74 or a fragment thereof. In some aspects, the target sequence can encompass a fragment of SEQ ID NO: 75 or SEQ ID NO: 76. In some aspects, the target sequence can be SEQ ID NO: 77 or a fragment thereof. In some
15 aspects, the target sequence can be SEQ ID NO: 78 or a fragment thereof. As used herein, the term “target sequence” as described herein is a target DNA sequence as used for definition of transcript variants in databases used for the purposes of designing siRNAs, whereas the specific compounds to be used will be RNA sequences defined as such.

A gene is “targeted” by a siRNA as described herein when, for example, the siRNA
20 molecule selectively decreases or inhibits the expression of the gene. The phrase “selectively decrease or inhibit” as used herein encompasses siRNAs that affect expression of one gene, in this case MSUT2. Alternatively, a siRNA targets a gene when (one strand of) the siRNA hybridizes under stringent conditions to the gene transcript, i.e., its mRNA. Hybridizing “under stringent conditions” means annealing to the target sequence under standard
25 conditions, e.g., high temperature and/or low salt content which tend to disfavor hybridization. A suitable protocol (involving 0.1.times.SSC, 68.degree. C. for 2 hours) is described in Maniatis, T., et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, 1982, on pages 387-389.

In some aspects, the target sequence can encompass the MSUT2 ZF domain or a part
30 or a portion of the MSUT2 ZF domain. The ZF domain is the functional part of the MSUT2 protein that binds poly(A) RNA. The short isoform of the MSUT2 protein encodes the ZF domain. The long isoforms of the MSUT2 protein can have additional domains. Targeting the other domains can allow the short isoform to continue carrying out the MSUT2 RNA

binding function. In some aspects, to achieve a strong loss of function, the siRNA sequence can target the MSUT2 ZF domain.

In some aspects, a target sequence described herein can comprise or consist of at least one sequence selected from SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 74 to SEQ ID NO: 76, SEQ ID NO: 77, and SEQ ID NO: 78.

Table 1: Examples of Target Sequences

Target Gene	Name	Sequence	SEQ ID NO.
MSUT2/ZC3H14	crRNA_human and mouse MSUT2 E6	5'-AATTTATCGACCACCTGCAAG-3'	1
MSUT2/ZC3H14	crRNA_mouse MSUT2 E13	5'-TACTGGCCTGCCTGTAAAAAT-3'	2
MSUT2/ZC3H14	crRNA_mouse MSUT2 E13	5'-GGCCTGCCTGTAAAAATGGGG-3'	3
MSUT2/ZC3H14	crRNA_mouse MSUT2 E16	5'-GCCACCAAGACACGCCTTGAA-3'	4
MSUT2/ZC3H14	MSUT2 sgRNA 3'UTR#1	5'-ATTAGACACTTCAGATAGAT-3'	5
MSUT2	ZF Domain	5'-GGTAGCTTTTCTAACGCTGAGATGA GTGAACTGAGTGTGGCACAGAAAC CAGAAAACTTTTGGAGCGCTGCAA GTACTGGCCTGCTTGTA AAAATGGG GATGAGTGTGCCTACCATCACCCCA TCTCACCTGCAAAGCCTTCCCCAA TTGTAAATTTGCTGAAAAATGTTTG TTTGTTACCCAAATTGTAAATATG ATGCAAAGTGTACTAAACCAGATT GTCCCTTCACTCATGTGAGTAGAAG AATTCCAGTACTGTCTCCAAAACCA	74

		GTTGCACCACCAGCACCACCTTCCA GTAGTCAGCTCTGCCGTTACTTCCCT GCTTGTAAGAAGATGGAATGTCCCT TCTATCATCCAAAACATTGTAGGTTT AACACTCAATGTACAAGACCGGACT GCACATTCTACCATCCCACCATTAAT GTCCCACCACGACATGCCTTGAAATG GATTTCGACCTCAAACCAGCGAATAA-3'	
MSUT2/ZC3H14	Standard MSUT2 RNAi	5'-ATGATGCAAAGTGACTAAACCAG-3'	77
MSUT2/ZC3H14	Standard MSUT2 RNAi	5'- TCTGGTTT TAGTACACTTTGCATCATAT- 3'	78

The mouse longest coding mRNA→ protein is: NM_029334.2 → NP_083610.2 (SEQ ID NO: 75).

5

10

15

20

25

30

35

40

1 ggggacgcgc acggcgaggc cggagcggcg gcggcagcgg cggcagcggc agcggcagcg
61 gcgtaggggg cccaggctgc aggggtggcag cccgcggcgg gctccaggta accgaggcgc
121 cgcgcagtg cagagcggcc gccgcgcgc gagccatgga aatcggcacc gagatcagcc
181 gcaagatccg gagtgccatt aaggggaaat tacaagaatt aggagcttac gtagatgaag
241 aacttcctga ttacattatg gtgatggtgg ccaacaagaa aagtcaggac caaatgacag
301 aggacctgtc cctgtttcta gggaacaaca caattcgatt caccgtatgg ctccatggtg
361 tattagataa actgcgctct gtcacgactg agccctctag tctaaagtct cctgacgcca
421 gcatcttcga tagtcacgtg ccttcaaaca agagcagttt cagtcgggga gatgagagaa
481 ggcacgaagc tgccgtccct ccccttgctg tttctagttc tagacctgaa aagagggatt
541 ccagagtttc tacaagttca caggagcaga aatccactaa tgtcagacat tcatatgatg
601 atggagcttc cacccggtca atgtcaacag tgaaacctct gagggaaacca gcacctctg
661 aagatgtgat tgatatcaag ccagaaccag atgatctcat tgatgaagac ctcaattttg
721 tgcaggagaa tcccttatct cagaaaaaac ctacagtga ccttacatac gggtctcttc
781 gcccttctat tgaaatttat cgaccacctg caagtagaaa tgcagacact ggtactcact
841 taaacaggct gcaacttcat ccgcagcaaa gcagtgtctc cgctgccaa g cagctggatg
901 tacaaagcag ccaggatatc gaagcaggac ggttggtgtga gccaccagt cttagcagcg
961 tagaagacac ttatagcccc ttcttcagaa acaacttgga taaaatgagt attgaggacg
1021 aaaactttcg aaagagaaaa ttgcctgtgg taagttcggg tggttaaagta aaaagattta
1081 gccatgatgg agaagaggag gaagaagatg aggattatgg gaccgcgata ggaagcttgt
1141 ccagcagcgt gtcagtacca gcaaagcctg agaggagacc ttctcttcca ccttctaaac
1201 aagctaacaa gaatctaatt ttgaaggcta tctctgaagc tcaagagtct gtaacaaaga
1261 caactaacta ttctgcagtt ccacagaaac agacacttcc agttgctccc agaactcgaa
1321 cttctcaaga agaattgcta gcagaaatgg tccaggggca aaacagggcc cccagaataa
1381 gtccccctgt taaagaagag gaagcaaaag gagataatac aggaaaaagt caaggaaactc
1441 aacagaggca attgttatcc cgactgcaaa ttgatccagt aatggtagaa acaatggaga
1501 tgaagtcaaga ttactatgac atgggaatcca tgggtccatgc agacacaaga tcattttatc
1561 tgaagaagcc aaagctgtct gaggaatatg tagtgacacc caaccaggat tcggggatga
1621 agactgcaga tgcccttcgg gtcctttcag gacaccttat gcagacacga gatcttgtac
1681 aaccagataa acctgcaagt cccaagttta tagtgacgct ggatggtgtc cccagccccc
1741 caggatacat gtcagatcaa gaggaggaga tgtgctttga aggaatgaaa ccgtaaaacc
1801 aaacttcagc ctcaaacaag ggactcagag gtctcctcca cccacagcag ttgcattttg
1861 tgagcaggca gcttgaggac ccagatggta gcttttccaa cgccgagatg actgacctga
1921 gtgtggcaca gaaaccagaa aaacttctgg agcgtgcaa gtactggcct gcctgtaaaa
1981 atggggatga gtgtgtatac catcatccca ttacacctg caaagccttt cccaactgta
2041 aatttgctga gaaatgtttg tttgtgcac caaattgtaa atatgacaca aagtgtacta
2101 aagcagattg tcccttcact cacatgagta gaagagcctc gatactgact ccaaaaccag
2161 tgtcgtcacc agcacgctct tctaattggc agctctgccg ttacttccct gcttgtaaga
2221 aaatggaatg tcccttctac caccctaaac actgtaggtt taacactcag tgtacgagac
2281 ctgactgcac attttatcac cccaccatta ctgtgccacc aagacaogcc ttgaaatgga

5 2341 ttcgacctca gagcagtgag tgatgcccta gtccctacctg gcagaagatc atgcagtttg
2401 aaagcttcca tcttctgatg agagatgttc tacagaactt gtcacgtctt tgaaatttag
2461 aatataattgc tttcataata cgaattttac tgccccactg aagtgtctaa tttttcaagt
2521 ttgtaagttt attaagtggg ttcaacattt tttgtttgtt cgttttgact atgaaaaaga
2581 cagttttaaag aaaagccaaa ttctattaaa acatttgctg catgtttgta cattgctggt
2641 taatatcatt tttggtaatg gtacttgtag cttagggctg tagtgctgtg ggaaggccag
2701 tgctctcaga gctgaagcac ttttcagctt tcccaaagg taatgcagtg tctgtaacco
2761 agcgtggtaa cagtggccag gctttgaaac tgaggcagct ttggaacaac tagtttaaat
10 2821 ttcttttttt agtgtctaaa tgaatttgct ctgagaagca taatgcagac tttattttga
2881 gtgctacttt ggtagagtgg accgagggtc tgtgcctttc tgaaagtgag cagagacatg
2941 gtcataaagg gtaagcatag ttggaatgac gatgtaaaaa tatatggaca gttcttttga
3001 atgctcccat ttactattag cttatcattt tataagtaat tttggaggga ctacattatc
3061 acaaaaagta acaaaaattt ttacaggcat atgtacagaa agtatcagaa aacagacttt
3121 gaactcacia gaataataat atacgtatat attcccatat tctgaaaaat atcatcagaa
15 3181 ataaccacc agaaaatata cttatgttat tactaaagat cattcttgaa atgtagaagt
3241 tgagatttaa gtggtatatt ttaaatagac gaactatatt gcagagatag gaaggtaaac
3301 ttgacaatag gatgaaactt ggctactgt actatggagt tttatgtgtg gtttttga
3361 ctgttaaggc aagatgtgtc atgtttttag actaaataac agacaactga tttcaaaaa
20 3421 gtgttggttt aaaaattaaa gtgtaaaccg tggtttagca aggggataat aaaagctcaa
3481 acattttgag gaccaaattt aactgttaag atacaataaa gtcacatcta taaaagtctg
3541 tgtttaataa tgtgaa

The human longest coding mRNA is: NM_024824.5 → NP_079100.2 (SEQ ID NO:
76).

25 1 ggaggcggtg gtgtcccggc tgcggggtag gagtccgcgg cagcctccgg gtaagccaag
61 cgccgcgcag tgctgagttc ccgcacgccg cagagccatg gagatcgga cagagatcag
121 ccgcaagatc cggagtgcc aataagggaa attacaagaa ttaggagctt atgttgatga
181 agaacttcct gattacatta tgggtgatgt ggccaacaag aaaagtcagg accaaatgac
30 241 agaggatctg tccctgtttc tagggaacaa cacaattcga ttcacgtat ggcttcattg
301 tgtattagat aaacttcgct ctgttacaac tgaaccctct agtctgaagt cttctgatac
361 caacatcttt gatagtaacg tgccttcaaa caagagcaat ttcagtcggg gagatgagag
421 gaggcagtaa gctgcagtgc caccacttgc cattcctagc gcgagacctg aaaaaagaga
481 ttccagagtt tctacaagtt cgcaggagtc aaaaaccaca aatgtcagac agacttacga
35 541 tgatggagct gcaacccgac taatgtcaac agtgaaacct ttgagggagc cagcaccctc
601 tgaagatgtg attgatatta agccagaacc agatgatctc attgacgaag acctcaactt
661 tgtgcaggag aatcccttat ctcagaaaaa acctacagtg acacttacat atggttcttc
721 tcgcccttct attgaaattt atcgaccacc tgcaagtaga aatgcagata gtggtgttca
781 tttaaacagg ttgcaatttc aacagcagca gaatagtatt catgctgcca agcagcttga
40 841 tatgcagagt agttgggtat atgaaacagg acgtttgtgt gaaccagagg tgcctaacag
901 cttagaagaa acgtatagtc cgttcttttag aaacaactcg gagaaaatga gtatggagga
961 tgaaaacttt cggaagagaa agttgcctgt ggttaagttca gttgttaaag taaaaaaatt
1021 caatcatgat ggagaagagg aggaagaaga tgatgattac gggctctcga caggaagcat
1081 ctccagcagt gtgtctgtgc ctgcaaagcc tgaaaggaga ccttctcttc caccctctaa
45 1141 acaagctaac aagaatctga ttttgaggcc tatatctgaa gctcaagaat ccgtaacaaa
1201 aacaactaac tactctacag ttccacagaa acagacactt ccagttgctc ccagaactcg
1261 aacttctcaa gaagaattgc tagcagaagt ggtccaggga caaagtagga cccccagaat
1321 aagtcccccc attaaagaag aggaacaaaa aggagattct gtagaaaaaa atcaaggaac
1381 tcaacagagg caattattat cccgactgca aatcgaccca gtaatggcag aaactctgca
50 1441 gatgagtcaa gattactatg acatggaatc catgggtccat gcagacacaa gatcatttat
1501 tctgaagaag ccaaagctgt ctgagggaag agtagtggca ccaaaccaag agtcggggat
1561 gaagactgca gattcccttc gggtagtttc aggacacctt atgcagacac gagatcttgt
1621 acaaccagat aaacctgcaa gtcccaagtt tatagtgaag ctggatgggtg tcccagccc
1681 cccaggatac atgtcagatc aagaggagga catgtgcttt gaaggaatga aaccctgtaa
55 1741 ccaaactgca gcctcaaaac agggactcag aggtctcctc caccacagc agttgcactt
1801 gctgagcagg cagcttgagg acccaaattg tagcttttct aacgctgaga tgagtgaact
1861 gagtgtggca cagaaaccag aaaaactttt ggagcgctgc aagtaactgg ctgcttgtaa
1921 aaatggggat gagtgtgcct accatcacc cactcacc tgcaaagcct tcccattg
1981 taaatttgct gaaaaatgtt tgtttgttca ccaaattgt aaatatgatg caaagtgtac
2041 taaaccagat tgtcccttca ctcatgtgag tagaagaatt ccagtactgt ctccaaaacc
60 2101 agcagttgca ccaccagcac cacttccag tagtcagctc tgccgttact tccctgcttg
2161 taagaagatg gaatgtccct tctatcatcc aaaacattgt aggtttaaca ctcaatgtac
2221 aagaccggac tgcacattct accatcccac cattaatgtc ccaccagac atgccttgaa
2281 atggattcga cctcaaaacca gcgaatagca cccagtcctg cctggcagaa gatcatgcag
2341 tttggaagtt ttcattgact gatgaaagat actctacaga acttgtaaaa tctttgaaac
65 2401 ttggaatata ttgctttcat aatatgaagt tttattgcct atctatctga agtgtcta
2461 ttttcaagtt tgtaagttta ttatgtggtt ttaacattgg gtgtttttgt tttgttttta
2521 ctatgaaaag acagcttaag gaagagctaa attctgttaa aatatttggg gcatgtttgt
2581 gcaactgctg tgtgaggatc agcatatgaa attgacatca tggtagtca tggtagtca
2641 gcttaggggg ctacacggtt gctgtgtgag tggagagatg cagtgaggca gttgtcatta
70 2701 ttctaaaaat tgtactactt tcaactttcc caaagattat ataattgtca taatccacca
2761 tgaaaacagc attggccaaa ggtactgagg ctgcttaaaa tattcaattc tgctttttta
2821 tttttaagtg aatttagttt gaaaagcatg attatacagg cctctcaggg tgagtgtctac

	2881	tttggtaaag	ttcccagttt	tcctgccttc	tgtgacagga	tgaatgaggt	gggtatggac
	2941	agtggaggca	gctggaatgg	caagtgcaga	aaataggaac	agttctatac	agtgcctctca
	3001	tttactaata	acataatgcc	ttctaaataa	tttttttggg	aaactacatt	atcacaaaat
5	3061	tatacaaatt	tttttacaag	tattttacata	ctgtatctga	aaacagactt	taaagtcaca
	3121	agattataaa	tgtacatata	tattctcaca	ttctgaaaaa	taacattctc	agaatccaca
	3181	gaaaatatac	ttagttacta	ctgaagataa	tttttgaaat	gtaaaaatta	gatttaaata
	3241	gtatatTTTT	aatgacagaa	ctataattac	agagatcaga	tcagataggt	aaactgcaag
	3301	atagatagga	tgaaactttt	ggcctactgt	attacttaca	gagttttttt	gtgtgtgggt
10	3361	tttaaaactg	ttaaggcaag	aagtgtcaaa	tgccttagag	ttaaataaca	gatoactgat
	3421	ttcaaagact	tggtgtatag	tgttaaaaat	taaagcttaa	aaggtgggta	gaaaagtggg
	3481	ttaatgcaaa	aggggtaata	aagactgcaa	cattctcagg	accaaattaa	actgctaaaa
	3541	aaaaaaaaaa	agttcattga	cttgcttagt	cgtatactca	aatgatgata	aacctacatg
	3601	tgcaaaggct	cacgtttaag	attgtcaagc	cagcagtcta	ctggtgtggt	gccattgctt
15	3661	ttccattggg	agaagaaaga	attaaaccag	cattaaacca	tttggtaagt	tgcactttgc
	3721	tgtgctgata	ccacaggaaa	ggcctgaaac	acgagaagca	gcaaagacag	agcacacaag
	3781	tgcataaggc	tgttgtcttc	ggcctgggtg	aaatgacagt	tcctcttcat	tctaaagggt
	3841	tactccattg	aatttaaggc	atttgttcat	tccagtgttg	agatgctttg	catctctgca
	3901	gaagaaattt	attttaaatt	gtttaaatat	ctggaaatac	ttttagctat	catttataaa
20	3961	gatagtTTTT	ttctcagttt	cactataaat	tatagaacaa	atgggaaaca	agggtttaat
	4021	ttagttcagc	catttttaca	ggaaataata	aaataactaaa	atctgattgt	tttttgctat
	4081	ttaatagcca	ctgcccagac	acataatttaa	gagtttaatc	tttcagttgc	tatggcttat
	4141	gaacaagcta	aggttgacca	taaaacattt	gttggaatgac	gtgggtttaaa	atgatcacca
	4201	caaaaaggga	ccacaaaaaa	aggaaggaaa	tgagcatggg	tggcgattgg	aagcaagggt
25	4261	accagagggc	acagtgtgct	ttggcatgca	ttttatacat	aaaatgaatg	gaacaaaagg
	4321	tgccagaagt	cccaggttac	acaatcagga	gcttagatac	tgcacacaaa	aataattatc
	4381	tggttataaa	aagtaaacat	agggcagatt	ctatatggcc	tatcatgttt	cttcaccttc
	4441	ccctcgttgc	tggtctgatac	agcgagggtg	tcagctgatg	actacttagt	caatatgacc
	4501	tttagtcgtg	aaactgacag	cagcagtgat	taaggctgac	ttaatcaggt	tggccacttt
30	4561	gaaggacaga	aatgcagtg	aaacagtttt	attctatgta	gtttacatgc	ttaaggttac
	4621	agagtttcta	cctgcactgt	aatggaaata	taatttctct	gtagccaaaa	gctggcaaac
	4681	ttgaccaga	gggaaaattt	aaaactgcag	caggctcaaa	tgtagagtat	ttttcttttt
	4741	atgggcaggt	tgttcaggga	tttttttcc	cctttaattt	attgactgac	tgtaaataca
	4801	tgagttagaaa	cttaatagtc	atgtattttca	aaatttggtc	taatttagga	gaatccactg
35	4861	atgaacaagt	accaactttac	gtttcaagct	tcttagcccc	ataatcagtc	cttcagccac
	4921	agctattttag	agcttttaaaa	ctaccagggt	caatcactgg	ttatgctttc	tgtgatgtaa
	4981	tttagtcatt	tctatttttta	gtatttaacca	agtattagac	acagaaaata	ggtatttaaga
	5041	atcttctatat	atcctgtcag	accaaattggg	attccaggaa	cctaaagcga	tctatttatgc
	5101	tataaagata	attaacacat	taaaaactca	taggggtcaat	acagcatctt	aaacctcaca
40	5161	cttagaaaaa	tatatTTTT	aatagcagtc	tacataattt	tcaatcttca	ggaaactaca
	5221	gataggctag	acagcgaatt	cctgaatgat	gagtagtgat	ctttggcagc	atttaaagtg
	5281	aaaagaaata	aggatctaag	aattcagccc	taatccacta	aaaaaaggaa	ttctaactga
	5341	caagtTTTT	caaattggagt	tgggctcatt	catttttgga	ataaacctat	ggagtggcac
	5401	acatctaaac	aaattttccc	aatagaaaaa	aggctataaa	aatttttatc	caagagtgat
45	5461	taaattgtat	aatgttgtat	atgtgaattt	aacacttttg	tttacatgtt	aaacaaatgt
	5521	gtatatatta	gactacatta	aatatgcaat	tctttcttcc	agttaaatac	tgttgctccc
	5581	taaaaccctt	acattgtaca	ccattgggaa	tgattgttca	tcatactact	tttccattag
	5641	tgaggctaca	gttatgtttt	aaatgtgcga	ttacagagat	ggcatctgaa	cataaactga
	5701	tggctcgaaa	atgaaaatgg	aaatgtagca	gccatatact	gctaactttg	gatctgttcc
50	5761	tgaattcaaa	actactagga	gaaaagtgtc	ctttataaaa	aaggacctta	ttaatgccta
	5821	aaaaacatca	tattctctag	gaaagcttgt	gtctgtttcc	ttagggaaaa	tgtttgcctt
	5881	ttaaaaactg	tgatcccttta	ggatgatcat	gactttccct	ttccttatgg	aaatgcaaga
	5941	ataaaaatatt	tcattaaaca	atgaaccttg	aaaataaaa	ataaacatta	agaaaccatt
	6001	ttgctaaaaa	gataatgaaa	attatccaaa	ttgggttttt	gagttcttct	gtaaagagtg
55	6061	ctctacccta	aatttttccc	gcagggtctgc	cgaaatcaca	cacttcccaa	tacaggggga
	6121	cttggccttt	accatcaagt	attcgatcct	tccttgaaat	ggcatttatc	ggcagtgtat
	6181	ggattacgga	ttatacccag	tgcatatagc	aaatatTTTT	aacagatcag	tctttcacta
	6241	ttttgatgat	tctgggcatt	tctccctgtt	acagtcttgg	gttagcacca	cttgaccatg
	6301	caggggttggg	ttttgggttt	tcttctctgt	aattctgggtc	tcaaagttaa	tttctgtagt
60	6361	catctcagca	tctctcagtg	aggtgtatgt	acacatttcc	agacaaataa	gctgcaatca
	6421	gagaagaaaa	ttgcagggag	tttaattatgt	tttttagattt	tcataacagt	ttaatatTTT
	6481	tcagttgtgc	tttcagggtta	catgtgtaat	atttttccctc	tttaactcct	tttattctgt
	6541	atttgcataa	atatgagatt	ctgaagagcc	atctgggttat	actacottct	actaatgttg
	6601	actagctgat	ttcataaacc	aaagctgtag	gagttgttgt	attaagtctc	ttaactagta
65	6661	acatagtctg	ctcttcatgg	gctgagaaag	ttactaacct	gcagtcacac	cctccagcac
	6721	taacaacatg	tcgatcacca	ctggtaaatc	gaatatTTTgt	cacatggggc	gaatgacca
	6781	agaacctttt	gtgtttttgcc	taaaaaacaa	tgacagacaa	gctcagggca	tttgggtgcac
	6841	acagaagtca	aaggctctta	ttaggaacta	taatctctat	gacaagagct	gtggagagag
	6901	tagggagtta	gcaccgcagc	cagtgattag	aatgcttttc	agcatgagta	gtggatctgc
70	6961	aaaaccaggc	tgtgtgggca	gtcagatgtc	tccaggtaact	ctgaccattt	ttctctaagg
	7021	aaaagcattt	gaaatttgat	aactgattat	aggttttggtg	aaaagcta	tacagctttt
	7081	gtaggatggg	tccaaagatg	gtattactcg	agggagagga	tttgtttcta	atagctttta
	7141	tttcaaagta	aatagattta	gaaagtTTTgg	ggaaaaattt	agaaattagg	acaaaacatt
	7201	ttaaatatat	ggggaaaagt	gctgatgata	agacatcaaa	attaggagta	aactgataat
75	7261	agtaaacaaa	acacaaactt	acaaattttt	ctggacatgg	gaagtcaaat	aacttaacca
	7321	tgccaaagtc	atctcctgta	acaagactga	ttcctgaatg	agatacacag	gcacagttga
	7381	catcagcttt	ctcagcatgt	ctggaccaga	ttcccaaaac	ctcatctcct	agaatactag

	7441	agggaaggaa	caaaagaaaa	ctcatcatgg	caagtgcggg	caggttgact	atattcaaaa
	7501	agttttcttg	caattaatct	ctaagtaccc	tatcatgtta	cttaaaatac	aggaagtaaa
	7561	ttatggtaag	ttgtttggag	acctgaattt	catcaggata	tcaactcctg	ccttttaaaa
5	7621	atgacatttt	ataatttgaa	gggtttctag	attaatcttt	ttaagattaa	agtagtactt
	7681	tatgaaaact	gatagaacta	ttttttcttt	tttttttttt	gagacggagt	tttogctctt
	7741	gttaccagg	ctggagtgca	atggcatgat	ctcggctcac	cgcaacctct	gcctcctggg
	7801	ttcaagcaat	tctcctgcct	cagcctcccc	agtagctggg	atcacaggca	tgcgctaaca
	7861	tgccccgctt	attttgtatt	tttagtagag	acagggtttc	tccatgttgg	tcaggctagt
10	7921	ctcgaactcc	cgacctcagg	tgatcacccc	cgtcggcct	cccaaagtgc	tgggattaca
	7981	ggctgagcca	ccgcgcctga	ctgaaaactg	atagaactat	ttttcaaatt	aaaagtgcga
	8041	cttggctggg	tccagcagca	cataccagta	atcccaacat	tttgggaggc	tgaggcagga
	8101	ggactgcttg	aggccaagag	tttgagacca	gcctgggcaa	tattgtgaga	tccttatctc
	8161	tacaaaaata	aaaatgactt	atgacatagg	aattaaaaaa	atttcagaga	tggggtcttg
15	8221	ctatgttgcc	caggctggta	tcaaaacttc	taggctcaag	tgatcctccc	acctoggcct
	8281	gctacatcag	agattacagg	catgagccac	tatatgcctg	gctgatacag	gaatttgatg
	8341	gcattttttca	ttggccaaaa	aaatggatag	tcatgggttac	ctgtcataca	gccaggaaat
	8401	ttgaacaaat	ttggaagctt	tgactttctaa	tagattcaag	atagcattcc	tttagataga
	8461	gaattaataa	cagttgctta	acagcaccca	ataccttttt	gccagtccatt	aaatttagca
20	8521	ttaagaaaaa	tatcagggta	tctttaaagt	taaaactttg	atttccttaa	aaaaaaaaact
	8581	tgataaatca	tggaaactga	taaaacatgg	aaatatattc	aataaaaaagg	ggtcccaaca
	8641	tgaacatacc	atttcaaaat	atggtaacaa	aaacttgaaa	ctcaattact	attccttatt
	8701	ggaatggctc	taacagttca	gaaataggat	tttctaactg	gccttcaaag	tcagttcttg
	8761	ccttgtgaat	atataagtat	ttacctagtc	catgtagccc	aagtaattct	gtcaatagcg
25	8821	gcatgatcca	taagatgttt	tcctgaaggc	acttcataga	catgccgttt	atagcagcca
	8881	ctagagacct	ttttcatcag	attaaaatgg	gacaagaatt	ccattagggtg	agagacaaaa
	8941	tccacagggg	gtttacagaa	tactagcata	ttgctacttg	atttacatgt	ctaacattat
	9001	taagtatgca	aaagatcact	acaaaaactt	aataggagaa	aagctctgat	aagtggggga
	9061	ggaaagggga	gctgtaggtc	agaagggtaca	aaggggaggag	ttgagaagct	ggagctctgg
30	9121	agctcaggaa	ctttaaatgc	attcactaac	acgaaatgta	aaagcagaag	aacttgccac
	9181	ctgggtatac	agtattggta	ctgtacctgg	agataactgc	tatctgcaga	gaagtccatt
	9241	tgaatgacaa	agcttggaat	gtctttgcag	tagctgattc	tgtaaagagt	ggggcccagc
	9301	gttaggtcat	aaaaatccac	tgagtttcca	ctagaacctc	ctgccagata	cogggaatcc
	9361	ggaactaaatc	tgaatcaaaa	caaaacgtaa	aaagtattag	accacatgaa	gtattataaa
35	9421	tacttaagat	cagtgaacttt	tcctttctag	ttcttaaaaag	taacgtgtga	taaggcctca
	9481	aatagattta	cctgtcagac	acaactgate	atgtatactg	agattgtctg	ggttacatga
	9541	aataaggaag	ctttatatatt	tacttaaaatt	ttaaatatatt	cccccaattgt	catctcccaa
	9601	ttccttttaa	aacgtctaatt	ggcttaaaaa	aactttctta	ggccaggccc	agtggctcac
	9661	acctataatc	ccagaacttt	gggaagcgga	ggcgggcaga	tcacctgagg	tcgagagttt
40	9721	gagaccagcc	tgaccaacat	agagaaaccc	tgtctctact	aaaaatacaa	aattagccag
	9781	gcatgggtgg	gcacgcctgt	aatcccatct	actcgggagg	ctgaagcagg	agaatcgctt
	9841	gaaccagga	ggcacagggt	gtgggtgagct	gagattgcac	cattgcactt	cagcatgggc
	9901	aacaagagca	aaactccaac	tcaaaacaaa	acaaaacaaa	atttaattttt	ttaaatagag
	9961	gcgggggtctc	actatgggtcc	caaaactcctg	gcctcaagca	atccttcccc	cttggcctcc
45	10021	caaggtactg	ggattacagg	tgtgagccac	aacacccagt	cagaacatct	cagcttttaa
	10081	aagccattag	cattacataa	ttaataagct	aacaattcat	taagatagtt	ttcttccatc
	10141	tggaaaaaac	gttgtcttaa	tattaagcaa	agaacacagc	ccagcttaac	taacctccag
	10201	ttattaaggt	gaaatgacac	aacttgaatc	ttggaagaag	aatTTTTTTT	TTTTgagacg
	10261	aagtctcgct	cttgtctccc	aggctggagt	gcgatggcgc	aacctccgcc	tccggggttc
50	10321	aagcgattct	cctgtttcag	ccccctgagt	agctgggatt	acagggcgct	gccaccagcg
	10381	ccggctgatt	tttgtatttt	tagttgagat	ggggtttcac	tatgttggcc	aggctggctg
	10441	agtactcctg	acttcagggtg	atctgcctgc	ctcggcctcc	caaagtgtctg	ggattacagg
	10501	catgagccac	cgcgcgccgc	ctgaagaact	tattttaaag	acaaagtga	atgctatttg
	10561	cctagcaatc	tttgaggtca	tatgggacaa	ttcagttctc	tgaaatggcc	catgagttct
55	10621	actgaggtac	gatagagaca	tgtaaaagct	aagggaagcc	actgttacta	ttttatatat
	10681	tgaagttctg	aggaagggtt	catttgttaa	aggattttac	tgatgaaaag	tgtacaagct
	10741	tttgacagac	ctagattcaa	taatcttata	tactgatcac	acggaagtac	tcogtaaatg
	10801	gtagccactg	ttgaaaaatg	cttaagcact	gaaaaacaaa	ggtttaagaa	acatttaaat
	10861	taatttggat	tctggaacat	ttaatcaata	ggtattgatt	aaattaatga	actacatatt
60	10921	cccaaactga	ggttactaag	agaagatatg	tttgaaatca	caactttagt	tttccagggt
	10981	gacaactttt	gaagggcaga	tagctctctt	gtattacagt	gggagatacc	tcttgggtggg
	11041	atgaacttaa	tggacatggc	taagtgttaa	catgaattca	tcaaacatta	cctactagta
	11101	cttgcattta	tagttgggtg	ccagtgggtt	tataatttag	caagaagaat	taagtagtat
	11161	acaaacagcc	atatttttag	atacaattta	taatacggga	aatgctacag	gccctgggga
65	11221	cctctttttg	aaggcaaggc	tatggaaaat	tttaciaaatg	gaagttaaat	caagtatata
	11281	ctagaaactc	tattccattt	gttcactaac	ctgatatacat	ggattgcaca	tctcctgtct
	11341	ctcttctttc	cccataattt	tagagaactc	actagtaaaa	tgataaatte	tccatttttc
	11401	attccaatag	ccaccatgtc	cccttcaggg	ctgtaacaca	cagtacgagc	agcatgtccc
	11461	aaattcactt	tgtttaacat	cttctgcatt	taaaaaaaaa	aaaaaaaaaga	gtcataggaa
70	11521	acattaagtg	aagtacttct	aaattataacc	agtttccctt	caaaatgtctc	aacagaattc
	11581	tggcagttct	ttaagtacta	gcaatttaga	acttccaact	tttctttttta	gaagttgtaa
	11641	cctcttttaa	aaaaattatc	tgtacttact	ttatcagcaa	tatcccaaag	tctcactgtc
	11701	ccatcttctg	cagcagaaag	gaaaaaatcc	ctggaaggat	gtgttgctag	tccccagatt
	11761	ggcccatcca	catgaccgtt	aactaaaata	ttacaagctg	cattttttctc	tccaacttctg
75	11821	attatttcag	cattccttgt	cccaacaagg	atcttgccct	gaaacacaag	caggaccaat
	11881	acagtgaatg	taataacaaca	gctgcttttc	ttcttcataa	tataaaaatg	acctatttga
	11941	cctgctttca	gagaactttt	tgctttgagc	taatctagta	gcaaggcagt	cattagctca

5	12001	tgcaaatttt	tctatgacta	caggcacaca	tctatctgtgta	agcacaatgg	gctagattac
	12061	atattagagt	ccatgctaca	gaatagaact	tttctgtggc	agtacacctg	gattcttcaa
	12121	taatcaaagt	ttttatttga	taatcttagg	atttcctaac	tgggggtcagt	gcagtgggat
	12181	ataggaaaa	ataatagaat	ttatttttta	gttaaaaagt	aaaagcttaa	ctacaattta
	12241	atatgcaggc	tgaagataat	atccgtatga	tttataaata	cacttaataa	gtacaaacac
10	12301	gctcaaaaat	tttcatagga	gttgtagttt	tgaattttta	ttttgaaatt	gacacataat
	12361	tatacatatc	tatagggcat	agggtaatac	gcataaccat	cacctcagac	atztatcatt
	12421	tctttgtgat	ggaaactttc	aaaatcctct	cttgtaaata	cctgaaaata	cataaatacg
	12481	tgattcttaa	ctatagtcac	cctacagtac	tacagaatac	taaaacatac	tattcctatc
	12541	tggctgtgta	aacttgtatc	ctttaaccag	tccttcctca	tccccctccc	cctccccctt
15	12601	gtccgcctcc	agtaaccact	attctactct	ccacctctgt	gggatcaact	tttttagttt
	12661	ctgcacagga	gtgagaacat	gtatttatct	ttctgtgcct	ggcttatttc	acttcacatc
	12721	atgtcctcca	gtctcatcca	tgttgccacc	aagaatgaca	gaatttcatt	attttttatg
	12781	gctgagtagt	atttcattgt	ttgtttatctg	cacgttttat	ctaggggaatg	tgtgtttttt
	12841	taaaaaatgg	agacagctgt	cctaataatga	gtcaactgcc	aagggttttc	aattatgtct
20	12901	actagagttg	ttaaattggc	agattctaga	aaatattgga	ggtttacata	cagtatttag
	12961	acagaatagc	ttcctagctt	atgcaccaca	ctggtgctaa	ctttggcaaa	gaaagcagca
	13021	aagacagagt	aatgttggca	agcaaatacca	tcgttatgca	ttattaagta	ttgttcatta
	13081	ggctgcaaag	ggtgagggaa	tcacagtaat	aaccactttc	tgttttctgc	tgcactgtat
	13141	cagctcatgg	aacatcttac	tttgccctctg	cacacagaac	gaacacaatc	tgtggcttgt
25	13201	cctgtctcaa	gcctgaaggc	acggcacccgc	ctcagttcct	gatccacag	tttaaccgct
	13261	cctccttctt	ttgacctaa	taaataacca	agccagagta	agtgttcatt	attggctact
	13321	ataattttta	ttataaacia	ataccaagtt	ataagcagaa	tctttttttt	ttaaaaaggc
	13381	cctgatattt	ataattttacc	tctaataatc	ttgtaaactt	tctatggcaa	tttgaggata
	13441	tactatatct	cagtcaaaaat	aaacatccag	tttcagtga	ttttattttg	agaaatactc
30	13501	tttttttctg	acatgagcat	aatttttat	agcctctaca	atacattaca	atacattatc
	13561	ctctctcata	atactttttt	ttttttttt	aagatgtagt	ctcgtctgt	ctcccaggct
	13621	tgagtgcagt	ggcatgatct	aggcttattg	caacctctgc	ctcccagggt	caagcgattc
	13681	tcctacctca	gcctcccgag	tagctagcat	tacaggtgtg	caccaccaca	cccagcta
	13741	ttctgtat	ttagtagaga	tgggggttca	ccatgttggc	caggctgggc	tcaaatacct
35	13801	tgacctcagg	tgatctgcct	gcctcggcct	cccaaagtgc	tgggattcca	ggtatgagcc
	13861	actgtgcctg	gcctcataat	acttcttgat	taggaagatg	taaaaaaaca	attttattaa
	13921	aaggataatg	gaaatgtaag	gcaaaataat	agaattacaa	atgctatgct	acagagttga
	13981	tttattttatt	tttttgagac	agagtgtcgc	tctgtcacct	ggcctggagt	gcagtgggtg
	14041	gatctcgget	cactgcaacc	tgtgcctccc	aggttcaage	gattcttctc	cttcagcctc
40	14101	ccaagtagct	gggattacag	gcaccatgcc	tggctaattt	ttgtattttt	agtagagatg
	14161	gagtttcacc	atattggcca	ggctgatccc	aaactcctga	cctcgtgatc	cgccacctc
	14221	ggcctcccaa	agtgttggga	ttacaggcgt	gagccactgc	aactggccca	gagcttattt
	14281	ttgaaggcca	aaacagaagc	atattttatc	cctatcaggt	gttaaaatat	ctcactggaa
	14341	cagtttagca	ggcttctagt	gagtgggggt	gtgcaggagt	aaatgacgtg	ggaaatacaa
45	14401	gtgttgagg	acgaaataga	gcccatattat	ggattttatt	cctggaagg	ctgaaaaatg
	14461	tattccttcc	ttttctgcta	gatgaattgc	ttgtctgaaa	gcatgcctat	gtgcattctt
	14521	cctttatgta	aaaggcacaa	attctgcgct	tgtgtttaat	taacatatgt	gggttctttc
	14581	aatcctgtat	tgaatgtac	ttcttagtca	actatatgtc	acattttttt	ttgtttttgt
	14641	ttttgttttt	taaatggggt	ctcactctgt	caccaggt	ggagtgcagt	ggcaccatca
50	14701	cagctcacta	aagccttgac	ctccccaggc	tcaagtgate	ctcccacctc	agcctcctga
	14761	gtagcaggga	ctacaggcat	gtgccaccac	acccggctaa	ttgttgtttt	ttatagcgat
	14821	ggggtttcac	catgttgccc	aggctgggtc	tgaactcctg	ggctcaagcg	atccacctgc
	14881	ctcagcctcc	caaagtgata	agattacagg	tgtgagccac	tgtgcctggc	ctacatgtca
	14941	tgtttcaaca	tgcataatgac	tatgttgggtg	acaaatcaaa	tcataagtat	ctggttactg
55	15001	ttgggagatt	tgaaaatcac	tcagaagaga	cctcttctca	aattttgagg	tcttgtataa
	15061	aacagtttaa	atttgcctca	agcaaaagga	aacaaggcag	ttctctctag	ttccctcatc
	15121	cttttctaaa	gcaacaatgt	gcattctact	ccttagaate	cattctgaac	aaaaagagag
	15181	caggcagtca	aaatacaacc	ctggctccag	attcccccat	gggcctccta	ctcagcaaat
	15241	catacacagg	catacagaca	ttaagaaaag	taactcaact	tgtaggacaa	ctacctatcc
60	15301	acacctcaga	aaaagtatca	ccccaacatg	aaaaaaattg	gaagtgaatt	aagaccagaa
	15361	atgagaatca	aatagaaggc	acataaaaag	taataaaagg	gaagcatatg	aggaggaagg
	15421	tcggagagga	cactctgtgt	agcctagaaa	caactagaat	aatttaactgc	aaacctcagg
	15481	taggtcacia	atgcataaat	attctgtgaa	aagaaagagg	actcacggcc	tttcccttcc
	15541	cccagtcacg	ataagtcac	ctcgcagggt	ggtgtacatg	gcaaacacag	gcccgttgtg
65	15601	agctctcgcc	acgattctac	acaatatgtg	atctttccac	acacagacat	caccactgat
	15661	ggtacctgta	aacgtcaagt	tattctgaaa	aggagtgggg	gagggggaga	caaatcctc
	15721	aaaagttcaa	atagagttta	aatagataat	tttctatgta	tgtgtaatgc	tgtctcacc
	15781	ttgatacaaa	gagcatgcat	cgtgtagtgg	cagcagcact	gaattcaoga	gtcaggaaac
	15841	ctgaacggga	ggcttagctt	tgtcaggacc	ttttcctttc	caagtctgtt	gcttatttag
70	15901	tagaataacc	ttagacaatt	cttcccttcc	aattctaaca	tactataatt	ctagggttta
	15961	ttttttat	ttttgagacg	gagtttctgc	ctttgttgcc	caggctggag	tgcaatgggtg
	16021	cgatctcagc	tcaccacaac	ctctgcttcc	caggttcaag	tgattctcct	gtctcagcct
	16081	cccaagtagc	tgggattaca	agcgccagcc	accacgccc	gctaattttt	gtatttttag
	16141	tagagacaga	gtttcacctt	gttagccagg	ctggtcttga	actcctgact	tcagggtgat
75	16201	ttcccgctt	ggcctcccta	agtgtggga	ttataggtgt	gagccactgt	gcccggcctg
	16261	agccacgggtg	cctggcctgg	tcttatatta	agaataccca	aaatgttcaa	ctgaaatttg
	16321	acatggcaca	aacattttcaa	tagtcttttt	ctcaaaaatg	taagtgtact	taaatattct
	16381	aaaattataa	cttttcctat	aagtattgca	taatcacaaa	aacaaaaaat	gcacttagtt
	16441	tttcgatgca	ccaaaggatt	tatacagcct	agccaatgca	ggatatttaa	ggaaagagat
	16501	gtggattgga	agccacagg	ccagatgaga	tggaaataaag	tgagaggaga	gcaggctctcc

5 16561 tgaacaccct tctgtcaggg ccaggaattg tgetatttcc ttctgtctca ctacctcctt
 16621 cttccctcga agtagagaca ctggcccaga gcacttccag ctgtatgata agcagtgtgt
 16681 taaatgataa aaagcaaagg aaatcctaaa ccctagtacc accttaaate atttgaaaat
 16741 catgtttctt gatttacctt tctctctgac aaatttttag gactatgaag aactactagg
 16801 aagacagaaa ttttaggata tttaggggtga caattagaag attaaggaag gcttttgagt
 16861 ataacagtag tccaaggaat caaatgttca tcagaatcct tattatggtg gctcatgcct
 16921 gtaaaccag cactttggga ggtcaagatg ggaggatcac atagcttagg agcttgagac
 16981 cacctaggca acatagcgaa accctgtctc tactaaaaat gaaagaaaaa ttagcctagc
 17041 atggtggttc ctgccttgta gtcccagcta ctaaggagge tgaggatcac ttgaacctgg
 10 17101 gagatggagg ctacagttag ctataatcgc accattgcac cccagcccag gcgacagagt
 17161 gagatactgt gtcaaaaaaa aaaaaaaate cttttccccc tctcattaac attcttttca
 17221 ctccctaatt tctgaaagaa ctagattttt gaaagatgaa atatatgctt gaccagggca
 17281 tgtaatgatt agcagatcac agtatcatct caacaacatt catgtggctg atgatctaag
 17341 gcaagagaat gtaaagtagt caaagtcaca ctatgtgcat tttaagagac atactgcacc
 15 17401 aaatgcaata gcgagcatgg tctgcatccg ggcatcttcc agtgtgctca gtaccctttt
 17461 tttgctaaga agagctcttc ctgccagggg ccagaacttc acatgtttta ctccactga
 17521 gacaaactgg gtatctgaat ctggtcggaa ttctgccaca aaaatacgtt gattgtgacc
 17581 agctctgctg gcaatttttg cacctgacaa gatacaacaa aattatctag gttattacaa
 20 17641 gaaccaagct aatcaacagc atcaaacaaa tatgtaaaat acatagttca aaaaacaaag
 17701 gcttagaaga gagggcaatg gcccctgctc tactacctag caatacatga tttacaatta
 17761 tttgtgtatt gagtctttt cacttatctt cgtctcatta acttttcttt atataacgta
 17821 aatgttttgt ctaaagtgtg gtaggtaata ttatctgct gatctgccat tatcattaga
 17881 aatatacata attttcataa gaatctccaa aaccaatcaa atcattaata ataaatacat
 25 17941 agtttcttgc tggaagaaaa tagcagtgaa tcatttataa tgctaataat ggtttcatta
 18001 atttatctgt tttgtgaggt tacagttcca ctgggctttt aaagtgaat atacctacag
 18061 taccactgtg tacagtatat tgcataggcc tccactgaat gattgtttca accaccaact
 18121 ttaagacaaa tattaataac agaattccta cta

Disclosed herein are siRNA molecules. Also, disclosed herein are compositions
 30 comprising any of the siRNA molecules described herein or recited in Table 2. In some
 aspects, the siRNA molecule can be a sense strand. In some aspects, the siRNA molecule can
 be an antisense strand.

Disclosed herein are compositions comprising a nucleic acid sequence or molecule
 wherein the nucleic acid comprises or consists of a sequence having the sequence set forth in:
 35 UUUUCUGGUUUCUGUGCCACACUCAGU (SEQ ID NO: 7),
 UUUUUCUGGUUUCUGUGCCACACUCAG (SEQ ID NO: 9),
 GUUUUUCUGGUUUCUGUGCCACACUCA (SEQ ID NO: 11),
 AGUUUUUCUGGUUUCUGUGCCACACUC (SEQ ID NO: 13),
 AAGUUUUUCUGGUUUCUGUGCCACACU (SEQ ID NO: 15),
 40 GCAGGCCAGUACUUGCAGCGCUCCAAA (SEQ ID NO: 17),
 AAGCAGGGAAGUAACGGCAGAGCUGAC (SEQ ID NO: 19),
 CAAGCAGGGAAGUAACGGCAGAGCUGA (SEQ ID NO: 21),
 ACAAGCAGGGAAGUAACGGCAGAGCUG (SEQ ID NO: 23),
 UACAAGCAGGGAAGUAACGGCAGAGCU (SEQ ID NO: 25)
 45 UUACAAGCAGGGAAGUAACGGCAGAGC (SEQ ID NO: 27),
 CUUACAAGCAGGGAAGUAACGGCAGAG (SEQ ID NO: 29),
 UCUUACAAGCAGGGAAGUAACGGCAGA (SEQ ID NO: 31),
 UUCUACAAGCAGGGAAGUAACGGCAG (SEQ ID NO: 33),

CACUCAUCUCAGCGUUAGAAAAGCUACC (SEQ ID NO: 35),
 UCUGGUUUCUGUGCCACACUCAGUUCAC (SEQ ID NO: 37),
 UACUUGCAGCGCUCCAAAAGUUUUUCUG (SEQ ID NO: 39),
 UCCCCAUUUUUACAAGCAGGCCAGUACU (SEQ ID NO: 41),
 5 GAUGGGGUGAUGGUAGGCACACUCAUCC (SEQ ID NO: 43),
 UUGGGGAAGGCUUUGCAGGGUGAGAUGG (SEQ ID NO: 45),
 AAACAUUUUUCAGCAAAUUUACAAUUGG (SEQ ID NO: 47),
 UAUUUACAAUUUGGGUGAACAAACAAAC (SEQ ID NO: 49),
 UCUGGUUUAGUACACUUUGCAUCAUAUU (SEQ ID NO: 51),
 10 UACUCACAUGAGUGAAGGGACAAUCUGG (SEQ ID NO: 53),
 UUGGAGACAGUACUGGAAUUCUUCUACU (SEQ ID NO: 55),
 GUGGUGCUGGUGGUGCAACUGGUUUUGG (SEQ ID NO: 57),
 ACGGCAGAGCUGACUACUGGAAGGUGGU (SEQ ID NO: 59),
 CCAUCUUCUUACAAGCAGGGAAGUAACGG (SEQ ID NO: 61),
 15 GUUUUGGAUGAUAGAAGGGACA UUCAU (SEQ ID NO: 63),
 UACAUUGAGUGUUAAACCUACAAUGUUU (SEQ ID NO: 65),
 GUAGAAUGUGCAGUCCGGUCUUGUACA U (SEQ ID NO: 67),
 UGGUGGGACA UUA AUGGUGGGAUGGUAG (SEQ ID NO: 69),
 UCGAAUCCA UUA AAGGCAUGUCGUGGU (SEQ ID NO: 71), or
 20 UUAUUCGCUGGUUUGAGGUCGAAUCCA U (SEQ ID NO: 73).

Disclosed herein are compositions comprising a nucleic acid sequence or molecule wherein the nucleic acid comprises or consists of a sequence having at least 90% identity to the sequence set forth in: UUUUCUGGUUUCUGUGCCACACUCAGU (SEQ ID NO: 7),
 UUUUUCUGGUUUCUGUGCCACACUCAG (SEQ ID NO: 9),
 25 GUUUUUCUGGUUUCUGUGCCACACUCA (SEQ ID NO: 11),
 AGUUUUUCUGGUUUCUGUGCCACACUC (SEQ ID NO: 13),
 AAGUUUUUCUGGUUUCUGUGCCACACU (SEQ ID NO: 15),
 GCAGGCCAGUACUUGCAGCGCUCCAAA (SEQ ID NO: 17),
 AAGCAGGGAAGUAACGGCAGAGCUGAC (SEQ ID NO: 19).
 30 CAAGCAGGGAAGUAACGGCAGAGCUGA (SEQ ID NO: 21),
 ACAAGCAGGGAAGUAACGGCAGAGCUG (SEQ ID NO: 23),
 UACAAGCAGGGAAGUAACGGCAGAGCU (SEQ ID NO: 25)
 UUACAAGCAGGGAAGUAACGGCAGAGC (SEQ ID NO: 27),

CUUACAAGCAGGGAAGUAAACGGCAGAG (SEQ ID NO: 29),
UCUUACAAGCAGGGAAGUAAACGGCAGA (SEQ ID NO: 31),
UUCUUACAAGCAGGGAAGUAAACGGCAG (SEQ ID NO: 33),
CACUCAUCUCAGCGUUAGAAAAGCUACC (SEQ ID NO: 35),
5 UCUGGUUUCUGUGCCACACUCAGUUCAC (SEQ ID NO: 37),
UACUUGCAGCGCUCCAAAAGUUUUUCUG (SEQ ID NO: 39),
UCCCCAUUUUUACAAGCAGGCCAGUACU (SEQ ID NO: 41),
GAUGGGGUGAUGGUAGGCACACUCAUCC (SEQ ID NO: 43),
UUGGGGAAGGCUUUGCAGGGUGAGAUGG (SEQ ID NO: 45),
10 AAACAUUUUUCAGCAAAUUUACAAUUGG (SEQ ID NO: 47),
UAUUUACAAUUUGGGUGAACAAACAAAC (SEQ ID NO: 49),
UCUGGUUUAGUACACUUUGCAUCAUAUU (SEQ ID NO: 51),
UACUCACAUGAGUGAAGGGACAAUCUGG (SEQ ID NO: 53),
UUGGAGACAGUACUGGAAUUCUUCUACU (SEQ ID NO: 55),
15 GUGGUGCUGGUGGUGCAACUGGUUUUGG (SEQ ID NO: 57),
ACGGCAGAGCUGACUACUGGAAGGUGGU (SEQ ID NO: 59),
CCAUCUUCUUACAAGCAGGGAAGUAAACGG (SEQ ID NO: 61),
GUUUUGGAUGAUAGAAGGGACAUUCCAU (SEQ ID NO: 63),
UACAUUGAGUGUUAACCUACAAUGUUU (SEQ ID NO: 65),
20 GUAGAAUGUGCAGUCCGGUCUUGUACAU (SEQ ID NO: 67),
UGGUGGGACAUAUAUGGUGGGAUGGUAG (SEQ ID NO: 69),
UCGAAUCCAUUUCAAGGCAUGUCGUGGU (SEQ ID NO: 71), or
UUAUUCGCUGGUUUGAGGUCGAAUCCAU (SEQ ID NO: 73).

Table 2: Examples of siRNA Sequences

Name	Sense	SEQ ID NO:	Anti-Sense	SEQ ID NO:
MnH_MSU U2si4	UGAGUGUGGCACAG AAACCAGAAAA	6	UUUUCUGGUUUCUGU GCCACACUCAGU	7
MnH_MSU U2si5	GAGUGUGGCACAGA AACCAGAAAAA	8	UUUUUCUGGUUUCUG UGCCACACUCAG	9

MnH_MSU U2si6	AGUGUGGCACAGAA ACCAGAAAAAC	10	GUUUUUCUGGUUUCU GUGCCACACUCA	11
MnH_MSU U2si7	GUGUGGCACAGAAA CCAGAAAAACU	12	AGUUUUUCUGGUUUC UGUGCCACACUC	13
MnH_MSU U2si8	UGUGGCACAGAAAC CAGAAAAACUU	14	AAGUUUUUCUGGUU UCUGUGCCACACU	15
MnH_MSU U2si9	UGGAGCGCUGCAAG UACUGGCCUGC	16	GCAGGCCAGUACUUG CAGCGCUCCAAA	17
MnH_MSU U2si10	CAGCUCUGCCGUUAC UUCCCUGCUU	18	AAGCAGGGAAGUAA GGCAGAGCUGAC	19
MnH_MSU U2si11	AGCUCUGCCGUUAC UUCCCUGCUUG	20	CAAGCAGGGAAGUAA CGGCAGAGCUGA	21
MnH_MSU U2si12	GCUCUGCCGUUACU UCCCUGCUUGU	22	ACAAGCAGGGAAGUA ACGGCAGAGCUG	23
MnH_MSU U2si13	CUCUGCCGUUACUUC CCUGCUUGUA	24	UACAAGCAGGGAAGU AACGGCAGAGCU	25
MnH_MSU U2si14	UCUGCCGUUACUUC CUGCUUGUAA	26	UUACAAGCAGGGAAG UAACGGCAGAGC	27
MnH_MSU U2si15	CUGCCGUUACUUCCC UGCUUGUAAG	28	CUUACAAGCAGGGAA GUAACGGCAGAG	29
MnH_MSU U2si16	UGCCGUUACUUCCCU GCUUGUAAGA	30	UCUUACAAGCAGGGA AGUAACGGCAGA	31
MnH_MSU U2si17	GCCGUUACUUCCCUG CUUGUAAGAA	32	UUCUUACAAGCAGGG AAGUAACGGCAG	33
hMSsiwalk 28	GGUAGCUUUUCUAA CGCUGAGAUGAGUG	34	CACUCAUCUCAGCGU UAGAAAAGCUACC	35
hMSsiwalk 53	GUGAACUGAGUGUG GCACAGAAACCAGA	36	UCUGGUUUCUGUGCC ACACUCAGUUCAC	37
hMSsiwalk 77	CAGAAAAACUUUUG GAGCGCUGCAAGUA	38	UACUUGCAGCGCUCC AAAAGUUUUUCUG	39
hMSsiwalk 101	AGUACUGGCCUGCU UGUAAAAAUGGGGA	40	UCCCCAUUUUUACAA GCAGGCCAGUACU	41

hMSsiwalk 126	GGAUGAGUGUGCCU ACCAUCACCCCAUC	42	GAUGGGGUGAUGGU AGGCACACUCAUCC	43
hMSsiwalk 149	CCAUCUCACCCUGCA AAGCCUUCGCCAA	44	UUGGGGAAGGCUUU GCAGGGUGAGAUGG	45
hMSsiwalk 173	CCAAUUGUAAAUUU GCUGAAAAAUGUUU	46	AAACAUUUUUCAGCA AAUUUACAAUUGG	47
hMSsiwalk 197	GUUUGUUUGUUCAC CCAAAUUGUAAAUA	48	UAUUUACAAUUUGG GUGAACAAACAAAC	49
hMSsiwalk 221	AAUAUGAUGCAAAG UGUACUAAACCAGA	50	UCUGGUUUAGUACAC UUUGCAUCAUAUU	51
hMSsiwalk 244	CCAGAUUGUCCCUUC ACUCAUGUGAGUA	52	UACUCACAUGAGUGA AGGGACAAUCUGG	53
hMSsiwalk 268	AGUAGAAGAAUUCC AGUACUGUCUCCAA	54	UUGGAGACAGUACUG GAAUUCUUCUACU	55
hMSsiwalk 292	CCAAAACCAGUUGC ACCACCAGCACCAC	56	GUGGUGCUGGUGGU GCAACUGGUUUUGG	57
hMSsiwalk 315	ACCACCUUCCAGUAG UCAGCUCUGCCGU	58	ACGGCAGAGCUGACU ACUGGAAGGUGGU	59
hMSsiwalk 340	CCGUUACUUCCUGC UUGUAAGAAGAUGG	60	CCAUCUUCUACAAG CAGGGAAGUACGG	61
hMSsiwalk 364	AUGGAAUGUCCCUU CUAUCAUCCAAAAC	62	GUUUUGGAUGAUAG AAGGGACAUAUCCA	63
hMSsiwalk 388	AAACAUUGUAGGUU UAACACUCA AUGUA	64	UACAUUGAGUGUUA AACCUACAAUGUUU	65
hMSsiwalk 411	AUGUACAAGACCGG ACUGCACAUUCUAC	66	GUAGAAUGUGCAGUC CGGUCUUGUACAU	67
hMSsiwalk 408	CUACCAUCCCACCAU UAAUGUCCCACCA	68	UGGUGGGACAUAUA UGGUGGGGAUGGUAG	69
hMSsiwalk 432	ACCACGACAUGCCUU GAAAUGGAUUCGA	70	UCGAAUCCAUAUCAA GGCAUGUCGUGGU	71
hMSsiwalk 450	AUGGAUUCGACCUC AAACCAGCGAAUAA	72	UUAUUCGCUGGUUUG AGGUCGAAUCCA	73

In some aspects, a siRNA molecule can comprise a double-stranded RNA molecule. In some aspects, the siRNA molecule can comprise a double-stranded RNA molecule whose antisense strand will comprise an RNA sequence substantially complementary to at least one sequence consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 or SEQ ID NO: 78, and whose sense strand will comprise an RNA sequence complementary to the antisense strand, wherein both strands are hybridised by standard base pairing between nucleotides. In some aspects, a siRNA molecule can comprise a double stranded RNA molecule, whose antisense strand will comprise an RNA sequence substantially complementary to SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 or SEQ ID NO: 78.

As used herein, “substantially complementary” to a target mRNA sequence, can also be understood as “substantially identical” to said target sequence. “Identity” is the degree of sequence relatedness between nucleotide sequences as determined by matching the order and identity of nucleotides between sequences. In some aspects, the antisense strand of an siRNA having 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% complementarity to the target mRNA sequence are considered substantially complementary and may be used in the present invention. The percentage of complementarity describes the percentage of contiguous nucleotides in a first nucleic acid molecule that can base pair in the Watson-Crick sense with a set of contiguous nucleotides in a second nucleic acid molecule. In some aspects, the antisense siRNA strand is 100% complementary to the target mRNA sequence, and the sense strand is 100% complementary to the antisense strand over the double stranded portion of the siRNA. The siRNA may also include unpaired overhangs, for example, 3’ dinucleotide overhangs, and, in some aspects, dTdT.

Generally, double stranded molecules can be from about 19 to about 25 nucleotides in length, and include blunt-ended structures as well as those with overhangs. Overhangs have been described to be advantageous and may be present on the 5’ ends or on the 3’ ends of either strand as they reduce recognition by RNases and imitate Dicer’s natural substrate. In some aspects, overhangs can be present on both 3’ ends of the molecules. In some aspects one overhang is present on one end of the molecule. Others have described the use of blunt-ended structures with specific modification patterns (EP1527176, WO2005062937, WO2008104978, EP2322617, EP2348133, US20130130377, and many others).

Overhangs can comprise between 1 and 5 nucleotides; typically overhangs are made up of dinucleotides. Classical molecules used in the field, comprise a 19 nucleotide double stranded molecule which further comprises 3’ dinucleotide overhangs preferably comprising

deoxynucleotides as taught in initial studies by Tuschl (WO0244321). These overhangs are said to further enhance resistance to nuclease (RNase) degradation. Later, Kim et al. 2005 (Kim et al., Nat. Biotechnol. 2005, Feb; 23(2): 222-6) describe that 21-mer products (containing dinucleotide overhangs) are important for loading onto RNA-induced silencing
5 complex (RISC). Further, Bramsen et al. 2009 (Bramsen et al. Nucleic Acids Res. 2009, May; 37(9): 2867-81) describe the introduction of possible destabilizing modifications to the overhangs to further increase silencing efficiency.

In some aspects, the siRNA molecules described herein can target at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID
10 NO: 77 and SEQ ID NO: 78 which comprises at least one overhang, preferably a 3' overhang in the sense and/or the antisense strand. In some aspects, wherein the siRNA molecule targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 or SEQ ID NO: 78, the siRNA can include an antisense strand of equivalent length and complementary to the target, and a sense strand of equivalent length and
15 complementary to the antisense strand. The antisense and sense strands can further include additional bases which are not complementary to the other strand or the target, and/or which are not paired in the double stranded portion of the siRNA.

In some aspects, the siRNA molecules described herein that target at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID
20 NO: 77 and SEQ ID NO: 78, wherein each strand of the double-stranded siRNA molecules is about 18 to about 28 or more (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 or more) nucleotides long.

Disclosed herein are siRNA molecules wherein the siRNA molecule specifically targets a sequence comprising or consisting of a sequence having the sequence of SEQ ID
25 NO: 1, 2, 3, 4, 5, 77 or 78 and reduces expression of mammalian suppressor of tauopathy 2 (MSUT2) gene in a cell, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity to a sequence comprising the sequence of SEQ ID NO: 6 to SEQ ID NO: 73

30 In some aspects, the siRNA molecules described herein comprising 18-28 nucleotides long or more and comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecules described herein comprising 18-28 nucleotides long or more and comprising a nucleotide sequence selected

from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, and 73. In some aspects, the double-stranded siRNA molecules can be at least 19 nucleotides long and selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

5 Also described herein are blunt-ended molecules. Disclosed herein are siRNA molecules wherein the siRNA molecules specifically target at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecules can reduce expression of mammalian suppressor of tauopathy 2 (MSUT2) gene in a cell. In some aspects, the siRNA molecules
10 comprise an 18- to 28-nucleotide, a 19- to 25-nucleotide or a 25- to 28-nucleotide blunt-ended double-stranded structure. In some aspects, the siRNA molecule comprises at least one sequence having at least 90% a sequence identity selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule comprises at least one sequence having at least 90% a sequence identity selected from the group consisting of
15 SEQ ID NOs: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, and 73.

In some aspects, the siRNA molecules comprise a 19 nucleotide double-stranded blunt-ended siRNA targeted against at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects,
20 the siRNA molecule comprises or consists of at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the antisense strand of this siRNA is at least 80%, at least 90%, complementary to at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78.

25 In some aspects, the siRNA molecules disclosed herein can comprise or consist of at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecules disclosed herein can comprise or consist of at least one sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, and
30 73.

In some aspects, the siRNA molecules disclosed herein can comprise or consist a sense strand which comprises or consists of at least one sequence selected from the group consisting of SEQ ID NOs: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40,

42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, and 72, and an antisense strand which is complementary to the sense strand.

siRNA molecules can be unstable in biological fluids due to the ubiquitous nature of RNases. Thus, the use of many different chemical modifications to nucleotides has been
5 described with the purpose of enhancing compound stability. Disclosed herein are siRNA molecules that are stability in biological fluids.

siRNA molecules can be immunogenetic, and in some instance, have been found to induce unspecific activation of the innate immune system, including up-regulation of certain cytokines.

10 Both of these effects, recognition by RNases and immunogenicity, have also been described to be sequence-dependent.

Described herein are chemical modifications that can enhance or are capable of enhancing siRNA molecule stability. In some aspects, the chemical modification can increase or enhance siRNA molecule stability by decreasing its susceptibility to RNases as well as
15 reduce induction of immune recognition and thus reduce the subsequent immune response.

In some aspects, the siRNA molecules described herein can further comprise at least one nucleotide with a chemical modification. In some aspects, at least one nucleotide of the siRNA molecule can comprise a chemical modification.

In some aspects, the chemical modification(s) that enhances stability and reduces
20 immunogenic effects can include but is not limited to 2'-O-methyl nucleotides, 2'-fluoro nucleotides, 2'-amino nucleotides, 2'-deoxy nucleotides, or nucleotides containing 2'-O or 4'-C methylene bridges. Examples of chemical modifications for exonuclease protection include but are not limited to the ExoEndoLight pattern of modification (EEL): modification of the pyrimidines in the sense strand to 2'-O-methyl residues, and modification of the
25 pyrimidines in a 5'-UA-3' or 5'-CA-3' motif in the antisense strand to 2'-O-methyl residues. In some aspects, position 1 of the sense strand can also be changed to 2'-O-methyl to prevent 5'-phosphorylation of the sense strand and thus increasing strand-specificity of the siRNA. In addition, the sense strand can also include a 2'-O-methyl modification in position 14, because 2'-O-Me residues at this position inactivate the sense strand and therefore increase strand-
30 specificity of the siRNA molecules. Additional examples of chemical modifications for nuclease protection include but are not limited to Methyl-Fluoro modification pattern (MEF): alternating 2'-fluoro and 2'-O-methyl modifications starting (5'-end) with a 2'-F on the sense strand and starting with 2'-O-Me on the antisense strand. In some aspects, position 1 of the

sense strand can also be changed to 2'-O-Me and position 1 of the antisense strand to 2'-F (as 2'F residues are compatible with 5'-phosphorylation whereas 2'O--Me residues are bulky and generally impair phosphorylation). This modification pattern can stabilize the molecule as well as disable the ability of the RISC to use the sense strand thus promoting strand-specificity. Also, modification of the ribonucleotide backbone can be performed by binding the nucleotides by using phosphorothioate bonds instead of phosphodiester links. In some aspects, the chemical modification can be a 4'Thioribose, 5-Propynyluracile 3',5'-methyluridine or the substitution of uracyl ribonucleotides with deoxythymidine (deoxyribonucleotides).

10 In some aspects, the chemical modification can include one or more amino acids, with amino acid, carbohydrates, or lipid moieties.

In some aspects, the at least one chemically modified nucleotide and/or the at least one chemical modification in the ribonucleotide backbone is on the sense strand, on the antisense strand or on both strands of the siRNA molecule. In some aspects, the chemical
15 modification is on the sense strand, on the antisense strand or on both strands of the siRNA molecule.

In some aspects, the siRNA molecule can comprise or consist of at least one sequence with a sense strand and/or an antisense strand selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise or consist of at
20 least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

In some aspects, the siRNA molecule can comprise or consists of a sense strand which comprises or consists of at least one sequence selected from the group of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64 SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, and SEQ ID NO: 72.

30 In some aspects, the siRNA molecule can comprise or consists of an antisense strand which is complementary to the sense strand which is selected from the group of SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO:

29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39,
 SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ
 ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO:
 61, SEQ ID NO: 63, SEQ ID NO: 65 SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, and
 5 SEQ ID NO: 73.

In some aspects, the siRNA molecule can comprise or consist of a sense strand which
 comprises or consists of at least one sequence selected from the group of SEQ ID NO: 6,
 SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID
 NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO:
 10 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38,
 SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ
 ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO:
 60, SEQ ID NO: 62, SEQ ID NO: 64 SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, and
 SEQ ID NO: 72; and an antisense strand which is complementary to the sense strand which is
 15 selected from the group of SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13,
 SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ
 ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO:
 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45,
 SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ
 20 ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65 SEQ ID NO:
 67, SEQ ID NO: 69, SEQ ID NO: 71, and SEQ ID NO: 73.

Any of the compositions disclosed herein can further comprise a pharmaceutically
 acceptable carrier. In some aspects, the pharmaceutically acceptable carrier for the siRNA
 molecule can be buffered saline. In some aspects, the pharmaceutically acceptable carrier can
 25 comprise a lipid-based or polymer-based colloid. In some aspects, the colloid can be a
 liposome, a hydrogel, a microparticle, a nanoparticle, or a block copolymer micelle. In some
 aspects, the compositions described herein can be formulated for intravenous, subcutaneous,
 intrathecal, intramuscular, oral, intrathecal or intraperitoneal administration. In some aspects,
 the therapeutically effective amount of any of the siRNA molecules disclosed herein reduces
 30 accumulation of phosphorylated and aggregated human tau.

siRNA molecules described herein can be delivered to the cell interior in their native
 structure using methods known in the art. In some aspects, when the siRNA molecules can be
 administered using standard transfection reagents. To achieve effects in vivo these siRNA

molecules can also be administered naked or using delivery enhancing agents such as for example liposomes, conjugation with a specific moiety, etc. although many different alternatives are known in the art, and are used differently depending on the desired target site within the body.

5 In some aspects, the siRNA molecules described herein can be expressed within cells from eukaryotic promoters. Recombinant vectors capable of expressing the siRNA molecules can be delivered and persist in target cells. Alternatively, vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siRNA molecule interacts with the target mRNA and
10 generates an RNA interfering response. The siRNA molecules produced in this manner are often termed shRNA (short hairpin RNA), as their sense and antisense strands are joined by a small loop of nucleotides. Delivery of siRNA molecules expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells explanted from a subject followed by reintroduction into the subject, or by any other means that
15 would allow for introduction into the desired target cell.

 Also disclosed is the use of siRNA targeting at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78 in the preparation of a medicament for use in a method of treatment Alzheimer's disease or dementia characterized by increased expression and/or activity of MSUT2. In some aspects,
20 the use comprises inhibiting expression of MSUT2 polynucleotide in a subject. The term inhibition is used to indicate a decrease or downregulation of expression or activity. In some aspects, the Alzheimer's disease or dementia can be associated with or related to an increase in phosphorylated or aggregated tau protein.

Method of Treatment

25 The methods disclosed herein can be useful for the treatment of a subject with Alzheimer's disease or dementia. In some aspects, the siRNA molecule can potentiate the neuroinflammatory response to pathological tau. In some aspects, the siRNA molecule can decrease astrogliosis and microgliosis. In some aspects, the siRNA molecule can reduce neuroinflammation. In some aspects, the siRNA molecule can inhibit expression of a MUST2
30 polynucleotide. In some aspects, the siRNA molecule can reduce accumulation of phosphorylated and aggregated human tau.

 In some aspects, the methods can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering

RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule
5 comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

10 In some aspects, the methods can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising a siRNA molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID
15 NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for inhibiting expression of a MSUT2
20 polynucleotide. In some aspects, the method can inhibit expression of a MSUT2 polynucleotide in a subject. The method can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID
25 NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID
30 NO: 6 to SEQ ID NO: 73, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for inhibiting expression of a MSUT2 polynucleotide. In some aspects, the method can inhibit expression of a MSUT2 polynucleotide in a subject. The method can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising a siRNA molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence of SEQ ID NO: 6 to SEQ ID NO: 73, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for reducing phosphorylated and aggregated human tau protein in a subject. The methods can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for reducing phosphorylated and aggregated human tau protein in a subject. The methods can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising a siRNA molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for suppressing expression of a MSUT2 polynucleotide. In some aspects, the method can suppress expression of a MSUT2 polynucleotide in a subject. The method can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for suppressing expression of a MSUT2 polynucleotide. In some aspects, the method can suppress expression of a MSUT2 polynucleotide in a subject. The method can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising a siRNA molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for potentiating a neuroinflammatory response to a pathological tau protein. In some aspects, the method can potentiate a neuroinflammatory response to a pathological tau protein in a subject. The method can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the

group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for potentiating a neuroinflammatory response to a pathological tau protein. In some aspects, the method can potentiate a neuroinflammatory response to a pathological tau protein in a subject. The method can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising a siRNA molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for decreasing astrogliosis or microgliosis. In some aspects, the method can decrease astrogliosis or microgliosis in a subject. The method can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for decreasing astrogliosis or microgliosis. In some aspects, the method can decrease astrogliosis or microgliosis in a subject. The method can comprise administering to a subject with Alzheimer's disease or

dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising a siRNA molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for reducing neuroinflammation. In some aspects, the method can reduce neuroinflammation in a subject. The method can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

The methods disclosed herein can be useful for reducing neuroinflammation. In some aspects, the method can reduce neuroinflammation in a subject. The method can comprise administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising a siRNA molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the therapeutically effective amount can reduce accumulation of phosphorylated and aggregated human tau.

In some aspects, the subject has Alzheimer's disease. In some aspects, the subject has dementia. In some aspects, the subject has mild-moderate Alzheimer's disease. In some

aspects, the subject has moderate-severe Alzheimer's disease. Alzheimer's disease typically progresses slowly in three general stages, mild (early stage), moderate (middle stage) and severe (late stage). In mild Alzheimer's disease (early stage), subjects can still function independently but may notice that they are having memory lapses such as forgetting familiar words or the location of everyday objects. During moderate Alzheimer's disease (middle stage), subjects may have greater difficulty performing tasks (e.g., paying bills) and confusing words, but may still remember significant details about their life. In addition, subjects in this stage may feel moody or withdrawn, are at an increased risk of wandering and becoming lost, and can exhibit personality and behavioral changes including suspiciousness and delusions or compulsive, repetitive behavior. In severe Alzheimer's disease (late stage), subjects lose the ability to respond to their environment, to carry on a conversation and eventually, to control movement. Also, during this severe stage, subjects need extensive help with daily activities and have increasing difficulty communicating.

In some aspects, the subject has an Alzheimer's-related dementia. In some aspects, the Alzheimer's-related dementia can be progressive supranuclear palsy, chronic traumatic encephalopathy, frontotemporal lobar degeneration, or other tauopathy disorders. The methods disclosed herein can be effective for targeting one or more genes, including mammalian suppressor of tauopathy 2 (MSUT2).

In some aspects, the methods also include the step of administering a therapeutic effective amount of any of the siRNA molecules disclosed herein. In some aspects, siRNA molecule comprises or consists of a sense strand which comprises or consists of at least one sequence selected from the group of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, and SEQ ID NO: 72.

In some aspects, siRNA molecule comprises or consists of an anti-sense strand which comprises or consists of at least one sequence selected from the group of SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39,

SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65 SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, and SEQ ID NO: 73.

5 In some aspects, the siRNA molecule comprises or consists of a sense strand which comprises or consists of at least one sequence selected from the group of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, 10 SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64 SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, and SEQ ID NO: 72; and an antisense strand which is complementary to the sense strand which is selected from the group of SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, 15 SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65 SEQ ID NO: 20 67, SEQ ID NO: 69, SEQ ID NO: 71, and SEQ ID NO: 73.

In some aspects, the methods of treating a subject can comprise contacting a cell or a subject with an effective amount of a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule 25 comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule 30 reduces accumulation of phosphorylated and aggregated tau.

In some aspects, the methods of treating a subject can comprise contacting a cell or a subject with an effective amount of a small interfering RNA (siRNA) molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure,

wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of inhibiting expression of a MSUT2 polynucleotide. In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of suppressing expression of a MSUT2 polynucleotide. In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods of potentiating a neuroinflammatory response to a pathological tau protein. In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods decreasing astrocytosis or microgliosis. In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected

from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

Disclosed herein are methods reducing neuroinflammation. In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78. In some aspects, the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

In some aspects, the methods can comprise contacting a cell with a small interfering RNA (siRNA) molecule wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

In some aspects, the cell can be a vertebrate, a mammalian or a human cell. In some aspects, the cell can be a brain cell. In some aspects, the cell can be a mammalian cell. In some aspects, the mammalian cell can be a brain cell.

In some aspects, at least one nucleotide of any of the siRNA molecules can comprise a chemical modification. In some aspects, the chemical modification can be on the sense strand, the antisense strand or on both. In some aspects, the siRNA molecule can comprise at least one sequence is selected from the group consisting of SEQ ID NO: 6 – SEQ ID NO: 73.

In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

5 In some aspects, the methods can further include the step of identifying a subject (e.g., a human patient) who has Alzheimer's disease or dementia and then providing to the subject any of the siRNA molecules disclosed herein or a composition comprising any of the siRNA molecules disclosed herein. In some aspects, the small interfering RNA (siRNA) molecule or the composition comprising the siRNA molecule specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and
10 SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73. In some aspects, the siRNA molecule can comprise at least one sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

15 In some aspects, the subject has an Alzheimer's-related dementia. In some aspects, the Alzheimer's-related dementia can be progressive supranuclear palsy, chronic traumatic encephalopathy, frontotemporal lobar degeneration, or other tauopathy disorders. In some aspects, the subject can be identified using standard clinical tests known to those skilled in the art. While a definite AD diagnosis requires post-mortem examination, skilled clinicians
20 can conduct an evaluation of cognitive function with over 95% accuracy. Examples of tests for diagnosing Alzheimer's disease or dementia include Mini-Mental State Examination (MMSE), Mini-cog® Score, Alzheimer's Disease Composite Score (ADCOMS), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) and Clinical Dementia Rating Sum of Boxes (CDR-SB).

25 The therapeutically effective amount can be the amount of the composition administered to a subject that leads to a full resolution of the symptoms of the condition or disease, a reduction in the severity of the symptoms of the condition or disease, or a slowing of the progression of symptoms of the condition or disease. The methods described herein can also include a monitoring step to optimize dosing. The compositions described herein
30 can be administered as a preventive treatment or to delay or slow the progression of degenerative changes. In some aspects, the therapeutically effective amount of any of the siRNA molecules disclosed herein can reduce accumulation of phosphorylated and aggregated human tau.

The compositions disclosed herein can be used in a variety of ways. For instance, the compositions disclosed herein can be used for direct delivery of modified therapeutic cells, or adeno-associated virus. The compositions disclosed herein can be used or delivered or administered at any time during the treatment process. The compositions described herein
5 including cells or a virus can be delivered to the one or more brain regions, one or more brain cells, or to brain regions or brain cells to stop or prevent one or more signs of symptoms of the disease or condition in an adjacent brain region or brain cell.

The dosage to be administered depends on many factors including, for example, the route of administration, the formulation, the severity of the patient's condition/disease,
10 previous treatments, the patient's size, weight, surface area, age, and gender, other drugs being administered, and the overall general health of the patient including the presence or absence of other diseases, disorders or illnesses. Dosage levels can be adjusted using standard empirical methods for optimization known by one skilled in the art. Administrations of the compositions described herein can be single or multiple (e.g., 2-, 3-, 4-, 6-, 8-, 10-,
15 20-, 50-, 100-, 150-, or more fold). Further, encapsulation of the compositions in a suitable delivery vehicle (e.g., polymeric microparticles or implantable devices) can improve the efficiency of delivery.

The therapeutically effective amount of the compositions described herein can include a single treatment or a series of treatments (i.e., multiple treatments or administered multiple
20 times). Treatment duration using any of compositions disclosed herein can be any length of time, such as, for example, one day to as long as the life span of the subject (e.g., many years). For instance, the composition can be administered daily, weekly, monthly, yearly for a period of 5 years, ten years, or longer. The frequency of treatment can vary. For example, the compositions described herein can be administered once (or twice, three times, etc.) daily,
25 weekly, monthly, or yearly for a period of 5 years, ten years, or longer.

In some aspects, the compositions disclosed herein can also be co-administered with another therapeutic agent. In some aspects, the methods disclosed herein can further comprise administering a cholinesterase inhibitor to the subject. In some aspects, the cholinesterase inhibitor can be galantamine, rivastigmine or donepezil. In some aspects, the
30 methods disclosed herein can further comprise administering an anti-inflammatory therapy to the subject.

In some aspects, the methods disclosed herein also include treating a subject having Alzheimer's disease or dementia. In some aspects, the methods disclosed herein can include the step of determining MSUT2 levels in a subject.

Pharmaceutical Compositions

As disclosed herein, are pharmaceutical compositions, comprising the compositions disclosed herein. In some aspects, the pharmaceutical composition can comprise any of siRNA molecules disclosed herein. In some aspects, the compositions can comprise at least one siRNA molecule disclosed herein. In some aspects, the pharmaceutical compositions can further comprise a pharmaceutically acceptable carrier.

Disclosed herein, are pharmaceutical compositions, comprising a nucleic acid sequence or molecule wherein the nucleic acid comprises or consists of a sequence having the sequence set forth in:

UUUUCUGGUUUCUGUGCCACACUCAGU (SEQ ID NO: 7),
 UUUUUCUGGUUUCUGUGCCACACUCAG (SEQ ID NO: 9),
 GUUUUUCUGGUUUCUGUGCCACACUCA (SEQ ID NO: 11),
 AGUUUUUCUGGUUUCUGUGCCACACUC (SEQ ID NO: 13),
 AAGUUUUUCUGGUUUCUGUGCCACACU (SEQ ID NO: 15),
 GCAGGCCAGUACUUGCAGCGCUCCAAA (SEQ ID NO: 17),
 AAGCAGGGAAGUAACGGCAGAGCUGAC (SEQ ID NO: 19).
 CAAGCAGGGAAGUAACGGCAGAGCUGA (SEQ ID NO: 21),
 ACAAGCAGGGAAGUAACGGCAGAGCUG (SEQ ID NO: 23),
 UACAAGCAGGGAAGUAACGGCAGAGCU (SEQ ID NO: 25)
 UUACAAGCAGGGAAGUAACGGCAGAGC (SEQ ID NO: 27),
 CUUACAAGCAGGGAAGUAACGGCAGAG (SEQ ID NO: 29),
 UCUUACAAGCAGGGAAGUAACGGCAGA (SEQ ID NO: 31),
 UUCUUACAAGCAGGGAAGUAACGGCAG (SEQ ID NO: 33),
 CACUCAUCUCAGCGUUAGAAAAGCUACC (SEQ ID NO: 35),
 UCUGGUUUCUGUGCCACACUCAGUUCAC (SEQ ID NO: 37),
 UACUUGCAGCGCUCCAAAAGUUUUUCUG (SEQ ID NO: 39),
 UCCCCAUUUUUACAAGCAGGCCAGUACU (SEQ ID NO: 41),
 GAUGGGGUGAUGGUAGGCACACUCAUCC (SEQ ID NO: 43),
 UUGGGGAAGGCUUUGCAGGGUGAGAUGG (SEQ ID NO: 45),
 AAACAUUUUUCAGCAAAUUUACAAUUGG (SEQ ID NO: 47),

UAUUUACAAUUUGGGUGAACAAACAAAC (SEQ ID NO: 49),
 UCUGGUUUAGUACACUUUGCAUCAUAUU (SEQ ID NO: 51),
 UACUCACAUGAGUGAAGGGACAAUCUGG (SEQ ID NO: 53),
 UUGGAGACAGUACUGGAAUUCUUCUACU (SEQ ID NO: 55),
 5 GUGGUGCUGGUGGUGCAACUGGUUUUGG (SEQ ID NO: 57),
 ACGGCAGAGCUGACUACUGGAAGGUGGU (SEQ ID NO: 59),
 CCAUCUUCUUACAAGCAGGGAAGUAACGG (SEQ ID NO: 61),
 GUUUUGGAUGAUAGAAGGGACAUCCAUC (SEQ ID NO: 63),
 UACAUUGAGUGUUAAACCUACAAUGUUU (SEQ ID NO: 65),
 10 GUAGAAUGUGCAGUCCGGUCUUGUACAUC (SEQ ID NO: 67),
 UGGUGGGACAUAUAAUGGUGGGAUGGUAG (SEQ ID NO: 69),
 UCGAAUCCAUAUUC AAGGCAUGUCGUGGU (SEQ ID NO: 71), or
 UUAUUCGCUGGUUUGAGGUCGAAUCCAUC (SEQ ID NO: 73).

Disclosed herein, are pharmaceutical compositions, comprising a nucleic acid
 15 sequence or molecule wherein the nucleic acid comprises or consists of a sequence having at
 least 90% identity to the sequence set forth in:

UUUUCUGGUUUCUGUGCCACACUCAGU (SEQ ID NO: 7),
 UUUUUCUGGUUUCUGUGCCACACUCAG (SEQ ID NO: 9),
 GUUUUUCUGGUUUCUGUGCCACACUCA (SEQ ID NO: 11),
 20 AGUUUUUCUGGUUUCUGUGCCACACUC (SEQ ID NO: 13),
 AAGUUUUUCUGGUUUCUGUGCCACACU (SEQ ID NO: 15),
 GCAGGCCAGUACUUGCAGCGCUCCAAA (SEQ ID NO: 17),
 AAGCAGGGAAGUAACGGCAGAGCUGAC (SEQ ID NO: 19).
 CAAGCAGGGAAGUAACGGCAGAGCUGA (SEQ ID NO: 21),
 25 ACAAGCAGGGAAGUAACGGCAGAGCUG (SEQ ID NO: 23),
 UACAAGCAGGGAAGUAACGGCAGAGCU (SEQ ID NO: 25)
 UUACAAGCAGGGAAGUAACGGCAGAGC (SEQ ID NO: 27),
 CUUACAAGCAGGGAAGUAACGGCAGAG (SEQ ID NO: 29),
 UCUUACAAGCAGGGAAGUAACGGCAGA (SEQ ID NO: 31),
 30 UUCUACAAGCAGGGAAGUAACGGCAG (SEQ ID NO: 33),
 CACUCAUCUCAGCGUUAGAAAAGCUACC (SEQ ID NO: 35),
 UCUGGUUUCUGUGCCACACUCAGUUCAC (SEQ ID NO: 37),
 UACUUGCAGCGCUCCAAAAGUUUUUCUG (SEQ ID NO: 39),

UCCCCAUUUUUACAAGCAGGCCAGUACU (SEQ ID NO: 41),
 GAUGGGGUGAUGGUAGGCACACUCAUCC (SEQ ID NO: 43),
 UUGGGGAAGGCUUUGCAGGGUGAGAUGG (SEQ ID NO: 45),
 AAACAUUUUUUCAGCAAAUUUACAAUUGG (SEQ ID NO: 47),
 5 UAUUUACAAUUUGGGUGAACAAACAAAC (SEQ ID NO: 49),
 UCUGGUUUAGUACACUUUGCAUCAUAUU (SEQ ID NO: 51),
 UACUCACAUGAGUGAAGGGACAAUCUGG (SEQ ID NO: 53),
 UUGGAGACAGUACUGGAAUUCUUCUACU (SEQ ID NO: 55),
 GUGGUGCUGGUGGUGCAACUGGUUUUGG (SEQ ID NO: 57),
 10 ACGGCAGAGCUGACUACUGGAAGGUGGU (SEQ ID NO: 59),
 CCAUCUUCUUACAAGCAGGGAAGUAACGG (SEQ ID NO: 61),
 GUUUUGGAUGAUAGAAGGGACAUAUCCA (SEQ ID NO: 63),
 UACAUUGAGUGUUAAACCUACAAUGUUU (SEQ ID NO: 65),
 GUAGAAUGUGCAGUCCGGUCUUGUACA (SEQ ID NO: 67),
 15 UGGUGGGACAUAUAAUGGUGGGAUGGUAG (SEQ ID NO: 69),
 UCGAAUCCAUAUUAAGGCAUGUCGUGGU (SEQ ID NO: 71), or
 UUAUUCGCUGGUUUGAGGUCGAAUCCA (SEQ ID NO: 73).

As used herein, the term “pharmaceutically acceptable carrier” refers to solvents,
 dispersion media, coatings, antibacterial, isotonic and absorption delaying agents, buffers,
 20 excipients, binders, lubricants, gels, surfactants that can be used as media for a
 pharmaceutically acceptable substance. The pharmaceutically acceptable carriers can be
 lipid-based or a polymer-based colloid. Examples of colloids include liposomes, hydrogels,
 microparticles, nanoparticles and micelles. The compositions can be formulated for
 administration by any of a variety of routes of administration, and can include one or more
 25 physiologically acceptable excipients, which can vary depending on the route of
 administration. Any of the nucleic acids, vectors, siRNAs, antisense siRNAs, and sense
 siRNAs described herein can be administered in the form of a pharmaceutical composition.

As used herein, the term “excipient” means any compound or substance, including
 those that can also be referred to as “carriers” or “diluent.” Preparing pharmaceutical and
 30 physiologically acceptable compositions is considered routine in the art, and thus, one of
 ordinary skill in the art can consult numerous authorities for guidance if needed. The
 compositions can also include additional agents (e.g., preservatives).

The pharmaceutical compositions as disclosed herein can be prepared for oral or parenteral administration. Pharmaceutical compositions prepared for parenteral administration include those prepared for intravenous (or intra-arterial), intramuscular, subcutaneous, intrathecal or intraperitoneal administration. Paternal administration can be in the form of a single bolus dose, or may be, for example, by a continuous pump. In some aspects, the compositions can be prepared for parenteral administration that includes dissolving or suspending the nucleic acids, polynucleic sequences, vectors or siRNA molecules in an acceptable carrier, including but not limited to an aqueous carrier, such as water, buffered water, saline, buffered saline (e.g., PBS), and the like. One or more of the excipients included can help approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents, detergents, and the like. Where the compositions include a solid component (as they may for oral administration), one or more of the excipients can act as a binder or filler (e.g., for the formulation of a tablet, a capsule, and the like). Where the compositions are formulated for application to the skin or to a mucosal surface, one or more of the excipients can be a solvent or emulsifier for the formulation of a cream, an ointment, and the like.

In some aspects, the compositions disclosed herein are formulated for oral, intramuscular, intravenous, subcutaneous, intrathecal or intraperitoneal administration.

The pharmaceutical compositions can be sterile and sterilized by conventional sterilization techniques or sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation, which is encompassed by the present disclosure, can be combined with a sterile aqueous carrier prior to administration. The pH of the pharmaceutical compositions typically will be between 3 and 11 (e.g., between about 5 and 9) or between 6 and 8 (e.g., between about 7 and 8). The resulting compositions in solid form can be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents, such as in a sealed package of tablets or capsules. The composition in solid form can also be packaged in a container for a flexible quantity, such as in a squeezable tube designed for a topically applicable cream or ointment. The compositions can also be formulated as powders, elixirs, suspensions, emulsions, solutions, syrups, aerosols, lotions, creams, ointments, gels, suppositories, sterile injectable solutions and sterile packaged powders. The active ingredient can be siRNA molecules, nucleic acids or vectors described herein in combination with one or more pharmaceutically acceptable carriers. As used herein “pharmaceutically acceptable” means molecules and compositions that do not

produce or lead to an untoward reaction (i.e., adverse, negative or allergic reaction) when administered to a subject as intended (i.e., as appropriate).

In some aspects, the vectors, siRNAs and nucleic acid sequences as disclosed herein can be delivered to a cell of the subject. In some aspects, such action can be achieved, for example, by using polymeric, biodegradable microparticle or microcapsule delivery vehicle, sized to optimize phagocytosis by phagocytic cells (e.g., macrophages).

In some aspects, the formulations include any that are suitable for the delivery of a virus (e.g., adeno-associated virus) and cells. In some aspects, the route of administration includes but is not limited to direct injection into the brain. Such administration can be done without surgery, or with surgery.

Kits

Disclosed herein are kits that comprise any combination of the compositions (e.g., any of siRNAs) described above and suitable instructions (e.g., written and/or provided as audio-, visual-, or audiovisual material). Disclosed herein are kits that comprise any combination of the pharmaceutical compositions described above and suitable instructions (e.g., written and/or provided as audio-, visual-, or audiovisual material). In some aspects, the kit comprises a predetermined amount of a composition or pharmaceutical composition comprising any of the siRNA molecules disclosed herein. The kit can further comprise one or more of the following: instructions, sterile fluid, syringes, a sterile container, delivery devices, and buffers or other control reagents.

EXAMPLES

Example 1: **Targeted Nucleic Acid Sequences for Silencing MSUT2/ZC3H14**

HEK293 cells were cultured under standard tissue culture conditions (DMEM, 10% defined fetal bovine serum, Penicillin (1000 IU/mL) Streptomycin (1000 mg/mL) (Wheeler et al., Science Translational Medicine, 2019 Dec. 18; 11(253)). RNA interference transfections were conducted following the manufacturer's protocol (RNAiMAX, Invitrogen). Cell pellet lysates were prepared for immunodetection (Wheeler et al., Science Translational Medicine, 2019 Dec. 18; 11(253)). Lysates were diluted in 0.1x sample buffer (1:25; Protein Simple) and analyzed on a Peggy Sue (Protein Simple) following manufacturer's protocols using 12-230kDa capillaries. MSUT2 was detected with the Rbt9857 antibody (Wheeler, et al 2019 (STM)) diluted at 1:10 in Antibody Diluent 2 (Protein Simple) and actin was detected with A4700 (SigmaAldrich) diluted at 1:200. Goat anti-rabbit secondary antibody (GE

Lifescience) was diluted to 1:100 in Antibody Diluent 2. MSUT2 knockdown was analyzed by peak height and peak area normalized to actin.

To measure the effectiveness of siRNA treatments, synthetic siRNAs were introduced into HEK293 cells using lipofectamine RNAimax reagent (Thermo) according to the manufacturer’s instructions. Three days post transfection siRNA treated cells were harvested and analyzed for MSUT2 protein levels using a ProteinSimple capillary immunoanalyzer. MSUT2 protein levels were compared to MSUT2 siRNA and mock treated cells and expressed as a percentage of endogenous MSUT2 levels. The results are shown in Table 3.

Table 3.

Sample	Name	Sense	SEQ ID NO:	Anti-Sense	SEQ ID NO:	%KD - MSUT2 relative to actin by Sally Assay
1	Standard MSUT2 RNAi	ATGATGC AAAGTGA CTAAACC AG	77	TCTGGTTT AGTACACT TTGCATCA TAT	78	75.83280863
3	MnH_MS UU2si4	UGAGUGU GGCACAG AAACCAG AAAA	6	UUUUCUGG UUUCUGUG CCACACUC AGU	7	77.00088007
4	MnH_MS UU2si5	GAGUGUG GCACAGA AACCAGA AAAA	8	UUUUUCUG GUUUCUGU GCCACACU CAG	9	79.82342853
5	MnH_MS UU2si6	AGUGUGG CACAGAA ACCAGAA AAAC	10	GUUUUUCU GGUUUCUG UGCCACAC UCA	11	77.56392345
6	MnH_MS UU2si7	GUGUGGC ACAGAAA	12	AGUUUUUC UGGUUUCU	13	82.96989508

		CCAGAAA AACU		GUGCCACA CUC		
7	MnH_MS UU2si8	UGUGGCA CAGAAAC CAGAAAA ACUU	14	AAGUUUUU CUGGUUUC UGUGCCAC ACU	15	77.52231763
8	MnH_MS UU2si9	UGGAGCG CUGCAAG UACUGGC CUGC	16	GCAGGCCA GUACUUGC AGCGCUCC AAA	17	13.8614351
9	MnH_MS UU2si10	CAGCUCU GCCGUUA CUUCCCU GCUU	18	AAGCAGGG AAGUAACG GCAGAGCU GAC	19	73.02265734
10	MnH_MS UU2si11	AGCUCUG CCGUUAC UUCCCU CUUG	20	CAAGCAGG GAAGUAAC GGCAGAGC UGA	21	79.91434341
11	MnH_MS UU2si12	GCUCUGC CGUUACU UCCCU UUGU	22	ACAAGCAG GGAAGUAA CGGCAGAG CUG	23	79.26631989
12	MnH_MS UU2si13	CUCUGCC GUUACUU CCCUGCU UGUA	24	UACAAGCA GGGAAGUA ACGGCAGA GCU	25	67.73347845
13	MnH_MS UU2si14	UCUGCCG UUACUUC CCUGCUU GUAA	26	UUACAAGC AGGGAAGU AACGGCAG AGC	27	75.19836445
14	MnH_MS UU2si15	CUGCCGU UACUUC	28	CUUACAAG CAGGGAAG	29	78.56434308

		CUGCUUG UAAG		UAACGGCA GAG		
15	MnH_MS UU2si16	UGCCGUU ACUUCCC UGCUUGU AAGA	30	UCUUACAA GCAGGGAA GUAACGGC AGA	31	67.74655341
16	MnH_MS UU2si17	GCCGUUA CUUCCCU GCUUGUA AGAA	32	UUCUUACA AGCAGGGA AGUAACGG CAG	33	56.89172238
17	hMSsiwalk 28	GGUAGCU UUUCUAA CGCUGAG AUGAGUG	34	CACUCAUC UCAGCGUU AGAAAAGC UACC	35	55.32188634
18	hMSsiwalk 53	GUGAACU GAGUGUG GCACAGA AACCAGA	36	UCUGGUUU CUGUGCCA CACUCAGU UCAC	37	80.62947589
19	hMSsiwalk 77	CAGAAAA ACUUUUG GAGCGCU GCAAGUA	38	UACUUGCA GCGCUCCA AAAGUUUU UCUG	39	52.02312009
20	hMSsiwalk 101	AGUACUG GCCUGCU UGUAAAA AUGGGGA	40	UCCCCAUU UUUACAAG CAGGCCAG UACU	41	70.07765806
21	hMSsiwalk 126	GGAUGAG UGUGCCU ACCAUCA CCCCAUC	42	GAUGGGGU GAUGGUAG GCACACUC AUCC	43	23.16656271
22	hMSsiwalk 149	CCAUCUC ACCCUGC	44	UUGGGGAA GGCUUUGC	45	82.6631096

		AAAGCCU UCCCCAA		AGGGUGAG AUGG		
23	hMSsiwalk 173	CCAAUUG UAAAUUU GCUGAAA AAUGUUU	46	AAACAUUU UUCAGCAA AUUUACAA UUGG	47	66.00892982
24	hMSsiwalk 197	GUUUGUU UGUUCAC CCAAAUU GUAAAUA	48	UAUUUACA AUUUGGGU GAACAAAC AAAC	49	56.22027712
25	hMSsiwalk 221	AAUAUGA UGCAAAG UGUACUA AACCAGA	50	UCUGGUUU AGUACACU UUGCAUCA UAUU	51	71.61900312
26	hMSsiwalk 244	CCAGAUU GUCCCUU CACUCAU GUGAGUA	52	UACUCACA UGAGUGAA GGGACAAU CUGG	53	74.78356031
27	hMSsiwalk 268	AGUAGAA GAAUUCC AGUACUG UCUCCAA	54	UUGGAGAC AGUACUGG AAUUCUUC UACU	55	82.55942726
28	hMSsiwalk 292	CCAAAAC CAGUUGC ACCACCA GCACCAC	56	GUGGUGCU GGUGGUGC AACUGGUU UUGG	57	69.89754374
29	hMSsiwalk 315	ACCACCU UCCAGUA GUCAGCU CUGCCGU	58	ACGGCAGA GCUGACUA CUGGAAGG UGGU	59	74.63956705
30	hMSsiwalk 340	CCGUUAC UUCCCUG CUUGUAA	60	CCAUCUUC UUACAAGC	61	76.18952012

		GAAGAUG G		AGGGAAGU AACGG		
31	hMSsiwalk 364	AUGGAAU GUCCCUU CUAUCAU CCAAAAC	62	GUUUUGGA UGAUAGAA GGGACAUI CCAU	63	78.9692047
32	hMSsiwalk 388	AAACAUI GUAGGUU UAACACU CAAUGUA	64	UACAUIUGA GUGUIAAA CCUACAAU GUUU	65	81.47011055
33	hMSsiwalk 411	AUGUACA AGACCGG ACUGCAC AUUCUAC	66	GUAGAAUG UGCAGUCC GGUCUUGU ACAU	67	53.31365239
34	hMSsiwalk 408	CUACCAU CCCACCA UUA AUGU CCCACCA	68	UGGUGGGA CAUUA AUG GUGGGAUG GUAG	69	64.99244605
35	hMSsiwalk 432	ACCACGA CAUGCCU UGAAAUG GAUUCGA	70	UCGAAUCC AUUUCAAG GCAUGUCG UGGU	71	68.24885441
36	hMSsiwalk 450	AUGGAUI CGACCUC AAACCAG CGAAUAA	72	UUAUUCGC UGGUUUGA GGUCGAAU CCAU	73	68.45608284

WHAT IS CLAIMED IS:

1. A composition comprising a nucleic acid sequence or molecule wherein the nucleic acid comprises or consists of a sequence having at least 90% identity to the sequence set forth in:

UUUUCUGGUUUCUGUGCCACACUCAGU (SEQ ID NO: 7),
 UUUUUCUGGUUUCUGUGCCACACUCAG (SEQ ID NO: 9),
 GUUUUUCUGGUUUCUGUGCCACACUCA (SEQ ID NO: 11),
 AGUUUUUCUGGUUUCUGUGCCACACUC (SEQ ID NO: 13),
 AAGUUUUUCUGGUUUCUGUGCCACACU (SEQ ID NO: 15),
 GCAGGCCAGUACUUGCAGCGCUCCAAA (SEQ ID NO: 17),
 AAGCAGGGAAGUAACGGCAGAGCUGAC (SEQ ID NO: 19),
 CAAGCAGGGAAGUAACGGCAGAGCUGA (SEQ ID NO: 21),
 ACAAGCAGGGAAGUAACGGCAGAGCUG (SEQ ID NO: 23),
 UACAAGCAGGGAAGUAACGGCAGAGCU (SEQ ID NO: 25),
 UUACAAGCAGGGAAGUAACGGCAGAGC (SEQ ID NO: 27),
 CUUACAAGCAGGGAAGUAACGGCAGAG (SEQ ID NO: 29),
 UCUUACAAGCAGGGAAGUAACGGCAGA (SEQ ID NO: 31),
 UUCUACAAGCAGGGAAGUAACGGCAG (SEQ ID NO: 33),
 CACUCAUCUCAGCGUUAGAAAAGCUACC (SEQ ID NO: 35),
 UCUGGUUUCUGUGCCACACUCAGUUCAC (SEQ ID NO: 37),
 UACUUGCAGCGCUCCAAAAGUUUUUCUG (SEQ ID NO: 39),
 UCCCCAUUUUUACAAGCAGGCCAGUACU (SEQ ID NO: 41),
 GAUGGGGUGAUGGUAGGCACACUCAUCC (SEQ ID NO: 43),
 UUGGGGAAGGCUUUGCAGGGUGAGAUGG (SEQ ID NO: 45),
 AAACAUUUUUCAGCAAAUUUACAAUUGG (SEQ ID NO: 47),
 UAUUUACAAUUUGGGUGAACAAACAAAC (SEQ ID NO: 49),
 UCUGGUUUAGUACACUUUGCAUCAUAUU (SEQ ID NO: 51),
 UACUCACAUGAGUGAAGGGACAAUCUGG (SEQ ID NO: 53),
 UUGGAGACAGUACUGGAAUUCUUCUACU (SEQ ID NO: 55),
 GUGGUGCUGGUGGUGCAACUGGUUUUGG (SEQ ID NO: 57),
 ACGGCAGAGCUGACUACUGGAAGGUGGU (SEQ ID NO: 59),
 CCAUCUUCUUACAAGCAGGGAAGUAACGG (SEQ ID NO: 61),

GUUUUGGAUGAUAGAAGGGACAUUCCA (SEQ ID NO: 63),
 UACAUUGAGUGUUAAACCUACAAUGUUU (SEQ ID NO: 65),
 GUAGAAUGUGCAGUCCGGUCUUGUACA (SEQ ID NO: 67),
 UGGUGGGACAUUAAUGGUGGGAUGGUAG (SEQ ID NO: 69),
 UCGAAUCCAUUUCAAGGCAUGUCGUGGU (SEQ ID NO: 71), or
 UUAUUCGCUGGUUUGAGGUCGAAUCCA (SEQ ID NO: 73).

2. A siRNA molecule wherein the siRNA molecule specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78 and reduces expression of mammalian suppressor of tauopathy 2 (MSUT2) gene in a cell, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence having at least 90% sequence identity selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.
3. The siRNA molecule of claim 2, wherein at least one nucleotide of the siRNA molecule comprises a chemical modification.
4. The siRNA molecule of claim 3, wherein the chemical modification is on the sense strand, the antisense strand or on both strands of the siRNA molecule.
5. The siRNA molecule of claim 2, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 – SEQ ID NO: 73.
6. The siRNA molecule of claim 2, wherein the siRNA molecule comprises or consists of a sense strand which comprises or consists of at least one sequence selected from the group of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, and SEQ ID NO: 72;

and an antisense strand which is complementary to the sense strand which is selected from the group of SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, and SEQ ID NO: 73.

7. A pharmaceutical composition, wherein the composition comprises at least one siRNA molecule according to any of the preceding claims.
8. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.
9. The composition of claim 8, wherein the pharmaceutically acceptable carrier comprises a lipid-based or polymer-based colloid.
10. The composition of claim 9, wherein the colloid is a liposome, a hydrogel, a microparticle, a nanoparticle, or a block copolymer micelle.
11. The siRNA molecule of claims 2 to 6, further comprising a pharmaceutically acceptable carrier.
12. The siRNA molecule of claim 11, wherein the pharmaceutically acceptable carrier comprises a lipid-based or polymer-based colloid.
13. The siRNA molecule of claim 12, wherein the siRNA molecule is formulated for intravenous, subcutaneous or intrathecal administration.
14. A method of treating Alzheimer's disease or dementia, the method comprising:
administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition

comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, and wherein the therapeutically effective amount reduces accumulation of phosphorylated and aggregated human tau.

15. A method of inhibiting expression of a MSUT2 polynucleotide in a subject, the method comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.
16. A method of reducing phosphorylated and aggregated human tau protein in a subject, the method comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.
17. A method of suppressing expression of a MSUT2 polynucleotide in a subject, the method comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ

ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

18. A method of potentiating a neuroinflammatory response to a pathological tau protein in a subject, the method comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.
19. A method of decreasing astrogliosis or microgliosis in a subject, the method comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.
20. A method of reducing neuroinflammation in a subject, the method comprising administering to a subject with Alzheimer's disease or dementia a therapeutically effective amount of a small interfering RNA (siRNA) molecule or a composition comprising the siRNA molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73.

21. The method of any of claims 14-20, wherein the subject is identified as being in need of treatment before the administration step.
22. The method of any of claims 14-21, wherein the subject is a human.
23. The method of any of claims 14-22, further comprising administering a cholinesterase inhibitor to the subject.
24. The method of claim 23, wherein the cholinesterase inhibitor is galantamine, rivastigmine or donepezil.
25. The method of any of claims 14-24, wherein the subject has Alzheimer's disease.
26. The method of claim 25, wherein the subject has mild-moderate Alzheimer's disease.
27. The method of claim 25, wherein the subject has moderate-severe Alzheimer's disease.
28. The method of any of claims 14-24, wherein the subject has dementia.
29. The method of any of claims 14-28, wherein the composition further comprises a pharmaceutically acceptable carrier.
30. The method of claim 29, wherein the pharmaceutically acceptable carrier comprises a lipid-based or polymer-based colloid.
31. The method of any of claims 14-30, wherein the siRNA molecule is formulated for intravenous, subcutaneous or intrathecal administration.
32. The method of any of claims 14-31, wherein the therapeutically effective amount of the siRNA molecule or a composition comprising the siRNA molecule is administered orally, intramuscularly, intraperitoneally, intravenously, subcutaneously or intrathecally.

33. A method of inhibiting expression of a MSUT2 polynucleotide, the method comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.
34. A method of suppressing expression of a MSUT2 polynucleotide, the method comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.
35. A method of potentiating a neuroinflammatory response to a pathological tau protein, the method comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.
36. A method of decreasing astrogliosis or microgliosis, the method comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule

comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.

37. A method of reducing neuroinflammation, the method comprising contacting a cell with a small interfering RNA (siRNA) molecule that specifically targets at least one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 5, SEQ ID NO: 77 and SEQ ID NO: 78, wherein the siRNA molecule comprises a 25- to 28-nucleotide blunt-ended double-stranded structure, wherein the siRNA molecule comprises at least one sequence selected from the group consisting of SEQ ID NO: 6 to SEQ ID NO: 73, wherein the siRNA molecule reduces accumulation of phosphorylated and aggregated tau.
38. The method of any of claims 15, 17, 33, or 34, wherein the expression of the MSUT2 polynucleotide is inhibited or suppressed by the siRNA molecule is by inhibiting the binding of poly(A) RNA to the MSUT2 polynucleotide.
39. The method of any of claims 33, 34, 35, 36, or 37, wherein the cell is a mammalian cell.
40. The method of claim 39, wherein the mammalian cell is a brain cell.
41. The method of any claims 33-35, wherein at least one nucleotide of the siRNA molecule comprises a chemical modification.
42. The method of claim 41, wherein the chemical modification is on the sense strand, the antisense strand or on both.
43. The method of any claims 33-38, wherein the siRNA molecule comprises at least one sequence is selected from the group consisting of SEQ ID NO: 6 – SEQ ID NO: 73.

44. The method of any of the preceding claims, wherein the siRNA molecule comprises or consists of a sense strand which comprises or consists of at least one sequence selected from the group of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, and SEQ ID NO: 72; and an antisense strand which is complementary to the sense strand which is selected from the group of SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, and SEQ ID NO: 73.

SEQUENCE LISTING

<110> United States Government as Represented by the Department
of Veterans Affairs

<120> Compositions and Methods for Suppressing MSUT2

<130> 37759.0352P1

<150> US 63/117,213

<151> 2020-11-23

<160> 78

<170> PatentIn version 3.5

<210> 1

<211> 21

<212> DNA

<213> Homo sapiens

<400> 1

aatttatcga ccacctgcaa g

21

<210> 2

<211> 21

<212> DNA

<213> Mus musculus

<400> 2

tactggcctg cctgtaaaaa t

21

<210> 3

<211> 21

<212> DNA

<213> Mus musculus

<400> 3

ggcctgcctg taaaaatggg g

21

<210> 4

<211> 21

<212> DNA

<213> Mus musculus

<400> 4

gccaccaaga cacgccttga a

21

<210> 5
 <211> 20
 <212> DNA
 <213> Mus musculus

 <400> 5
 attagacact tcagatagat 20

<210> 6
 <211> 25
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 6
 ugaguguggc acagaaacca gaaaa 25

<210> 7
 <211> 27
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 7
 uuuucugguu ucugugccac acucagu 27

<210> 8
 <211> 25
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 8
 gaguguggca cagaaaccag aaaaa 25

<210> 9
 <211> 27
 <212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 9

uuuuucuggu uucugugcca cacucag

27

<210> 10

<211> 25

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 10

aguguggcac agaaaccaga aaaac

25

<210> 11

<211> 27

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 11

guuuuucugg uuucugugcc acacuca

27

<210> 12

<211> 25

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 12

guguggcaca gaaaccagaa aaacu

25

<210> 13

<211> 27

<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 13
aguuuuucug guuucugugc cacacuc 27

<210> 14
<211> 25
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 14
uguggcacag aaaccagaaa aacuu 25

<210> 15
<211> 27
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 15
aaguuuuucu gguuucugug ccacacu 27

<210> 16
<211> 25
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 16
uggagcgcug caaguacugg ccugc 25

<210> 17
<211> 27
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 17
gcaggccagu acuugcagcg cuccaaa 27

<210> 18
<211> 25
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 18
cagcucugcc guuacuuccc ugcuu 25

<210> 19
<211> 27
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 19
aagcagggaa guaacggcag agcugac 27

<210> 20
<211> 25
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 20
agcucugccg uuacuucccu gcuug 25

<210> 21
<211> 27
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 21

caagcagggga aguaacggca gagcuga 27

<210> 22
<211> 25
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 22
gcucugccgu uacuucccug cuugu 25

<210> 23
<211> 27
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 23
acaagcaggg aaguaacggc agagcug 27

<210> 24
<211> 25
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 24
cucugccguu acuucccugc uugua 25

<210> 25
<211> 27
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 25
uacaagcagg gaaguaacgg cagagcu 27

<210> 26
 <211> 25
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 26
 ucugccguua cuucccugcu uguaa 25

<210> 27
 <211> 27
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 27
 uuacaagcag ggaaguaacg gcagagc 27

<210> 28
 <211> 25
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 28
 cugccguuac uucccugcuu gaaag 25

<210> 29
 <211> 27
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 29
 cuuacaagca gggaaguaac ggcagag 27

<210> 30

<211> 25
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 30
 ugccguuacu ucccugcuug uaaga 25

<210> 31
 <211> 27
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 31
 ucuuacaagc agggaaguaa cggcaga 27

<210> 32
 <211> 25
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 32
 gccguuacuu cccugcuugu aagaa 25

<210> 33
 <211> 27
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 33
 uucuuacaag cagggaagua acggcag 27

<210> 34
 <211> 28
 <212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 34

gguagcuuuu cuaacgcuga gaugagug

28

<210> 35

<211> 28

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 35

cacucaucuc agcguuagaa aagcuacc

28

<210> 36

<211> 28

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 36

gugaacugag uguggcacag aaaccaga

28

<210> 37

<211> 28

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 37

ucugguuucu gugccacacu caguucac

28

<210> 38

<211> 28

<212> RNA

<213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 38
 cagaaaaacu uuuggagcgc ugcaagua 28

<210> 39
 <211> 28
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 39
 uacuugcagc gcuccaaaag uuuuucug 28

<210> 40
 <211> 28
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 40
 aguacuggcc ugcuuuuuuu aaugggga 28

<210> 41
 <211> 28
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 41
 uccccaauuuu uacaagcagg ccaguacu 28

<210> 42
 <211> 28
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 42
ggaugagugu gccuaccauc accccauc 28

<210> 43
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 43
gaugggguga ugguaggcac acucaucc 28

<210> 44
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 44
ccaucucacc cugcaaagcc uuccccaa 28

<210> 45
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 45
uuggggaagg cuuugcaggg ugagaugg 28

<210> 46
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 46

ccaauuguaa auuugcugaa aaauguuu 28

<210> 47
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 47
aaacauuuuu cagcaauuu acaauugg 28

<210> 48
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 48
guuuguuugu ucacccaaau uguaaaau 28

<210> 49
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 49
uaauuacaau uugggugaac aaacaaac 28

<210> 50
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 50
aaauaugauc aaaguguacu aaaccaga 28

<210> 51
 <211> 28
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 51
 ucugguuuag uacacuuugc aucauauu 28

<210> 52
 <211> 28
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 52
 ccagauuguc ccuucacuca ugugagua 28

<210> 53
 <211> 28
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 53
 uacucacaug agugaaggga caaucugg 28

<210> 54
 <211> 28
 <212> RNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic construct

 <400> 54
 aguagaagaa uuccaguacu gucuccaa 28

<210> 55

<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 55
uuggagacag uacuggaauu cuucuacu 28

<210> 56
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 56
ccaaaaccag uugcaccacc agcaccac 28

<210> 57
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 57
guggugcugg uggugcaacu gguuuugg 28

<210> 58
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 58
accaccuucc aguagucagc ucugccgu 28

<210> 59
<211> 28
<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 59

acggcagagc ugacuacugg aagguggu

28

<210> 60

<211> 29

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 60

ccguuacuuc ccugcuugua agaagaugg

29

<210> 61

<211> 29

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 61

ccaucuucuu acaagcaggg aaguaacgg

29

<210> 62

<211> 28

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 62

auggaauguc ccuucuauc uccaaaac

28

<210> 63

<211> 28

<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 63
guuuuggaug auagaaggga cauuccau 28

<210> 64
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 64
aaacauugua gguuuuacac ucaaugua 28

<210> 65
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 65
uacauugagu guuaaaccua caauguuu 28

<210> 66
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 66
auguacaaga ccggacugca cauucuac 28

<210> 67
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 67
guagaaugug caguccgguc uuguacau 28

<210> 68
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 68
cuaccauccc accauuaaug ucccacca 28

<210> 69
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 69
uggugggaca uuaauggugg gaugguag 28

<210> 70
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 70
accacgacau gccuugaaau ggauucga 28

<210> 71
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 71

ucgaauccau uucaaggcau gucguggu 28

<210> 72
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 72
auggauucga ccucaaacca gcgaauaa 28

<210> 73
<211> 28
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 73
uuauucgcug guuugagguc gaauccau 28

<210> 74
<211> 477
<212> DNA
<213> Homo sapiens

<400> 74
ggtagctttt ctaacgctga gatgagtga ctgagtgtgg cacagaaacc agaaaaactt 60
ttggagcgct gcaagtactg gcctgcttgt aaaaatgggg atgagtgtgc ctaccatcac 120
cccatctcac cctgcaaagc cttccccaat tgtaaatttg ctgaaaaatg tttgtttgtt 180
cacccaaatt gtaaatatga tgcaaagtgt actaaaccag attgtccctt cactcatgtg 240
agtagaagaa ttccagtact gtctccaaaa ccagttgcac caccagcacc accttcagtg 300
agtcagctct gccgttactt ccctgcttgt aagaagatgg aatgtccctt ctatcatcca 360
aaacattgta ggtttaacac tcaatgtaca agaccggact gcacattcta ccatcccacc 420
attaatgtcc caccacgaca tgccttgaaa tggattcgac ctcaaaccag cgaataa 477

<210> 75
<211> 3556
<212> DNA
<213> Mus musculus

<400> 75
ggggacgcgc acggcggagg cggagcggcg gcggcagcgg cggcagcggc agcggcagcg 60
gcgtagggggg cccaggctgc aggggtggcag cccgcggcgg gctccaggta accgaggcgc 120
cgcgcagtgc cgagccggcc gcccgccgcc gagccatgga aatcggcacc gagatcagcc 180
gcaagatccg gagtgccatt aaggggaaat tacaagaatt aggagcttac gtagatgaag 240
aacttcctga ttacattatg gtgatgggtg ccaacaagaa aagtcaggac caaatgacag 300
aggacctgtc cctgttttcta gggaacaaca caattcgatt caccgtatgg ctccatgggtg 360
tattagataa actgcgctct gtcacgactg agccctctag tctaaagtct cctgacgcc 420
gcatcttcga tagtcacgtg ctttcaaaca agagcagttt cagtcgggga gatgagagaa 480
ggcacgaagc tgccgtccct ccccttgctg tttctagttc tagacctgaa aagagggatt 540
ccagagtttc tacaagttca caggagcaga aatccactaa tgtcagacat tcatatgatg 600
atggagcttc caccgggcta atgtcaacag tgaaacctct gagggaaacca gcaccctctg 660
aagatgtgat tgatatcaag ccagaaccag atgatctcat tgatgaagac ctcaattttg 720
tgcaggagaa tcccttatct cagaaaaaac ctacagtgc acttacatac ggttctttctc 780
gcccttctat tgaaatttat cgaccacctg caagtagaaa tgcagacact ggtactcact 840
taaacaggct gcaacttcat ccgcagcaaa gcagtgtca cgctgccaag cagctggatg 900
tacaaagcag ccaggtatcc gaagcaggac ggttgtgtga gccaccagtg cttagcagcg 960
tagaagacac ttatagcccc ttcttcagaa acaacttgga taaaatgagt attgaggacg 1020
aaaactttcg aaagagaaaa ttgcctgtgg taagttcggg tgttaaagta aaaagattta 1080
gccatgatgg agaagaggag gaagaagatg aggattatgg gaccgcata ggaagcttgt 1140
ccagcagcgt gtcagtacca gcaaagcctg agaggagacc ttctcttcca ctttctaaac 1200
aagctaacaa gaatctaatt ttgaaggcta tctctgaagc tcaagagtct gtaacaaaga 1260
caactaacta ttctgcagtt ccacagaaac agacacttcc agttgctccc agaactcgaa 1320

cttctcaaga agaattgcta gcagaaatgg tccaggggca aaacagggcc cccagaataa	1380
gtccccctgt taaagaagag gaagcaaaag gagataatac aggaaaaagt caaggaactc	1440
aacagaggca attgttatcc cgactgcaaa ttgatccagt aatggtagaa acaatggaga	1500
tgagtcaaga ttactatgac atggaatcca tggatccatgc agacacaaga tcattttattc	1560
tgaagaagcc aaagctgtct gaggaaatag tagtgacacc caaccaggat tcggggatga	1620
agactgcaga tgcccttcgg gtcctttcag gacaccttat gcagacacga gatcttgtac	1680
aaccagataa acctgcaagt cccaagttta tagtgacgct ggatgggtgtc cccagcccc	1740
caggatacat gtcagatcaa gaggaggaga tgtgctttga aggaatgaaa cccgtaaacc	1800
aaacttcagc ctcaaacaag ggactcagag gtctcctcca cccacagcag ttgcatttgc	1860
tgagcaggca gcttgaggac ccagatggta gcttttccaa cgccgagatg actgacctga	1920
gtgtggcaca gaaaccagaa aaacttctgg agcgctgcaa gtactggcct gcctgtaaaa	1980
atggggatga gtgtgtatac catcatcca tttcaccttg caaagccttt cccaactgta	2040
aatttgctga gaaatgtttg tttgtgcatc caaattgtaa atatgacaca aagtgtacta	2100
aagcagattg tcccttcact cacatgagta gaagagcctc gatactgact ccaaaaccag	2160
tgtcgtcacc agcaccgtct tctaattggc agctctgccg ttactttcct gcttgtaaga	2220
aaatggaatg tcccttctac cacccaaac actgtaggtt taacactcag tgtacgagac	2280
ctgactgcac attttatcac cccaccatta ctgtgccacc aagacacgcc ttgaaatgga	2340
ttcgacctca gagcagtgag tgatgcccta gtcctacctg gcagaagatc atgcagtttg	2400
aaagcttcca tcttctgatg agagatgttc tacagaactt gtcacgtctt tgaaatttag	2460
aatatattgc tttcataata cgaattttac tgccccactg aagtgtctaa tttttcaagt	2520
ttgtaagttt attaagtggg ttcaacattt tttgtttgtt cgttttgact atgaaaaaga	2580
cagtttaaag aaaagccaaa ttctattaaa acatttgcgg catgtttgta cattgctgtt	2640
taatatcatt tttggtaatg gtacttgcag cttagggctg tagtgctgtg ggaaggccag	2700
tgtcctcaga gctgaagcac ttttcagctt ttcccaaagg taatgcagtg tctgtaaccc	2760
agcgtggtaa cagtggccag gctttgaaac tgaggcagct ttggaacaac tagttttaat	2820

ttcttttttt agtgtctaaa tgaatttgct ctgagaagca taatgcagac tttattttga	2880
gtgctacttt ggtagagtgg accgaggtcc tgtgcctttc tgaaagtgag cagagacatg	2940
gtcataaagg gtaagcatag ttggaatgac gatgtaaaaa tatatggaca gttcttttga	3000
atgctcccat ttactattag cttatcattt tataagtaat tttggaggga ctacattatc	3060
acaaaagtat acaaaaattt ttacaggcat atgtacagaa agtatcagaa aacagacttt	3120
gaactcacia gaatataaat atacgtatat attcccatat tctgaaaaat atcatcagaa	3180
ataaccccac agaaaatata cttatgttat tactaaagat cattcttgaa atgtagaagt	3240
tgagatttaa gtggtatatt ttaaatagaca gaactatatt gcagagatag gaaggtaaac	3300
ttgacaatag gatgaaactt ggcctactgt actatggagt tttatgtgtg gtttttgaaa	3360
ctgttaaggc aagatgtgtc atgttttaga actaaataac agacaactga tttcaaaaac	3420
gtgttgTTTT aaaaattaaa gtgtaaacgg tggttagcaa aggggataat aaaagctcaa	3480
acattttgag gaccaaattt aactgttaag atacaataaa gtcacatcta taaaagtctg	3540
tgtttaataa tgtgaa	3556

<210> 76
 <211> 18153
 <212> DNA
 <213> Homo sapiens

<400> 76	
ggaggcggtg gtgtcccggc tgcggggtag gagtccgcgg cagcctccgg gtaagccaag	60
cgccgcgcag tgctgagttc ccgcacgccg cagagccatg gagatcggca ccgagatcag	120
ccgcaagatc cggagtgcc a ttaaggggaa attacaagaa ttaggagctt atgttgatga	180
agaacttcct gattacatta tggatgatggg ggccaacaag aaaagtcagg accaaatgac	240
agaggatctg tccctgtttc tagggaacaa cacaattcga ttcaccgtat ggcttcatgg	300
tgtattagat aaacttcgct ctgttacaac tgaaccctct agtctgaagt cttctgatac	360
caacatcttt gatagtaacg tgccttcaaa caagagcaat ttcagtcggg gagatgagag	420
gaggcatgaa gctgcagtgc caccacttgc cattcctagc gcgagacctg aaaaaagaga	480
ttccagagtt tctacaagtt cgcaggagtc aaaaaccaca aatgtcagac agacttacga	540

tgatggagct gcaacccgac taatgtcaac agtgaacct ttgagggagc cagcacccctc	600
tgaagatgtg attgatatta agccagaacc agatgatctc attgacgaag acctcaactt	660
tgtgcaggag aatccccttat ctcaaaaaa acctacagtg acacttacat atgggttcttc	720
tcgcccttct attgaaattt atcgaccacc tgcaagtaga aatgcagata gtggtgttca	780
tttaaacagg ttgcaatttc aacagcagca gaatagtatt catgctgcca agcagcttga	840
tatgcagagt agttgggtat atgaaacagg acgtttgtgt gaaccagagg tgcttaacag	900
cttagaagaa acgtatagtc cgttcttttag aaacaactcg gagaaaatga gtatggagga	960
tgaaaacttt cggaagagaa agttgcctgt ggtaagttca gttgttaaag taaaaaaatt	1020
caatcatgat ggagaagagg aggaagaaga tgatgattac ggggtctcgaa caggaagcat	1080
ctccagcagt gtgtctgtgc ctgcaaagcc tgaaaggaga ctttctcttc caccttctaa	1140
acaagctaac aagaatctga ttttgaaggc tatatctgaa gctcaagaat ccgtaacaaa	1200
aacaactaac tactctacag ttccacagaa acagacactt ccagttgctc ccagaactcg	1260
aacttctcaa gaagaattgc tagcagaagt ggtccaggga caaagtagga cccccagaat	1320
aagtcccccc attaaagaag aggaaacaaa aggagattct gtagaaaaaa atcaaggaac	1380
tcaacagagg caattattat cccgactgca aatcgaccca gtaatggcag aaactctgca	1440
gatgagtcaa gattactatg acatggaatc catgggtccat gcagacacaa gatcatttat	1500
tctgaagaag ccaaagctgt ctgaggaagt agtagtgga ccaaaccaag agtcggggat	1560
gaagactgca gattcccttc ggggtactttc aggacacctt atgcagacac gagatcttgt	1620
acaaccagat aaacctgcaa gtcccaagtt tatagtgacg ctggatgggtg tccccagccc	1680
cccaggatac atgtcagatc aagaggagga catgtgcttt gaaggaatga aaccgtaaa	1740
ccaaactgca gcctcaaaca agggactcag aggtctcctc caccacagc agttgcactt	1800
gctgagcagg cagcttgagg acccaaattg tagcttttct aacgctgaga tgagtgaact	1860
gagtgtggca cagaaaccag aaaaactttt ggagcgctgc aagtactggc ctgcttgtaa	1920
aaatggggat gagtgtgcct accatcacc catctcacc tgcaaagcct tccccaatg	1980
taaatttgct gaaaaatgtt tgtttgttca ccaaattgt aaatatgatg caaagtgtac	2040

taaaccagat tgtcccttca ctcatgtgag tagaagaatt ccagtactgt ctccaaaacc	2100
agcagttgca ccaccagcac caccttccag tagtcagctc tgccgttact tccctgcttg	2160
taagaagatg gaatgtccct tctatcatcc aaaacattgt aggtttaaca ctcaatgtac	2220
aagaccggac tgcacattct accatccac cattaatgtc ccaccacgac atgccttgaa	2280
atggattcga cctcaaacca gcgaatagca cccagtcctg cctggcagaa gatcatgcag	2340
tttggaagtt ttcatgtact gatgaaagat actctacaga acttgtcaaa tctttgaaac	2400
ttggaatata ttgctttcat aatatgaagt ttattgcct atctatctga agtgtcta	2460
ttttcaagtt tgtaagttta ttatgtggtt ttaacattgg gtgtttttgt tttgttttta	2520
ctatgaaaag acagcttaag gaagagctaa attctgttaa aatatttggg gcatgtttgt	2580
gcactgctgt tgtgaggatc agcatatgaa attgacatca tggttagtca tggtagtgc	2640
gcttaggggg ctacacggtt gctgtgtgag tggagagatg cagtgaggca gttgtcatta	2700
ttctaaaaat tgtactactt tcacttttcc caaagattat ataattgtca taatccacca	2760
tgaaaacagc attggccaaa ggtactgagg ctgcttaaaa tattcaattc tgctttttta	2820
tttttaagtg aatttagttt gaaaagcatg attatacagg cctctcaggc tgagtgtctac	2880
tttggtaaaag ttcccagttt tcctgccttc tgtgacagga tgaatgaggt gggatatggac	2940
agtggaggca gctggaatgg caagtgcaga aaataggaac agttctatac agtgctctca	3000
tttactaata acataatgcc ttctaaataa ttttttggg aaactacatt atcacaaaat	3060
tatacaaatt tttttacaag tatttacata ctgtatctga aaacagactt taaagtcaca	3120
agattataaa tgtacatata tattctcaca ttctgaaaaa taacattctc agaatccaca	3180
gaaaatatac ttagttacta ctgaagataa tttttgaaat gtaaaaatta gatttaaata	3240
gtatatttta aatgacagaa ctataattac agagatcaga tcagataggt aaactgcaag	3300
atagatagga tgaaactttt ggcctactgt attacttaca gagttttttt gtgtgtggtt	3360
tttaaaactg ttaaggcaag aagtgtcaaa tgcttttagag ttaaataaca gatcactgat	3420
ttcaaagact tgggtgtatag tgttaaaaat taaagcttaa aaggtggtta gaaaagtgga	3480
ttaatgcaaa aggggtaata aagactgcaa cattctcagg accaaattaa actgctaaaa	3540

aaaaaaaaa agttcattga cttgcttagt cgtataactca aatgatgata aacctacatg	3600
tgcaaaggct cacgtttaag attgtcaagc cagcagtcta ctgttgtgtt gccattgctt	3660
ttccattggg agaagaaaga attaaccagt cattaaacca tttggtaagt tgcactttgc	3720
tgtgctgac ccacaggaaa ggcttgaaac acgagaagca gcaaagacag agcacacaag	3780
tgcataaggc tgttgtcttc ggcttgggtg aaatgacagt tcctcttcat tctaaagggt	3840
tactccattg aatttaaggc atttgttcat tccagtgttg agatgctttg catctctgca	3900
gaagaaattt attttaaatt gtttaaatat ctggaaatac ttttagctat catttataaa	3960
gatagttttg ttctcagttt cactataaat tatagaacaa atgggaaaca agggtttaat	4020
ttagttcagc cattttacia ggaaataata aaatactaaa atctgattgt tttttgctat	4080
ttaatagcca ctgcccagac acatatttaa gagtttaatc tttcagttgc tatggcttat	4140
gaacaagcta aggttgacca taaaacattt gttggatgac gtggtttaaa atgataacca	4200
caaaaaggga ccacaaaaaa aggaaggaaa tgagcatggt tggcgattgg aagcaagggt	4260
accagagggc acagtgtgct ttggcatgca ttttatacat aaaatgaatg gaacaaaagg	4320
tgccagaagt cccaggttac acaatcagga gcttagatac tgcacacaaa aataattatc	4380
tgggttaaaa aagtaaacad agggcagatt ctatatggcc tatcatgttt cttcaccttc	4440
ccctcgttgc tggctgatac agcgaggtgg tcagctgatg actacttagt caatatgacc	4500
tttagtcgtg aaactgacag cagcagtgat taaggctgac ttaatcaggt tggccacttt	4560
gaaggacaga aatgcagtgg aaacagtttt attctatgta gtttacctgc ttaaggttac	4620
agagtttcta cctgcactgt aatggaaata taatttctct gtagccaaaa gctggcaaac	4680
ttgaccaga gggaaaattt aaaactgcag caggctcaaa tgtagagtat ttttcttttt	4740
atgggcaggt tgttcaggga tttttttcct cttttaattt attgactgac tgtaaataca	4800
tgagtagaaa cttaatagtc atgtatttca aaatttggct taatttagga gaatccactg	4860
atgaacaagt accaacttac gtttcaagct tcttagcccc ataatacagtc cttcagccac	4920
agctatttag agctttaaaa ctaccagggt caatcactgg ttatgctttc tgtgatgtaa	4980
tttagtcatt tctattttta gtattaacca agtattagac acagaaaata ggtattaaga	5040

atcttcatat atcctgtcag accaaatggg attccaggaa cctaaagcga tctattatgc	5100
tataaagata attaacacat taaaaactca taggggtcaat acagcatctt aaacctcaca	5160
cttagaaaaa tatattttta aatagcagtc tacataatth tcaatcttca ggaaactaca	5220
gataggctag acagcgaatt cctgaatgat gagtagtgat ctttggcagc atttaaagtg	5280
aaaagaaata aggatctaag aattcagccc taatccacta aaaaaaggaa ttctaactga	5340
caagttttta caaatggagt tgggctcatt ctttttgga ataaacctat ggagtggcac	5400
acatctaaac aaattttccc aatagaaaaa aggctataaa aattttattc caagagtgat	5460
taaattgtat aatgttgtat atgtgaatth aacacttttg tttacatgth aaacaaatgt	5520
gtatatatta gactacatta aatatgcaat tctttcttcc agttaaatac tgttgctccc	5580
taaaaccctt acattgtaca ccattgggaa tgattgttca tcatactact tttccattag	5640
tgaggctaca gttatgtttt aaatgtgcga ttacagagat ggcatctgaa cataaactga	5700
tggctcgaaa atgaaaatgg aaatgtagca gccatatact gctaactttg gatctgttcc	5760
tgaattcaaa actactagga gaaaagtgtc ctttataaaa aaggacctta ttaatgccta	5820
aaaaacatca tatttcttag gaaagcttgt gtctgtttcc ttagggaaaa tgtttgcctt	5880
ttaaaaactg tgatccttta ggatgatcat gactttccct ttccttatgg aaatgcaaga	5940
ataaaatatt tcattaaaca atgaaccttg aaaataaaat ataaacatta agaaaccatt	6000
ttgctaaaaa gataatgaaa attatccaaa ttgggttttt gagttcttct gtaaagagtg	6060
ctctacccta aattttccca gcaggtctgc cgaaatcaca cacttcccaa tacaggggga	6120
cttggccttt accatcaagt attcgatcct tccttgaaat ggcatctatc ggcatgtat	6180
ggattacgga ttataccag tgcatatagc aaatattttg aacagatcag tctttcacta	6240
ttttgatgat tctgggcatt tctccctgtt acagtcttgg gttagcacca cttgaccatg	6300
cagggttggg ttttggtttt tcttctctgt aattctggtc tcaaagttaa tttctgtagt	6360
catctcagca tctctcagt aggtgtatgt acacatttcc agacaaataa gctgcaatca	6420
gagaagaaaa ttgcaggag ttaattatgt ttttagatth tcataacagt ttaatattth	6480
tcagttgtgc tttcaggta catgtgtaat atttttcctc ttttaactct tttattctgt	6540

at ttgcataa	atatgagatt	ctgaagagcc	atctggttat	actaccttct	actaatgttg	6600
actagctgat	ttcataaacc	aaagctgtag	gagttgttgt	attaagtctc	ttaactagta	6660
acatagtctg	ctcttcatgg	gctgagaaag	ttactaacct	gcagtcatca	cctccagcac	6720
taacaacatg	tcgatcacca	ctggtaaadc	gaatatttgt	cacatggggc	gaatgaccca	6780
agaacctttt	gtgttttgcc	taaaaaaca	tgacagacaa	gctcagggca	tttgggtgcac	6840
acagaagtca	aaggctctta	ttaggaacta	taatctctat	gacaagagct	gtggagagag	6900
tagggagtta	gcaccgcagc	cagtgattag	aatgcttttc	agcatgagta	gtggatctgc	6960
aaaaccaggc	tgtgtgggca	gtcagatgtc	tccaggtact	ctgaccattt	ttctctaagg	7020
aaaagcattt	gaaatttgat	aactgattat	aggtttggtg	aaaagctaata	tacagctttt	7080
gtaggatggt	tccaaagatg	gtattactcg	agggagagga	tttgtttcta	atagctttta	7140
tttcaaagta	aatagattta	gaaagtttgg	ggaaaaattt	agaaattagg	acaaaacatt	7200
ttaaataatat	ggggaaaagt	gctgatgata	agacatcaaa	attaggagta	aactgataat	7260
agtaaacaaa	acacaaactt	acaaattttt	ctggacatgg	gaagtcaaat	aacttaacca	7320
tgccaaagtc	atctcctgta	acaagactga	ttcctgaatg	agatacacag	gcacagttga	7380
catcagcttt	ctcagcatgt	ctggaccaga	ttcccaaac	ctcatctcct	agaatactag	7440
agggaaggaa	caaaagaaaa	ctcatcatgg	caagtgcggg	caggttgact	atattcaaaa	7500
agtttcttgg	caattaatct	ctaagtacc	tatcatgtta	cttaaaatac	aggaagtaaa	7560
ttatggtaag	ttgtttggag	acctgaattt	catcaggata	tcaactcctg	ccttttaaaa	7620
atgacatttt	ataatttgaa	gggtttctag	attaatcttt	ttaagattaa	agtagtactt	7680
tatgaaaact	gatagaacta	ttttttcttt	tttttttttt	gagacggagt	tttcgctctt	7740
gttaccagg	ctggagtgc	atggcatgat	ctcggctcac	cgcaacctct	gcctcctggg	7800
ttcaagcaat	tctcctgcct	cagcctccc	agtagctggg	atcacaggca	tgcgctaaca	7860
tgcccggctt	at tttgtatt	tttagtagag	acagggtttc	tccatgttgg	tcaggctagt	7920
ctcgaactcc	cgacctcagg	tgatcacccc	cgctcggcct	cccaaagtgc	tgggattaca	7980
ggctgagcca	ccgcgcctga	ctgaaaactg	atagaactat	ttttcaaatt	aaaagtgcata	8040

cttggctggg tccagcagca cataccagta atcccaacat tttgggaggc tgaggcagga	8100
ggactgcttg aggccaagag tttgagacca gcctgggcaa tattgtgaga tccctatctc	8160
tacaaaaata aaaatgactt atgacatagg aattaataaaa atttcagaga tgggggtcttg	8220
ctatgttgcc caggctggta tcaaaacttc taggctcaag tgatcctccc acctcggcct	8280
gctacatcag agattacagg catgagccac tatatgcctg gctgatacag gaatttgatg	8340
gcatttttca ttggccaaaa aaatggatag tcatggttac ctgtcataca gccaggaaat	8400
ttgaacaaat ttggaagctt tgacttctaa tagattcaag atagcattcc tttagataga	8460
gaattaataa cagttgctta acagcaccca ataccttttt gccagtcatt aaatttagca	8520
ttaagaaaaa tatcagggta tctttaagt taaaactttg atttccttaa aaaaaaact	8580
tgataaatca tggaaactga taaaacatgg aaatatattc aataaaaagg ggtcccaaca	8640
tgaacatacc atttcaaaat atggtaacaa aaacttgaaa ctcaattact attccttatt	8700
ggaatggctc taacagttca gaaataggat tttctaactg gccttcaaag tcagttcttg	8760
ccttgatgaat atataagtat ttacctagtc catgtagccc aagtaattct gtcaatagcg	8820
gcatgatcca taagatgttt tcctgaaggc acttcataga catgccgttt atagcagcca	8880
ctagagacct ttttcatcag attaaaatgg gacaagaatt ccattaggtg agagacaaaa	8940
tccacagggg gtttacagaa tactagcata ttgctacttg atttcatgt ctaacattat	9000
taagtatgca aaagatcact aaaaaactt aataggagaa aagctctgat aagtggggga	9060
ggaaagggga gctgtaggtc agaaggtaca aaggaggag ttgagaagct ggagctctgg	9120
agctcaggaa ctttaaatgc attcactaac acgaaatgta aaagcagaag aacttgccac	9180
ctgggtatac agtattggta ctgtacctgg agataactgc tatctgcaga gaagtccatt	9240
tgaatgacaa agcttggaat gtctttgcag tagctgattc tgttaagagt ggggccagc	9300
gtaggtcat aaaaatccac tgagttctca ctagaacctg ctgccagata ccgggaatcc	9360
ggactaaatc tgaatcaaaa caaacgtaa aaagtattag accacatgaa gtattataaa	9420
tacttaagat cagtgacttt tcctttctag ttcttaaaag taacgtgtga taaggcctca	9480
aatagattta cctgtcagac acaactgatc atgtatactg agattgtctg ggttacatga	9540

aataaggaag ctttatat	ttt tactttaatt	ttaaatat	ttt cccaattgt	catctcccaa	9600
ttcctttaaa aacgtcta	at ggcttaaaaa	aactttctta	ggccaggccc	agtggtcac	9660
acctataatc ccagaact	ttt gggaagcgga	ggcgggcaga	tcacctgagg	tcgagagttt	9720
gagaccagcc tgaccaac	at agagaaaccc	tgtctctact	aaaaatacaa	aattagccag	9780
gcatggtggt gcacgcct	gt aatcccatct	actcgggagg	ctgaagcagg	agaatcgctt	9840
gaacccagga ggcacagg	tt gtggtgagct	gagattgcac	cattgcactt	cagcatgggc	9900
aacaagagca aaactcca	ac tcaaaacaaa	acaaaacaaa	atttaatttt	ttaaatagag	9960
gcgggggtctc actatg	gtcc caaactcctg	gcctcaagca	atccttcccc	cttggcctcc	10020
caagggtactg ggattac	agg tgtgagccac	aacacccagt	cagaacatct	cagcttttaa	10080
aagccattag cattacata	aa ttaataagct	aacaattcat	taagatagtt	ttcttccatc	10140
tggaaaaaac gttgtctta	aa tattaagcaa	agaacacagc	ccagcttaac	taacctccag	10200
ttattaaggt gaaatgac	ac aacttgaatc	ttggaagaag	aatttttttt	ttttgagacg	10260
aagtctcgct cttgtctccc	aggctggagt	gcgatggcgc	aacctccgcc	tcccgggttc	10320
aagcgattct cctgtttcag	ccccctgagt	agctgggatt	acaggcgcct	gccaccacgc	10380
ccggctgatt tttgtat	ttt tagttgagat	ggggtttcac	tatgttggcc	aggctggtcg	10440
agtactcctg acttcagg	tgt atctgcctgc	ctcggcctcc	caaagtgctg	ggattacagg	10500
catgagccac cgcgccggc	ctgaagaact	tatttaaaag	acaaagtgaa	atgctat	10560
cctagcaatc tttggagt	ca tatgggacaa	ttcagtctct	tgaaatggcc	catgagtctt	10620
actgaggtag gatagaga	c tgtaaaagct	aagggaagcc	actgttacta	ttttatatat	10680
tgaagtcttg aggaagg	ttt catttgtaaa	aggattttac	tgatgaaaag	tgtacaagct	10740
tttgacagac ctagatt	caa taatcttatc	tactgatcac	acggaagtac	tccgtaa	10800
gtagccactg ttgaaaa	atg cttaagcact	gaaaaacaaa	ggtttaagaa	acatttaa	10860
taatttggat tctggaac	at ttaatcaata	ggtattgatt	aaattaatga	actacatatt	10920
cccaaactga ggttacta	ag agaagatatg	tttgaaatca	caactttagt	tttccagggt	10980
gacaactttt gaagggc	aga tagctctctt	gtattacagt	gggagatacc	tcttggtggg	11040

atgaacttaa tggacatggc taagtgttaa catgaattca tcaaacatta cctactagta	11100
cttgctatta tagttgggtgc ccagtgggtt tataatntag caagaagaat taagtagtat	11160
acaaacagcc atatnttagc atacaattta taatacggga aatgctacag gccctgggga	11220
cctctttttg aaggcaaggc tatggaaaat ttacaaaatg gaagttaaatt caagtatata	11280
ctagaaaactc tattccattt gttcactaac ctgatatcat ggattgcaca tctcctgtct	11340
ctcttctttc cccatatttt tagagaactc actagtaaaa tgataaattc tccatttttc	11400
attccaatag ccacatgtc cccttcaggg ctgtaacaca cagtacgagc agcatgtccc	11460
aaattcactt tgtttaacat cttctgcatt taaaaaaaaa aaaaaaaga gtcataggaa	11520
acattaagtg aagtacttct aaattatacc agtttcccct caaatgctc aacagaattc	11580
tggcagttct ttaagtacta gcaatttaga acttccaact tttcttttta gaagttgtaa	11640
cctcttttaa aaaaattatc tgtacttact ttatcagcaa tatcccaaag tctcactgtc	11700
ccatcttctg cagcagaaag gaaaaaatcc ctggaaggat gtgttgctag tccccagatt	11760
ggcccatcca catgaccgtt aactaaaata ttacaagctg catTTTTtctc tccaacttcg	11820
attatttcag cattccttgt cccaacaagg atcttgccct gaaacacaag caggaccaat	11880
acagtgaatg taatacaaca gctgcttttc ttcttcataa tataaaaatg accctattga	11940
cctgctttca gagaactttt tgctttgagc taatctagta gcaaggcagt cattagctca	12000
tgcaaatttt tctatgacta caggcacaca tctatctgta agcacaatgg gctagattac	12060
atattagagt ccatgctaca gaatagaact tttctgtggc agtacacctg gattcttcaa	12120
taatcaaagt ttttatttga taatcttagg atttccaaac tggggtcagt gcagtgggat	12180
ataggaaaaa ataatagaat ttatttttta gttaaaaagt aaaagcttaa ctacaattta	12240
atatgcaggc tgaagataat atccgtatga ttataaata cacttaataa gtacaaacac	12300
gctcaaaaat tttcatagga gttgtagttt tgaattttta ttttgaaatt gacacataat	12360
tatacatatc tatagggcat agggtaatac gcataacat cacctcagac atttatcatt	12420
tctttgtgat ggaaactttc aaaatcctct cttgtaaata cctgaaaata cataaatacg	12480
tgattcttaa ctatagtcac cctacagtac tacagaatac taaaacatac tattcctatc	12540

tggtgtgta aacttgatc ctttaaccag tccttccta tccccctccc cctccccctt	12600
gtccgcctcc agtaaccact attctactct ccacctctgt gggatcaact tttttagttt	12660
ctgcacagga gtgagaacat gtatttatct ttctgtgcct ggcttatttc acttcacatc	12720
atgtcctcca gtctcatcca tgttgccacc aagaatgaca gaatttcatt attttttatg	12780
gctgagtagt atttcattgt ttgtttactg cacgttttat ctagggaatg tgtgtttttt	12840
taaaaaatgg agacagctgt cctaatatga gtcaactgcc aagggttttc aattatgtct	12900
actagagttg ttaaatggc agattctaga aaatattgga ggtttacata cagtatttag	12960
acagaatagc ttcctagctt atgcaccaca ctggtgctaa ctttggcaaa gaaagcagca	13020
aagacagagt aatgttggca agcaaatacca tcgttatgca ttattaagta ttgttcatta	13080
ggctgcaaag ggtgaggga tcacagtaat aaccactttc tgttttctgc tgcactgtat	13140
cagctcatgg aacatcttac tttgcctctg cacacagaac gaacacaatc tgtggcttgt	13200
cctgtctcaa gcctgaaggc acggcaccgc ctgagttcct gatcccacag ttttaaccgt	13260
cctccttctt ttgacctag taaataacca agccagagta agtggttcatt attggctact	13320
ataattttta ttataaaca ataccaagtt ataagcagaa tctttttttt ttaaaaaggc	13380
cctgatattt ataatttacc tctaataattc ttgtaaactt tctatggcaa tttgaggata	13440
tactatatct cagtcaaaat aaacatccag tttcagtga ttttattttg agaaatactc	13500
tttttttctg acatgagcat aattttattt agcctctaca atacattaca atacattatc	13560
ctctctcata atactttttt tttttttttt aagatgtagt ctgctctgt ctcccaggct	13620
tgagtgcagt ggcatgatct aggcttattg caacctctgc ctcccagggt caagcgattc	13680
tcctacctca gcctcccag tagctagcat tacaggtgtg caccaccaca cccagctaata	13740
ttctgtattt ttagtagaga tgggggttca ccatgttggc caggctggtc tcaaatacct	13800
tgacctcagg tgatctgcct gcctcggcct cccaaagtgc tgggattcca ggtatgagcc	13860
actgtgcctg gcctcataat acttcttgat taggaagatg taaaaaaca attttattaa	13920
aaggataatg gaaatgtaag gcaaaataat agaattacaa atgctatgct acagagttga	13980
tttatttatt tttttgagac agagtgtcgc tctgtcacct ggcctggagt gcagtggtgt	14040

gatctcggct cactgcaacc tgtgcctccc aggttcaagc gattcttctc cttcagcctc	14100
ccaagtagct gggattacag gcaccatgcc tggctaattt ttgtattttt agtagagatg	14160
gagtttcacc atattggcca ggctgatccc aaactcctga cctcgtgatc cgcccacctc	14220
ggcctcccaa agtgttggga ttacaggcgt gagccactgc aactggccca gagcttattt	14280
ttgaaggcca aaacagaagc atatttattc cctatcaggt gttaaaatat ctcactggaa	14340
cagtttagca ggcttctagt gagtgggggt gtgcaggagt aaatgacgtg ggaaatacaa	14400
gtgttggagg acgaaataga gcccatthtat ggattttatt cctggaaggg ctgaaaaatg	14460
tattccttcc ttttctgcta gatgaattgc ttgtctgaaa gcatgcctat gtgcattctt	14520
cctttatgta aaaggcacia attctgctgt tgtgtttaat taacatatgt gggttctttc	14580
aatcctgtat tgaaatgtac ttcttagtca actatatgtc acattttttt ttgtttttgt	14640
ttttgtttt taaatgggggt ctcactctgt caccaggt ggagtgcagt ggcacatca	14700
cagctcacta aagccttgac ctcccaggc tcaagtgatc ctcccacctc agcctcctga	14760
gtagcaggga ctacaggcat gtgccaccac acccggttaa ttgttgtttt ttatagcgat	14820
ggggtttcac catgttgccc aggctgggtc tgaactcctg ggctcaagcg atccacctgc	14880
ctcagcctcc caaagtgata agattacagg tgtgagccac tgtgcctggc ctacatgtca	14940
tgtttcaaca tgcatatgac tatgttggtg acaaatcaaa tcataagtat ctggttactg	15000
ttgggagatt tgaaaatcac tcagaagaga cctcttctca aattttgagg tcttgataa	15060
aacagtttaa atttgcctca agcaaaagga aacaaggcag ttctctctag ttccctcatc	15120
cttttctaaa gcaacaatgt gcattctact cttagaatc cattctgaac aaaaagagag	15180
caggcagtca aaatacaacc ctggctccag attcccccat gggcctccta ctcagcaaat	15240
catacacagg catacagaca ttaagaaaag taactcaact tgtaggacaa ctacctatcc	15300
acacctcaga aaaagtatca cccaacatg aaaaaattg gaagtgaatt aagaccagaa	15360
atgagaatca aatagaaggc acataaaagg taataaagga gaagcatatg aggaggaagg	15420
tcggagagga cactctgtgt agcctagaaa caactagaat aattaactgc aaacctcagg	15480
taggtcacia atgcataaat attctgtgaa aagaaagagg actcacggcc tttcctttcc	15540

cccagtcacg ataagttccat ctcgcagggt ggtgtacatg gcaaacacag gcccgttgtg	15600
agctctcgcc acgattctac acaatatgtg atctttccac acacagacat caccactgat	15660
ggtacctgta aacgtcaagt tattctgaaa aggagtgggg gagggggaga caaactcatc	15720
aaaagttcaa atagagttta aatagataat tttctatgta tgtgtaatgc tgtctcacc	15780
ttgatacaaa gagcatgcat cgtgtagtgg cagcagcact gaattcacga gtcaggaaac	15840
ctgaacggga ggcttagctt tgtcaggacc ttttcctttc caagtctgtt gcttattagc	15900
tagaataacc ttagacaatt cttcccttcc aattctaaca tactataatt ctagggttta	15960
ttttttatth ttttgagacg gagtttcgct ctttgttgcc caggctggag tgcaatggtg	16020
cgatctcagc tcaccacaac ctctgcttcc caggttcaag tgattctcct gtctcagcct	16080
cccaagtagc tgggattaca agcgccagcc accacgccg gctaattttt gtatttttag	16140
tagagacaga gtttcacctt gttagccagg ctggtcttga actcctgact tcaggtgatc	16200
ttcccgctt ggctcccta agtgctggga ttataggtgt gagccactgt gcccgctg	16260
agccacggtg cctggcctgg tcttatatta agaataccca aaatgttcaa ctgaaatttg	16320
acatggcaca aacatttcaa tagtcttttt ctcaaaaatg taagtgtact taaatattct	16380
aaaattataa cttttcttat aagtattgca taatcacaaa aacaaaaaat gcacttagtt	16440
tttcgatgca ccaaaggatt tatacagcct agccaatgca ggatattaaa ggaaagagat	16500
gtggattgga agccacaggt ccagatgaga tggaataaag tgagaggaga gcaggtctcc	16560
tgaacaccct tctgtcaggg ccaggaattg tgctatttcc ttctgtctca ctacctctt	16620
cttccctcga agtagagaca ctggcccaga gcacttccag ctgtatgata agcagtgtgt	16680
taaatgataa aaagcaaagg aaatcctaaa ccctagtacc accttaaadc atttgaaaat	16740
catgtttctt gatttacctt tctctctgac aaatttttag gactatgaag aactactagg	16800
aagacagaaa ttttaggata tttagggtga caattagaag attaaggaag gcttttgagt	16860
ataacagtag tccaaggaat caaatgttca tcagaatcct tattatggtg gctcatgcct	16920
gtaaaccag cactttggga ggtcaagatg ggaggatcac atagcttagg agcttgagac	16980
cacctaggca acatagcgaa accctgtctc tactaaaaat gaaagaaaaa ttagcctagc	17040

atggtgggttc ctgccctgta gtcccagcta ctaaggaggc tgaggatcac ttgaacctgg	17100
gagatggagg ctacagttag ctataatcgc accattgcac cccagcccag gcgacagagt	17160
gagatactgt gtcaaaaaaa aaaaaaaatc cttttccccc tctcattaac attcttttca	17220
ctccctaatt tctgaaagaa ctagatTTTT gaaagatgaa atatatgctt gaccagggca	17280
tgtaatgatt agcagatcac agtatcatct caacaacatt catgtggctg atgatctaag	17340
gcaagagaat gtaaagtagt caaagtcaca ctatgtgcat ttttaagagac atactgcacc	17400
aaatgcaata gcgagcatgg tctgcatccg ggcatcttcc agtgtgctca gtagcccttt	17460
tttgctaaga agagctcttc ctgccagggt ccagaacttc acatgtttta ctcccactga	17520
gacaaactgg gtatctgaat ctggctcgga ttctgccaca aaaatacggt gattgtgacc	17580
agctctgctg gcaattttgg cacctgacaa gatacaacaa aattatctag gttattacaa	17640
gaaccaagct aatcaacagc atcaaacaaa tatgtaaaat acatagttca aaaaacaaag	17700
gcttagaaga gaggccaatg gcccctgctc tactacctag caatacatga tttacaatta	17760
tttgtgtatt gagtcttttt cacttatctt cgctccatta acttttcttt atataacgta	17820
aatgttttgt ctaaagtgtg gtaggtaata ttatcctgct gatctgccat tatcattaga	17880
aatatacata attttcataa gaatctcaa aaccaatcaa atcattaata ataaatacat	17940
agtttcttgc tggaagaaaa tagcagtga tcatTTataa tgctaataat ggtttcatta	18000
atttatctgt tttgtgagggt tacagttcca ctgggctttt aaagtgaaat atacctacag	18060
taccactgtg tacagtatat tgcataggcc tccactgaat gattgtttca accaccaact	18120
ttaagacaaa tattaataac agaattccta cta	18153

<210> 77
 <211> 23
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 77
 atgatgcaaa gtgactaaac cag

<210> 78
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 78
tctggtttag tacactttgc atcatat