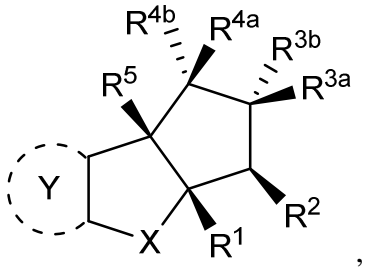
CLAIMS

1. A compound according to Formula (I):



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

X is ~~CR^6R^7,~~ O, S, ~~NH, $N(C_1$-$C_8)$alkyl, C(O), $C{=}CR^6R^7$, $N(CO)R^8$,~~ S(O) or $S(O)_2$;

Y is a 5-membered heteroaryl or a 6-membered aryl or heteroaryl;

R^1 and R^2 ~~independently~~ are aryl~~, heterocyclyl, heteroaryl or cycloalkyl~~;

R^{3a}, R^{3b}, R^{4a} and R^{4b} independently are H, halogen, CN, ~~C_1-C_8(alkyl),~~$(C_1$-$C_8)$alkyl, (C_1-C_8)haloalkyl, ~~C_2-C_8(alkenyl),~~$(C_2$-$C_8)$alkenyl, (C_2-C_8)alkynyl, OR^9, NHR^9, NR^9R^9, [(C_1-C_8)alkylene]OR^9, [(C_1-C_8)alkylene]NHR^9, [(C_1-C_8)alkylene]NR^9R^9, $C(O)R^8$, $C(O)NHR^9$, $C(O)NR^9R^9$, $C(O)[(C_1$-$C_8)$alkylene]NHR^9, $C(O)[(C_1$-$C_8)$alkylene]NR^9R^9, CO_2R^9, $C(S)NHR^9$, $C(S)NR^9R^9$, SR^9, $S(O)R^9$, SO_2R^9, SO_2NHR^9, $SO_2NR^9R^9$, $NH(CO)R^8$, $NR^9(CO)R^8$, $NH(CO)NHR^9$, $NH(CO)NR^9R^9$, $NR^9(CO)NHR^9$, $NR^9(CO)NR^9R^9$, $P(O)(OH)(OR^9)$, $P(O)(OR^9)(OR^9)$, aryl, heteroaryl, cycloalkyl or heterocyclyl; or

R^{3a} and R^{3b}, and R^{4a} and R^{4b} independently combine to form oxo or alkenyl, or a cycloalkyl or heterocyclyl ring; or

R^{3a} and R^{4a}, R^{3b} and R^{4b} or R^{4a} and R^5 together with the carbon atom to which they are attached form a cycloalkyl or heterocyclyl ring; or

R^2 and R^{3a} together with the carbon atom to which they are attached form a bicyclic ring system;

R^5 is H, halogen, OH, CN, N_3, SR^9, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$haloalkyl, $O(C_1\text{-}C_8)$alkyl, $O(C_1\text{-}C_8)$haloalkyl, $(C_2\text{-}C_8)$alkynyl, $NHC(O)(C_1\text{-}C_8)$alkyl or heteroaryl;

~~R^6 and R^7 independently are H, CN, halogen, OR^9, SR^9, $(C_1\text{-}C_8)$alkyl, $NH(R^9)$ or NR^9R^9;~~

R^8 is H, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$haloalkyl, $O(C_1\text{-}C_8)$alkyl, $O(C_1\text{-}C_8)$haloalkyl, cycloalkyl, O(cycloalkyl), heterocyclyl, O(heterocyclyl), aryl, O(aryl), heteroaryl or O(heteroaryl);

R^9 is H, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$haloalkyl, cycloalkyl, heterocyclyl, $[(C_1\text{-}C_8)$alkylene] heterocyclyl, aryl, $[(C_1\text{-}C_8)$alkylene] aryl or heteroaryl;

wherein the two R^9's together with the nitrogen atom to which they are attached of NR^9R^9, $[(C_1\text{-}C_8)$alkylene$]NR^9R^9$, $C(O)NR^9R^9$, $C(O)[(C_1\text{-}C_8)$alkylene$]NR^9R^9$, $C(S)NR^9R^9$, $SO_2NR^9R^9$, $NH(CO)NR^9R^9$ or $NR^9(CO)NR^9R^9$, optionally form a heterocyclyl ring;

wherein any alkyl, alkenyl, cycloalkyl, heterocyclyl, heteroaryl or aryl is optionally substituted with 1, 2, or 3 groups selected from OH, CN, SH , SO_2NH_2, $SO_2(C_1\text{-}C_4)$alkyl, $SO_2NH(C_1\text{-}C_4)$alkyl, halogen, NH_2, $NH(C_1\text{-}C_4)$alkyl, $N[(C_1\text{-}C_4)\text{alkyl}]_2$, $C(O)NH_2$, COOH, COOMe, acetyl, $(C_1\text{-}C_8)$alkyl, $O(C_1\text{-}C_8)$alkyl, $O(C_1\text{-}C_8)$haloalkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, haloalkyl, thioalkyl, cyanomethylene, alkylaminyl, NH_2-C(O)-alkylene , NH(Me)-C(O)-alkylene, CH_2-C(O)-lower alkyl, C(O)-lower alkyl, alkylcarbonylaminyl, CH_2-$[CH(OH)]_m$-$(CH_2)_p$-OH, CH_2-$[CH(OH)]_m$-$(CH_2)_p$-NH_2 or CH_2-aryl-alkoxy;

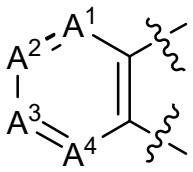
or wherein any alkyl, cycloalkyl or heterocyclyl is optionally substituted with oxo;

"m" and "p" are 1, 2, 3, 4, 5 or 6; and

wherein when Y is a 6-membered aryl then X is not O.

2. The compound according to claim 1 wherein X is O.

3. The compound according to claim 1 wherein the 6-membered aryl or heteroaryl is



wherein

A^1 is N or CR^{10};

A^2 is N or CR^{11};

A^3 is N or CR^{12};

A^4 is N or CR^{13}; and

R^{10}, R^{11}, R^{12} and R^{13} independently are H, halogen, C_1-C_8(alkyl), (C_1-C_8)haloalkyl, C(O)O(C_1-C_8)alkyl, C(O)(C_1-C_8)alkyl, SO_2(C_1-C_8)alkyl, C_1-C_8(alkenyl), (C_1-C_8)alkynyl, OR^9, NHR^9, NR^9R^9, CN, [(C_1-C_8)alkylene]OR^9, [(C_1-C_8)alkylene]NHR^9, [(C_1-C_8)alkylene]NR^9R^9, C(O)R^8, C(O)NHR^9, C(O)NR^9R^9, C(O)[(C_1-C_8)alkylene]NHR^9, C(O)[(C_1-C_8)alkylene]NR^9R^9, CO_2R^9, C(S)NHR^9, C(S)NR^9R^9, SR^9, S(O)R^9, SO_2R^9, $SO_2N(H)(R^9)$, $SO_2NR^9R^9$, NH(CO)R^8, NR^9(CO)R^8, NH(CO)NHR^9, NH(CO)NR^9R^9, NR^9(CO)NHR^9, NR^9(CO)NR^9R^9, P(O)(OH)(OR^9), P(O)(OR^9) (OR^9), aryl, heteroaryl, cycloalkyl, or heterocyclyl.

4. The compound according to claim 3~~1~~ wherein

A^2 and A^4 are N, A^1 is CR^{10} and A^3 is CR^{12}, wherein R^{10} and R^{12} independently are H, CN, halogen or OR^9;

A^2 is N, A^1 is CR^{10}, A^3 is CR^{12} and A^4 is CR^{13}, wherein R^{10}, R^{12} and R^{13} independently are H, CN, halogen or OR^9;

A^3 is N, A^1 is CR^{10}, A^2 is CR^{11} and A^4 is CR^{13}, wherein R^{10}, R^{11} and R^{13} independently are H, CN, halogen or OR^9; or

A^4 is N, A^1 is CR^{10}, A^2 is CR^{11} and A^3 is CR^{12}, wherein R^{10}, R^{11} and R^{12} independently are H, CN, halogen or OR^9.

5.____–The compound according to claim 4 wherein A^2 is N, A^1 is CR^{10}, A^3 is CR^{12} and A^4 is CR^{13}, wherein R^{10}, R^{12} and R^{13} independently are H, CN, halogen or OR^9; or

A^3 is N, A^1 is CR^{10}, A^2 is CR^{11} and A^4 is CR^{13}, wherein R^{10}, R^{11} and R^{13} independently are H, CN, halogen or OR^9.

~~6. The compound according to claim 1 wherein R^1 and R^2 are aryl.~~

6~~7~~. The compound according to claim 1 wherein R^{3a}, R^{3b}, R^{4a} and R^{4b} independently are H, halogen, ~~C_1-C_8(alkyl),~~(C_1-C_8)alkyl, (C_1-C_8)haloalkyl, OH, CN, [(C_1-C_8)alkylene]OR^9, [(C_1-C_8)alkylene]NHR^9, [(C_1-C_8)alkylene]NR^9R^9, C(O)NH_2, C(O)NHR^9, C(O)NR^9R^9, C(O)R^9, CO_2R^9, C(S)NH_2, S(O)R^9, SO_2R^9, SO_2NHR^9, $SO_2NR^9R^9$, heteroaryl or cycloalkyl, wherein R^9 is

a ~~C_1-C_8(alkyl)~~ (C_1-C_8)alkyl or (C_1-C_8)haloalkyl, or wherein the two R^9's together with the nitrogen atom to which they are attached of [(C_1-C_8)alkylene]NR^9R^9, $C(O)NR^9R^9$ or $SO_2NR^9R^9$, optionally form a heterocyclyl ring.

7~~8~~. The compound according to claim 1 wherein R^{3b} is [(C_1-C_8)alkylene]NHR^9 or [(C_1-C_8)alkylene]NR^9R^9, wherein R^9 is ~~C_1-C_8(alkyl)~~ (C_1-C_8)alkyl or (C_1-C_8)haloalkyl, or wherein the two R^9's together with the nitrogen atom to which they are attached of [(C_1-C_8)alkylene]NR^9R^9 optionally form a heterocyclyl ring.

8~~9~~. The compound according to claim 7~~8~~ wherein R^{3b} is [(C_1-C_8)alkylene]NR^9R^9 and R^9 is ~~C_1-C_8(alkyl)~~(C_1-C_8)alkyl.

9~~10~~. The compound according to claim 1 wherein R^{4b} is OH.

10~~11~~. The compound according to claim 1 wherein R^5 is OH.

11~~12~~. The compound according to claim 1 wherein R^6 and R^7 are H or ~~C_1-C_8(alkyl)~~(C_1-C_8)alkyl.

12~~13~~. The compound according to claim 1 wherein R^9 is H or ~~C_1-C_8(alkyl)~~(C_1-C_8)alkyl.

13~~14~~. A~~The~~ compound ~~according to claim 1~~ selected from

(5a*R*,6*S*,7*S*,8*R*,8a*S*)-7-((Dimethylamino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 147F),

4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-Chloro-8,8a-dihydroxy-1-methoxy-7-((4-methylpiperazin-1-yl)methyl)-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridin-5a-yl)benzonitrile (Cpd. No. 198aF),

(5a*R*,6*S*,7*S*,8*R*,8a*S*)-7-(Azetidin-1-ylmethyl)-5a-(4-cyanophenyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 212F),

(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-Chlorophenyl)-7-((dimethylamino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 145F),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-7-((dimethylamino)methyl)-1-methoxy-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-8,8a-diol (Cpd. No. 144F),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-5a-(4-(difluoromethyl)phenyl)-7-((dimethylamino)methyl)-1-methoxy-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-8,8a-diol (Cpd. No. 143F),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-5a-(4-chlorophenyl)-7-((dimethylamino)methyl)-1-methoxy-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-8,8a-diol (Cpd. No. 142F),

Rac-4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-7-(((2,2-difluoroethyl)amino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridin-5a-yl)benzonitrile (Cpd. No. 196F),

(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-Cyanophenyl)-7-((dimethylamino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 139F),

Rac-4-((5aR,6S,7S,8R,8aS)-3-chloro-7-((3,3-difluoroazetidin-1-yl)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]furo[3,2-c]pyridin-5a-yl)benzonitrile (Cpd. No. 207bF),

Rac-4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-1-methoxy-7-(morpholinomethyl)-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridin-5a-yl)benzonitrile (Cpd. No. 152F),

Rac-4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-7-((4,4-difluoropiperidin-1-yl)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridin-5a-yl)benzonitrile (Cpd. No. 157bF),

Rac-4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-1-methoxy-6-phenyl-7-(pyrrolidin-1-ylmethyl)-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridin-5a-yl)benzonitrile (Cpd. No. 158bF),

4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-7-((Dimethylamino)methyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridin-5a-yl)benzonitrile (Cpd. No. 231F),

Rac-4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-7-((diethylamino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridin-5a-yl)benzonitrile (Cpd. No. 159bF),

4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-Chloro-7-((dimethylamino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridin-5a-yl)benzonitrile (Cpd. No. 140F),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-(difluoromethyl)phenyl)-7-((dimethylamino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 146F),

(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-Cyanophenyl)-8,8a-dihydroxy-1-methoxy-7-(morpholinomethyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 151F),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-cyanophenyl)-7-(((2,2-difluoroethyl)amino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 197F),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-cyanophenyl)-7-((3,3-difluoroazetidin-1-yl)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 207aF),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-cyanophenyl)-7-((4,4-difluoropiperidin-1-yl)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 157cF),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-cyanophenyl)-7-((3,3-difluoropyrrolidin-1-yl)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 153F),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-cyanophenyl)-7-((diethylamino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 159cF),

Rac-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-7-(pyrrolidin-1-ylmethyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-3-carbonitrile (Cpd. No. 158cF),

Rac-4-((4b*R*,5*R*,6*R*,7*S*,7a*R*)-4b-hydroxy-6-(hydroxymethyl)-4-methoxy-5-(morpholino-methyl)-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (Cpd. No. 180F),

Rac-4-((4b*R*,5*R*,6*R*,7*S*,7a*R*)-5-((dimethylamino)methyl)-4b-hydroxy-6-(hydroxymethyl)-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (Cpd. No. 206F),

4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((Dimethylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (Cpd. No. 66F),

(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-Chlorophenyl)-6-((dimethylamino)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (Cpd. No. 272F),

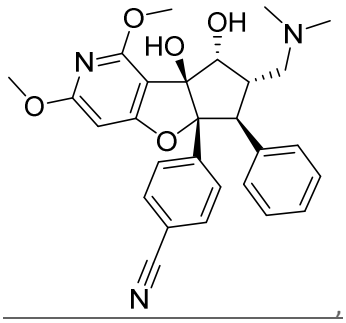
(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-(Difluoromethyl)phenyl)-6-((dimethylamino)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (Cpd. No. 106F), and

(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((Dimethylamino)methyl)-4-methoxy-7-phenyl-7a-(4-(trifluoromethyl)phenyl)-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (Cpd. No. 107F);

or pharmaceutically acceptable salts thereof.

1415. A pharmaceutical composition comprising (i) a therapeutically effective amount of at least one compound according to claim 1 or a stereoisomer, a tautomer or a pharmaceutically acceptable salt thereof; (ii) in combination with a pharmaceutically acceptable carrier, diluent or excipient.

15. A compound having the structure:



or a stereoisomer, a tautomer or a pharmaceutically acceptable salt thereof.

~~16. A method for treating a eIF4A dependent condition in a mammal in need thereof comprising administering to the mammal (i) a therapeutically effective amount of at least one compound according to claim 1 or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, or (ii) a pharmaceutical composition of claim 15.~~

~~17. The method according to claim 16 wherein the eIF4A dependent condition is a disease of uncontrolled cell growth, proliferation and/or survival, or is a disease of inappropriate cellular inflammatory responses.~~

~~18. The method according to claim 17 wherein the eIF4A dependent condition is cancer.~~

~~19. The method of claim 17 wherein the eIF4A dependent condition is a solid tumor, colorectal cancer, bladder cancer, gastric cancer, thyroid cancer, esophageal cancer, head and neck cancer, brain cancer, malignant glioma, fibrotic diseases, glioblastoma, hepatocellular cancers, thyroid cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, melanoma, multiple melanoma, myeloma, pancreatic cancer, pancreatic carcinoma, renal cell carcinoma, renal cancer, cervical cancer, urothelial cancer, prostate cancer, castration-resistant prostate cancer, ovarian cancer, breast cancer, triple-negative breast cancer, leukemia, acute myeloid leukemia, Hodgkins lymphoma, non-Hodgkins lymphoma, B-cell lymphoma, T-cell lymphoma, hairy cell lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma, multiple myeloma, myelodysplastic syndrome, Alzheimer's, Parkinson's, Fragile X Syndrome and autism disorders.~~

~~20. The method of claim 19 wherein the eIF4A dependent condition is diffuse large B-cell lymphoma, hepatocellular cancers, acute myeloid leukemia, breast cancer, colorectal cancer, small cell lung cancer and non-small cell lung cancer.~~