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(54) **Title**: METHODS AND AGENTS FOR MODULATING CELLULAR METABOLISM AND TREATING CANCER

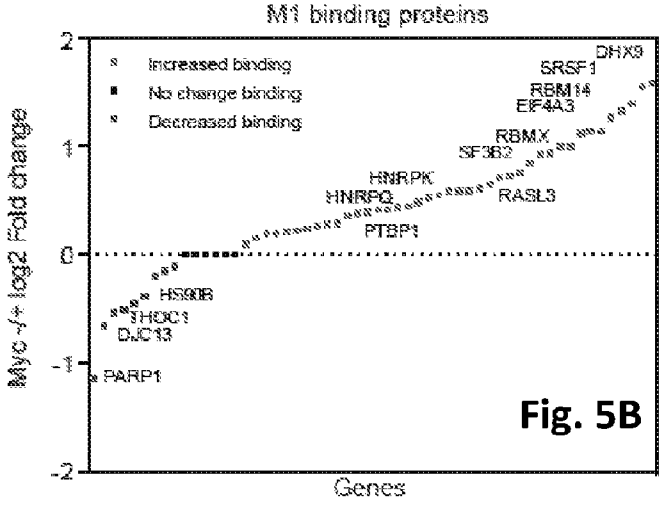

Fig. 5B

(57) **Abstract**: Methods are provided for modulating cellular metabolism by exposing cells to an agent that reduces translation of MYC dependent mRNA transcripts. Such methods and agents are useful for treatment of cancer, and altering cellular metabolism.

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METHODS AND AGENTS FOR MODULATING CELLULAR METABOLISM AND TREATING CANCER

Government Support

[001] This invention was made with government support under National Cancer Institute grant CA142798, and National Institutes of Health Grants GM-067041 and GM-073855. The government has certain rights in the invention.

Background of the Invention

[002] The MYC transcription factor is a key cancer and stem cell gene and accordingly there is much interest in understanding exactly how MYC controls gene expression to affect cell behaviour. MYC has been described as a universal amplifier of gene expression that broadly increases the abundance of any expressed mRNA. MYC has profound effects on cell biology beyond transcription including effects on the control of mRNA translation. For example, MYC increases ribosome biogenesis, the efficiency of mRNA capping, involvement with mTORC1 signaling, and increase the expression of the oncogenic cap binding factor eIF4E. These mechanisms may act to broadly enhance translation capacity and provide proteins to fuel cell growth. MYC has also been implicated in increased translation of mRNAs related to migration and metastasis. However, precise mechanisms that explain how MYC may control specific sets of functionally related transcripts have not been defined.

[003] It is toward a better understanding of the role of MYC responsive translation control element and their contribution to cellular physiology that the present invention is directed.

Brief Summary of the Invention

[004] In one embodiment, methods are provided for modulating cellular metabolism by exposing cells to an agent that modulates translation of MYC dependent mRNA transcripts. In one embodiment, the MYC dependent mRNA encodes a cellular metabolism gene. In one embodiment, modulation of translation is reducing translation. In one embodiment, the cellular metabolism gene encodes an electron transport protein. In one embodiment, the reduced translation of a MYC dependent mRNA is achieved by preventing binding of a MYC dependent mRNA transcription factor to the 5'-UTR of the MYC dependent mRNA. In one embodiment the 5'-UTR of the MYC dependent mRNA comprises a sequence or sequence motif. In one embodiment the sequence is selected from among GCTAAGTCA and TAACGGAAG. In another embodiment, the sequence comprises, at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G. In another embodiment, the sequence comprises, at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G.

[005] In another embodiment, the 5'-UTR of the MYC dependent mRNA comprises a sequence selected from among CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1). Other sequences. In another embodiment, the sequence comprises, at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position, A. In another embodiment, the sequence comprises, at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or

T. In another embodiment, the sequence comprises, at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2). Any combination of the aforementioned selections may comprise the aforementioned sequence.

[006] In one embodiment the sequence motif of the MYC dependent mRNA 5'-UTR is a target for the binding of a MYC-dependent mRNA 5'UTR binding protein. In one embodiment the RNA binding protein is SRSF1 or RBM42/HNRNPK. In other embodiments the RNA binding protein is HNRNPK, EIF4A3, RBM14, RBMX, HNRNPA3 or DHX9. In other embodiments the RNA binding protein is RBM42, LIN28A, RBM5, QKI, SRSF9, HNRNPH2, SRSF1, DAZAP1, LIN28A or PABPN1. In another embodiment the RNA binding protein is prevented from binding the 5'-UTR of the MYC dependent RNA by exposure to an agent. In one embodiment the agent comprises the sequence of the 5'-UTR present in RNA which translation is MYC dependent. In one embodiment the agent binds to the RNA binding protein and reduces binding to the 5'UTR. In one embodiment the agent has the sequence motif selected from among GCTAAGTCA and TAACGGAAG. In another embodiment, the agent has a sequence that comprises, at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G. In another embodiment, the agent has a sequence that comprises, at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G. In another embodiment, the agent has a sequence is selected from among CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1). In

another embodiment, the agent has a sequence that comprises, at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position, A. In another embodiment, the agent has a sequence that comprises, at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T. In another embodiment, the agent has a sequence that comprises, at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2). Any combination of the aforementioned selections may comprise the aforementioned sequence.

[007] The aforementioned agent may be an oligonucleotide, synthetic nucleotide, a peptide, or any agent comprising an aforementioned sequence or having the biological activity of an aforementioned sequence, wherein the agent can target a MYC dependent RNA 5'UTR binding protein, such as but not limited to SRSF1 or RBM42, and reduce 5'UTR binding, mRNA translation, or the resulting levels of the protein encoded by the mRNA. In one embodiment the agent is GCTAAGTCA or TAACGGAAG, or any of the sequence variations mentioned above. In another embodiment, a pharmaceutical composition comprising the agent is provided. The composition may include a carrier, excipient, diluent, or other component to enhance delivery to the desired cell, tumor, tissue or organ.

[008] In one embodiment, a method is provided for preventing or treating cancer comprising exposing tumor cells or cells capable of developing into a tumor with an agent that reduces translation of MYC dependent mRNA. Any of the foregoing agents are useful for this purpose. In

one embodiment, exposure is in vivo. In another embodiment exposure is in vitro. In another embodiment, exposure is ex vivo.

[009] In addition to use in treatment or prevention of cancer, the aforementioned methods and agents are useful for modulating cellular metabolism, which may be useful for increasing or decreasing cellular respiration, for the purpose, for example, or correcting a metabolic or mitochondrial disease, for promoting weight gain or weight loss, among other desirable purposes. The invention is not so limiting as to the uses for modulating the translation, or the transcription, of MYC-dependent genes.

[0010] In another embodiment, a method for preventing or treating cancer is provided comprising exposing tumor cells or cells capable of developing into a tumor to an agent that reduces the translation of a MYC dependent mRNA. The exposing can be in vivo, ex vivo or in vitro.

[0011] In another embodiment, a method is provided for treating or correcting a metabolic or mitochondrial disease, or for promoting weight gain or weight loss by administering to a subject in need thereof an agent that reduces translation of MYC dependent mRNA. In one embodiment, the agent binds to the RNA binding protein and reduces binding to the 5'UTR. In one embodiment of the foregoing methods, the agent is an oligonucleotide, synthetic nucleotide, a peptide, or any agent comprising an aforementioned sequence or having the biological activity of an aforementioned sequence, wherein the agent can target a MYC dependent mRNA 5'UTR binding protein and reduce 5'UTR binding, mRNA translation, or the resulting levels of the protein encoded by the mRNA. Non-limiting examples of such agents include an oligonucleotide selected from among GCTAAGTCA, TAACGGAAG, CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1), or is an oligonucleotide sequence comprising:

(1) at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G; or

(2) at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G; or

(3) at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position; or

(4) at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T; or

(5) at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2).

[0012] In another embodiment, an isolated oligonucleotide is provided selected from among GCTAAGTCA, TAACGGAAG, CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1), or consists of a sequence comprising:

(1) at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G; or

(2) at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G; or

(3) at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position; or

(4) at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T; or

(5) at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2);

or a pharmaceutical composition thereof.

[0013] This application claims priority to U.S. Provisional patent application serial no. 62/307,193, filed March 11, 2016, the contents of which are incorporated herein by reference in their entirety.

Brief Description of the Figures

[0014] Figure 1 A-E shows ribosome footprinting defines effects of Myc on translation;

Figure 2 A-I shows ribosome profiling quality control data and effects on translation;

Figure 3 A-D shows Myc dependent transcripts harbour sequence specific regulatory motifs in the 5'UTR;

Figure 4 A-E shows 5' UTR analysis of transcripts affected by Myc;

Figure 5 A-G shows splicing Factors SRSF1 and RBM42 bind and regulate translation of Myc responsive sequence motifs in the 5'UTR;

Figure 6 A-J shows splicing factors SRSF1 and RMB42 bind and regulate translation of Myc responsive sequence motifs in 5' UTR;

Figure 7 A-J shows Myc dependent translation affects genes involved in cellular metabolism; and

Figure 8 A-G further shows that Myc dependent translation affects genes involved in cellular metabolism.

Detailed Description of the Invention

[0015] MYC is a critical cancer and stem cell gene with broad effects on transcription and cellular physiology. Recently, MYC has been described as a universal amplifier of transcription whose transcriptional output is shaped through interactions with co-factors. As is shown herein,

MYC has selective effects on the translation of a set of mRNAs that are defined by specific 5'UTR sequence motifs. Specifically, using transcriptome-scale ribosome footprinting the transcriptional and translational effects of MYC were separated, and a number of mRNAs were identified whose translation depends on MYC. These MYC dependent transcripts are highly significantly enriched for two 5'-UTR sequence motifs that bind to RNA binding proteins, including but not limited to SRSF1 and RBM42. Three additional 5'-UTR sequence motifs were found that are negatively regulated by MYC. The MYC dependent transcripts encode the majority of protein components of the electron transport chain and contribute to MYC and SRSF1/RBM42/HNRNPK sensitive effects on cellular respiration. Hence, in one embodiment, MYC shapes gene expression and cellular physiology in part by controlling the translation of selective transcripts.

[0016] Thus, a sequence-dependent mechanism is described by which the MYC oncogene controls the translation of a defined set of mRNAs into proteins. These include in particular most components of the electron transport chain and leading to increased cellular respiration. Sequence specificity is achieved through increased binding by MYC induced RNA binding proteins such as SRSF1 and associated factors. Many of these are transcriptional targets of MYC and hence act in a feed forward mechanism on metabolic output.

[0017] Specific MYC responsive translation control sequences, which in other embodiments include the mTORC1 sensitive TOP, TOP-like, PRTE motifs, eIF4A dependent translation of G quadruplexes, and others. Together, these findings indicate that mRNA translation is a highly controlled and selective mechanism, where the production of specific proteins (or groups of proteins) is encoded in regulatory motifs that respond to specific translation co-factors and RNA binding proteins. Targeting these regulatory motifs can therefore be employed to modulate the expression of specific proteins or groups of proteins, and in so doing, can alter cellular

metabolism including cellular survival. In one embodiment, targeting the binding of RNA binding proteins to the 5'-UTR of MYC-dependent transcripts can downregulate or dysregulate electron transport in specific cells, which, for MYC related cancers, can disrupt or destroy such cells. The findings herein have broader implications for taking control of patterns of protein expression for manipulating cellular metabolism, from cellular activation to cellular destruction. Uses such as in cancer, for weight control, for correcting defects in metabolic or mitochondrial disease, are embraced herein. Any such uses of the findings shown herein are fully embraced herein.

[0018] In one embodiment, methods are provided for modulating cellular metabolism by exposing cells to an agent that reduces translation of MYC dependent mRNA transcripts. In other embodiments, the agent can increase translation of MYC dependent mRNA transcripts. In one embodiment, the MYC dependent mRNA encodes a cellular metabolism gene. In one embodiment, the cellular metabolism gene encodes an electron transport protein. In one embodiment, the reduced translation of a MYC dependent mRNA is achieved by preventing binding of a MYC dependent mRNA transcription factor to the 5'-UTR of the MYC dependent mRNA.

[0019] In one embodiment the 5'-UTR of the MYC dependent mRNA comprises a sequence motif. In one embodiment the sequence is selected from among GCTAAGTCA and TAACGGAAG, or comprises the sequence motifs as shown in Figure 3D. Other variations in these sequences are shown in Figure 4E, and these motifs are set forth as follows. In another embodiment, the sequence comprises, at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G. In another embodiment, the

sequence comprises, at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G. In another embodiment, the sequence motif is selected from among CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1) or comprises either the sequence motifs as shown in Figure 4D. In another embodiment, the sequence comprises, at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position, A. In another embodiment, the sequence comprises, at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T. In another embodiment, the sequence comprises, at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2). Any combination of the aforementioned selections may comprise the sequence. Any of the aforementioned sequences or those based upon the sequence motifs as described above are embraced herein.

[0020] In one embodiment the sequence motif of the MYC dependent mRNA 5'-UTR is a target for the binding of a MYC-dependent mRNA 5'UTR binding protein. In one embodiment the RNA binding protein is SRSF1 or RBM42/HNRNPK. In other embodiments, the RNA binding protein is HNRNPK, EIF4A3, RBM14, RBMX, HNRNPA3 or DHX9. In other embodiments the RNA binding protein is RBM42, LIN28A, RBM5, QKI, SRSF9, HNRNPH2, SRSF1, DAZAP1, LIN28A or PABPN1.

[0021] In one embodiment the RNA binding protein is prevented from binding the 5'-UTR of the MYC dependent RNA by exposure to an agent. In one embodiment, the RNA binding protein binding to the MYC dependent RNA is modulated by exposure to an agent. In one embodiment the agent comprises the sequence of the 5'-UTR present in RNA which translation is MYC dependent. In one embodiment the agent binds to the RNA binding protein and modulates binding to the 5'UTR. In one embodiment, modulates is reducing. In one embodiment the agent has the sequence selected from among GCTAAGTCA and TAACGGAAG, or comprises any of the sequences motifs as shown in Figure 3D. In one embodiment, the agent has a sequence that comprises, at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G. In another embodiment, the agent has a sequence that comprises, at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G. In another embodiment, the agent has a sequence is selected from among CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1) or a sequence motif as shown in Figure 4E. Other variations in these sequences are shown in Figure 4E, and are set forth as follows. In another embodiment, the agent has a sequence that comprises, at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position, A. In another embodiment, the agent has a sequence that comprises, at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T. In another embodiment, the agent has a sequence that comprises, at the first position, T or C; at the

second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2). Any combination of the aforementioned selections may comprise the sequence. Any of the above oligonucleotide sequences or those based on the above described motifs are useful for the various purposes described herein.

[0022] The aforementioned agent may be an oligonucleotide, synthetic nucleotide, a peptide, or any agent comprising an aforementioned sequence or having the biological activity of an aforementioned sequence, wherein the agent can target a MYC dependent RNA 5'UTR binding protein, such as but not limited to SRSF1, RBM42, SRSF1, HNRNPK, EIF4A3, RBM14, RBMX, HNRNPA3 or DHX9, LIN28A, RBM5, QKI, SRSF9, HNRNPH2, SRSF1, DAZAP1, LIN28A or PABPN1, and reduce 5'UTR binding, mRNA translation, or the resulting levels of the protein encoded by the mRNA. In one embodiment the agent is GCTAAGTCA, TAACGGAAG, CAGCCTA, GGATCCAGA or TTGCTGTCTG (SEQ ID NO:1) or any of the sequence variations of the motifs mentioned above.

[0023] Any of the above described oligonucleotides or agents with such activity can be provided in a pharmaceutical composition, further comprising a carrier, excipient or diluent. Such pharmaceutical composition may further contain any component to enhance delivery to the desired cells, tumor, tissue, organ, or location in the body where modulation of MYC regulated translation is desired. Such delivery may be facilitated by the use of polymers, nanoparticles such as lipid or polymer based nanoparticles, covalent or non-covalent conjugates with antibodies or polymers, or in plasmids or vectors, by way of non-limiting examples. The pharmaceutical composition may be exposed to the desired cells or other targets in vitro, ex vivo or in vivo. In vivo, the pharmaceutical composition may be delivered parenterally or orally, or by direct

infusion or application to affected cells, tumor, tissue or organ. The dose and frequency of said delivery will be based upon the desired outcome, bioavailability of the agent by the route of administration utilized, and other factors readily determined.

[0024] Moreover, variations on the aforementioned oligonucleotides having the same biological activity are embraced herein. Use of alternate or modified nucleotides or deoxynucleotides, or linkages between them, as well as other means to aid in synthesis, enhance stability, improve delivery or reduce or eliminate degradation are contemplated herein. Such alternate nucleotides and linkages, and other means for optimal synthesis and delivery of oligonucleotides are well known in the art and full embraced herein.

[0025] In one embodiment, a method is provided for preventing or treating cancer comprising exposing tumor cells or cells capable of developing into a tumor with an agent that reduces translation of MYC dependent mRNA. Any of the foregoing agents are useful for this purpose.

[0026] In one embodiment the cancer is a MYC-driven cancer. In other embodiments, the cancer is, by way of non-limiting examples, T-cell acute lymphoblastic leukemia, small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, neuroblastoma and pancreatic cancer. In one embodiment the subject has cancer. In one embodiment, the subject is at risk for developing cancer. In one embodiment, the subject is in remission from cancer. In other embodiments, the cancer is transformed follicular lymphoma, mantel cell lymphoma, breast cancer, ovarian cancer, hepatocellular carcinoma, and non-small cell lung cancer, as well as gastric cancer, Ewing sarcoma and lung adenocarcinoma. These are merely examples of cancers amenable to the methods and uses of the agents herein described.

[0027] In addition to use in treatment or prevention of cancer, the aforementioned methods and agents are useful for modulating cellular metabolism, which may be useful for increasing or

decreasing cellular respiration, for the purpose, for example, or correcting a metabolic disease or mitochondrial disease, for promoting weight gain or weight loss, and other desirable purposes. The invention is not so limiting as to the uses for modulating the translation, or the transcription, of MYC-dependent genes, such as those encoding electron transport proteins, other cellular metabolic genes, and other MYC regulated genes.

[0028] As noted above, interfering with binding of a 5'UTR RNA binding protein to the 5'UTR of a MYC-dependent mRNA is useful for the purposes of the invention. Said interfering may be achieved by any of the aforementioned methods, including by not limited to interfering with the RNA binding protein complex that include proteins such as SRSF1, RBM42/HNRNPK, HNRNPK, EIF4A3, RBM14, RBMX, HNRNPA3 and DHX9, RBM42, LIN28A, RBM5, QKI, SRSF9, HNRNPH2, SRSF1, DAZAP1, LIN28A or PABPN1 or any combination thereof. In one embodiment, the agent activates one of more of RNA binding protein such as but not limited to those mentioned above. In one embodiment said activating is achieved by an agent described herein.

[0029] In another embodiment, an isolated oligonucleotide is described, selected from among GCTAAGTCA, TAACGGAAG, CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1), or consists of sequence comprising:

(1) at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G; or

(2) at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G;

at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G; or

(3) at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position; or

(4) at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T; or

(5) at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2).

[0030] In one embodiment the oligonucleotide is provided in a pharmaceutical composition. In one embodiment the pharmaceutical composition may comprise a carrier, excipient or diluent.

Examples

[0031] **Ribosome footprinting**. KOPT-K1 cells were treated with silvestrol (25 nM) or DMSO for 45 minutes, followed by cycloheximide treatment for 10 minutes. Total RNA and ribosome protected fragments were isolated following published protocol. Deep sequencing libraries were generated from these fragments and sequenced on the HiSeq 2000 platform. Genome annotation was from the GENCODE project (http://www.gencodegenes.org/releases/14.html). Ribosome footprint intensity (reads per million, RPM) and the expression value (reads per kilobase per

million, RPKM) were measured from total mRNA-seq data and translation values were measured from ribosome footprint data. To evaluate the translation efficiency (TE) change between Silvestrol- and vehicle-treated samples, using the calculation TE = $RPKM_{footprint}$ / $RPKM_{mRNA}$. Changes in ribosome footprint profiles were determined using the DEXSeq algorithm.

[0032] **Other Methods**. In order to measure MYC sensitive mRNA translation ribosome footprinting was performed on an established human B-cell lymphoma cell line P493-6 containing conditional tetracycline regulated MYC. Doxycycline addition readily abrogates MYC expression and loss of the MYC protein **(Figure 1A)**. Metabolic labelling of mRNA translation with L-azidohomoalanine (AHA) labelling reveals that loss of MYC expression causes a 20% decrease in global translation within 24 hours ($p < 0.0001$) **(Figure 1B)**. Ribosome footprinting in conjunction with deep RNA sequencing is used to identify ribosome-protected RNA fragments and compare them to total transcript levels to isolate effects on mRNA translation **(Figure 1C)**. Ribosome footprinting was performed on 6 samples including three untreated samples (MYC ON) and three samples that were collected after 24h exposure to doxycycline (MYC OFF). Reads mapping to ribosomal RNAs, non-coding RNAs, library linkers, and incomplete alignments were removed **(Figure 2A)**. The majority of the remaining reads between 25-35 nucleotides in length mapped to protein coding genes **(Figure 2A)**.

[0033] First, the change in transcript levels was related to changes in ribosome protected sequences **(Figure 1D)**. As expected for most transcripts the change in total mRNA abundance (RPKM: reads per kilobase per million reads in presence and absence of doxycycline) correlated well with the number of ribosome protected reads (given as gene specific RF reads per one million total reads; RPM) **(Figure 1D)**. However, for subsets of genes significantly higher and lower ribosome occupancy than expected was observed, based on the change in mRNA level alone **(Figure 1D)**. To define the translational efficiency (TE) for each mRNA by normalizing

the RF frequency to transcript length and total transcript abundance (RPKM: reads per kilobase per million reads). This analysis isolates changes in mRNA translation and identifies mRNAs whose translation is disproportionally affected by the presence or absence of MYC **(Figure 1E)**. Specifically, the DEXSeq algorithm. (Differential Expression-normalized Ribosome-occupancy; based on DEXseq) was used to identify mRNAs that were most strongly affected by MYC. Specifically, a group of 882 mRNA were identified whose translation is the most MYC dependent and decreased upon MYC inactivation (MYC dependent / TE down (left bars; p/FDR. <0.01) On the other hand, the translation of 315 mRNAs is the most MYC independent (MYC independent / TE up; TE p/FDR<0.01). Hence, in addition to a global effect on translation effect that is proportional to the change in mRNA abundance, differential effects on the translation of specific mRNAs were identified.

[0034] Expanded description of Figure 1. **a)** Lysates of P493 cells treated with doxycycline (0.1 ug/ml) for indicated hours and probed as indicated. **b)** Mean fluorescence intensity of incorporated L-azidohomoalanine (AHA) in newly synthesized proteins in P493 cells treated with doxycycline (0.1 ug/ml) for the indicated time period, n = 3 biological replicates. **c)** Schematic of the ribosome footprinting study; **d)** Comparison of total RNA and ribosome footprint counts in untreated (Myc ON) and tetracycline treated (Myc OFF) P493 cells, samples n = 3 biological replicates **e)** Frequency distribution of the ratio of translational efficiency (TE) in untreated (Myc ON) and tetracycline treated (Myc OFF) P493 cells (TE_{Myc-}/ TE_{Myc+}). More or less affected mRNAs identified as TE down (left cluster of bars) and TE up (right cluster of bars); n = 3 replicates.

[0035] Expanded description of Figure 2. **a-f)** Read length frequency histograms and mapping analysis of ribosome footprint data after quality control filtering for indicated samples. **g)** Read count correlation plots of three replicates from untreated and tetracycline treated ribosome

footprinting and total RNA samples. **h**) Frequency distribution of the ratio of total mRNA in untreated (Myc ON) and tetracycline treated (Myc OFF) P493 cells (RNA_{Myc-}/ RNA_{Myc+}). More or less affected mRNAs identified as down (red) and up (blue); n = 3 replicates

[0036] Next, the MYC dependent (TE down) mRNAs were analyzed for features that might account for their differential translation. The MYC dependent TE down group includes 882 mRNAs (865 with annotated 5'UTRs), the MYC independent TE up group include 315 mRNAs (308 with annotated 5'UTRs), and the background list 1537 mRNAs with annotated 5'UTR. There is no significant difference in 5'UTR length or GC content between the three groups **(Figures 4A** and **4B).** We find no predilection for known regulatory elements including the mTORC1 sensitive TOP, TOP-like sequences, pyrimidine rich translational elements (PRTEs), or eIF4A dependent G-quadruplex motifs, or for cap-independent IRES elements **(Figure 3A)**. Next, the DREME algorithm was used to identify any sequence motifs that may be enriched in any of the groups and anywhere across the transcripts. A significant enrichment was found of four 5'UTR sequence motifs in the TE down group (M1-M4; p values 0.0012, 0.000043, 0.00023, 0.0086 respectively), moreover motifs 1 and 4 (M1 and M4) further showed a significant depletion from the TE up group of mRNAs **(Figure 3B).** In the TE up group 3 enriched 5'UTR motifs were found, however none showed depletion in the TE down list and we did not find differentially represented motifs in the coding sequence or 3'UTRs in any group (**Figure 4C** and **4D**).

[0037] Next, the potential translation regulatory function of these sequence motifs was tested using a reporter assay. Briefly, a reporter system was constructed to test how MYC affected the sequence motifs compared to a random sequence of comparable length (NC) and using IRES firefly luciferase as internal control (**Figure 3C, inset**). MYC inactivation by doxycycline treatment reduced the translation of the M1 and M4 constructs and did not affect M2, M3 or the

NC control constructs (**Figure 3C**). Conversely, the TE up motif M1 showed increased translation upon MYC loss (**Fig. 4D** and **4E**). Hence, RNA elements were identified that mark MYC dependent transcripts and control their translation in response to MYC (**Figure 3D**).

[0038] Expanded description of Figure 3. **a**) Prevalence of the indicated 5'UTR motifs among the TE down, TE up and background genes (left to right for each gene; n.s.: not significant $p > 0.05$); **b**) Prevalence of new sequence motifs identified in 5'UTR of TE down transcripts enriched against TE up and background genes (left to right for each gene: TE down, background, TE up). **c**) Reporter system with capped renilla luciferase (red) containing three tandem repeat of indicated TE down motifs and capped firefly luciferase as control (black); (below) ratio of renilla luciferase (red) and firefly (black) luciferase in untreated and tetracycline (0.1 ug/ml; 24 hrs) treated P493 cells, Mean/SD, n = 3 biological replicates; **d**) Sequence of Myc responsive motifs.

[0039] Expanded description of Figure 4. **a and b)** Comparison of 5'UTRs lengths and GC content for TE down or TE up versus background genes. n = 3 biological replicates. **c**) Prevalence of new sequence motifs identified in 5'UTR of TE up transcripts enriched against TE down and background genes (left to right for each gene: TE down, background, TE up). **d**) Reporter system with capped renilla luciferase (red) containing three tandem repeat of indicated TE up motifs and capped firefly luciferase as control (black); (below) ratio of renilla luciferase (red) and firefly (black) luciferase in untreated and tetracycline (0.1 ug/ml; 24 hrs) treated P493 cells, Mean/SD, n = 3 biological replicates; **e**) Sequence of Myc responsive TE up motifs.

[0040] In order to explore the mechanisms underlying MYC dependent translation protein factors were identified that bound to the sequence motifs in a MYC dependent manner. Briefly, proteins bound to RNA oligomers were immune-precipitated and identified as encoding motifs M1 and M4 and a random RNA sequence of similar GC content with total protein lysates from MYC

expressing and MYC deficient cells **(Figure 5A)**. 55 and 51 proteins were identified that showed differential binding to motif M1 and motif M4 in response to MYC, respectively, and that were not bound to a control oligomer **(Figure 5B and 5C).** Among these 29 proteins bound to both motif M1 and M4 and these included MEME predicted binders such as SRFSF1 and known SRSF1 interaction partners such as HNRNPK, EIF4A3, RBM14, RBMX, HNRNPA3 and DHX9 **(Figure 6A-C).** Although RBMX and RBM14 were identified as binding proteins, strong prediction was observed for RBM42 for these motifs. Interestingly RBM42, RBM14 and RBMX show strong evidence of interaction with HNRNPK, they can be present on the similar protein complexes with SRSF1 factor (**Figure 6A-C**). Analysis of gene expression data showed small but significant changes in mRNA levels for some of these factors in MYC expressing cells consistent with transcriptional activation **(Figure 5D)**. Sequence specific binding to motif M1 and M4 was confirmed by biotin pull down combined with western blot detection for SRSF1 and RBM42, whereas the unrelated PCBP2 protein was not detected **(Figure 5)**. Hence, RNA binding proteins including SRSF1 and associated factors show selective binding to motifs that mark MYC transcripts.

[0041] Next, translation reporter assays were used to test the contribution of SRSS1 and RBM42 to MYC dependent translation. First, knockdown of SRSF1 and RBM42 resulted in increased translation of a reporter controlled by motif M1 and motif M4, whereas knockdown of the unrelated PCBP2 protein had no effect and neither factor affected translation from a control UTR **(Figure 5D)**. Next, the contribution of these RNA binding proteins to MYC dependent translation was tested. Inactivation of MYC readily causes loss of translation for both M1 and M4 reporters, and this effect was reversed by knockdown of RBM42 and SRSF1 using two different shRNAs **(Figure 5E and F, Fig. 6H).** Hence, SRSF1 and RBM42 mediate MYC dependent translation in a RNA sequence dependent manner.

[0042] Expanded description of Figure 5. **a**) Schematic showing the identification of RNA binding proteins in Myc On/Off P493 cell lysates using dual Biotin-labelled RNA oligos specific for motifs. **b and c**) Log2 fold change on RNA binding proteins in Myc Off vs On P493 samples that showed differential binding to Motif M1 and M4 compared to random RNA sequence as detected by Biotin-pull down and Mass spectrometry analysis (more than 5 peptides detected at FDR of 0.1%). **d**) Biotin- pull down followed by western blot detection for RBM42 and SRSF1 binding to M1, M4 and NC in untreated and tetracycline treated P493 cells. **e**) Reporter system with capped renilla luciferase (red) containing three tandem repeat of indicated motifs and capped firefly luciferase as control (black); (below) ratio of renilla luciferase (red) and firefly (black) luciferase in control, shSRSF1, shRBM42 and shPCBP2 P493 cells, Mean/SD, n > 3 biological replicates; **f and g**) Reporter system with capped renilla luciferase (red) containing three tandem repeat of indicated TE down motifs and capped firefly luciferase as control (black); (below) ratio of renilla luciferase (red) and firefly (black) luciferase in control, shSRSF1, shRBM42 and shPCBP2 P493 cells treated with tetracycline (0.1 ug/ml; 24 hrs) Mean/SD, n > 3 biological replicates.

[0043] Expanded description of Figure 6. **a)** MEME/TOMTOM results for RNA binding proteins significantly predicted to bind TE down motifs M1 and M6 to full sequence or partial region of the motif. **b**) STRING analysis of interaction network among the RNA binding protein that binds to both M1 and M4 obtained from biotin-pull down/MS analysis. **c**) Comparison of RNA binding proteins in Myc Off vs On P493 samples that showed differential binding to Motif M1 and M4 compared to random RNA sequence as detected by Biotin-pull down and Mass spectrometry analysis (more than 5 peptides detected at FDR of 0.1%). **d**) RNA fold change of M1 and M4, RNA binding proteins in Myc Off vs On P493 samples. **e-g**) qRT-PCR showing knockdown of SRSF1, RBM42 and PCBP2 in stable shRNA P493 cells in untreated and tetracycline treated

(0.01 ug/ml; 24 hrs) for indicated hairpins respectively. **h**) Western blot analysis of SRSF1, RBM42 and PCBP2 in stable shRNA P493 cells for indicated hairpins respectively. **i-k**) Reporter system with capped renilla luciferase (red) containing three tandem repeat of indicated TE down motifs or random sequence and capped firefly luciferase as control (black); (below) ratio of renilla luciferase (red) and firefly (black) luciferase in control, shSRSF1, shRBM42 and shPCBP2 with indicated hairpins in P493 cells treated with tetracycline (0.1 ug/ml; 24 hrs) Mean/SD, n > 3 biological replicates.

[0044] Further, the biological consequences of MYC dependent mRNAs were examined. 882 mRNAs were identified that depend on MYC for translation (TE down, $q<0.01$) and 315 mRNA that do not depend on MYC for translation (TE up, $q<0.01$). Among these TE affected mRNA, those mRNAs that also show significant changes in transcript levels suggest that MYC regulate gene expression of these at both the transcriptional and translational level.

[0045] Gene ontology analysis reveals an enrichment of genes related to oxidative phosphorylation, ErbB signalling, ribosome and insulin signalling in TE down genes **(Figure 7A).** Strikingly, 42 of 810 MYC dependent transcripts encode proteins related to the electron transport chain. For example, protein subunits of complex 1 and multiple members of complexes 3, 4, 5 are among the TE down genes of most MYC dependent transcripts **(Figure 7B).** The ribosome footprinting methodology provides positional and quantitative information about RF distribution. Individual RF tracks readily confirm loss of ribosome occupancy across the 5'UTR and coding sequences for protein components of the electron transport chain (examples shown in **Figure 7C-F**). Immunoblots for three candidates readily show loss of protein expression in the absence of significant mRNA changes **(Figure 7D and 4E).**

[0046] Next, the effect of MYC dependent translation was examined on cellular respiration. First, MYC inactivation was found to lead to significant reduction in oxygen consumption rate as determined by mitochondria stress assay (**Figure 7G**). Reporter assays have shown that MYC dependent translation depends, at least in part, on the RNA binding proteins SRSF1 and RBM42. Therefore, knockdown of these factors was explored as they might be able to reverse the metabolic effects. Indeed, knockdown of SRSF1 and RBM42 each produced the opposite effect on respiration in the presence of MYC. Moreover, in the absence of MYC knockdown of SRSF1, and less so RBM42, was able to rescue the decrease in oxygen consumption rate upon MYC inactivation suggesting that oxidative phosphorylation is indeed affected by Myc via translational regulation.

[0047] Expanded description of Figure 7. **a**) Comparison of mRNA and TE changes for TE down and TE up genes. Genes affected significantly only on TE (shown in green) and genes affected on both mRNA and TE (shown in red) at FDR <0.01. Summary of GSEA KEGG pathway analysis is indicated for TE down and TE up genes. **b**) TE down genes ranked by q value (FDR>0.05) showing genes involved in mitochondrial respiration, complex I (green), complex III (red), complex IV (blue), complex V (purple) and lysosomal ATPase (pink). **c-f**) Ribosome profile on individual transcript of indicated genes down regulated upon Myc depletion. **g and h**) Mitochondrial stress assay to measure oxygen consumption rate (OCR) in P493 cells with indicated treatment or indicated shRNA stable cells. **i and j**) Basal OCR in P493 control and shSRSF1 or shRBM42 stable cells treated with tetracycline (0.1 ug/ml; 24 hr).

[0048] Expanded description of Figure 8. **a-b)** GSEA KEGG pathway analysis for TE down and TE up genes (FDR<0.05). **c**) Schematic showing identification of different groups of genes affected by Myc on transcriptional and translational levels. **d**) Log2 Fold change comparison of genes significantly affected by Myc at mRNA and TE (FDR<0.01). Top most significant

pathways obtained from GSEA KEGG pathway analysis of genes represented in four quadrants are indicated in color-coded text. **e**) Comparison of mRNA and TE changes for significantly affected genes on only total RNA and not on TE (FDR <0.01). Summary of GSEA KEGG pathway analysis is indicated for RNA down and RNA up genes. **f**) Western blot analysis of indicated proteins identified as TE down **g**) Log2 fold change in mRNA and TE of the indicated genes in tetracycline treated (0.01 ug/ml; 24 hrs) P493 cells. For each protein: left bar, mRNA; right, TE.

[0049] Sequence listing. SEQ ID NO:1 is ttgctgtctg. SEQ ID NO:2 is N1tN3N4tN6N7N8N9g, where N1 is t or c; N3 is g or c; N4 is c, an or g; N6 is g or t; N7 is t, g or a; N8 is c, g or t; and N9 is t, g or a.

What is claimed is:

1. A method for preventing, treating or intervening in the recurrence of a cancer in a subject comprising administering to the subject an agent that interferes with binding of a 5'UTR RNA binding protein to the 5'UTR of a MYC-dependent mRNA, thereby preventing, treating or intervening in the recurrence of the cancer.

2. The method of claim 1 wherein the cancer is T-cell acute lymphoblastic leukemia, small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, neuroblastoma, pancreatic cancer, transformed follicular lymphoma, mantel cell lymphoma, breast cancer, ovarian cancer, hepatocellular carcinoma, non-small cell lung cancer, gastric cancer, Ewing sarcoma or lung adenocarcinoma.

3. A method for modulating cellular metabolism by exposing cells to an agent that reduces translation of MYC dependent mRNA.

4. The method of claim 3 wherein the MYC dependent mRNA encodes a cellular metabolism gene.

5. The method of claim 4 wherein the cellular metabolism gene encodes an electron transport protein.

6. The method of claim 3 wherein the reduced translation of a MYC dependent mRNA is achieved by preventing binding of a MYC dependent mRNA transcription factor to the 5'-UTR of the MYC dependent mRNA.

7. The method of claim 1 or 6 wherein the 5'-UTR of the MYC dependent mRNA comprises a sequence or a sequence motif.

8. The method of claim 7 wherein the sequence is selected from among GCTAAGTCA, TAACGGAAG, CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1), or the sequence comprises:

(1) at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G; or

(2) at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G; or

(3) at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position; or

(4) at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T; or

(5) at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2).

9. The method of claim 7 wherein the sequence motif of the MYC dependent mRNA 5'-UTR is a target for the binding of a MYC-dependent mRNA 5'UTR binding protein.

10. The method of claim 1 or 9 wherein the RNA binding protein is SRSF1, RBM42/HNRNPK, HNRNPK, EIF4A3, RBM14, RBMX, HNRNPA3 and DHX9, RBM42, LIN28A, RBM5, QKI, SRSF9, HNRNPH2, SRSF1, DAZAP1, LIN28A or PABPN1.

11. The method of claim 1 or 6 wherein RNA binding protein is prevented from binding the 5'-UTR of the MYC dependent mRNA by exposure to an agent.

12. The method of claim 11 wherein the agent comprises the sequence of the 5'-UTR present in mRNA which translation is MYC dependent.

13. The method of claim 11 wherein the agent binds to the RNA binding protein and reduces binding to the 5'UTR.

14. The method of any one of claims 1 or 11-13 wherein the agent has the sequence selected from among GCTAAGTCA, TAACGGAAG, CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1); or the agent has a sequence that comprises,

(1) at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G; or

(2) at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G; or

(3) at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position; or

(4) at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T; or

(5) at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2).

15. The method of any one of claims 1 or 11-14 wherein the agent is an oligonucleotide, synthetic nucleotide, a peptide, or any agent comprising an aforementioned sequence or having the biological activity of an aforementioned sequence, wherein the agent can target a MYC dependent mRNA 5'UTR binding protein and reduce 5'UTR binding, mRNA translation, or the resulting levels of the protein encoded by the mRNA.

16. The method of claim 15 wherein the MYC dependent mRNA 5'UTR binding protein or associated factor is SRSF1, RBM42/HNRNPK, HNRNPK, EIF4A3, RBM14, RBMX, HNRNPA3 and DHX9, RBM42, LIN28A, RBM5, QKI, SRSF9, HNRNPH2, SRSF1, DAZAP1, LIN28A or PABPN1

17. A method for preventing or treating cancer comprising exposing tumor cells or cells capable of developing into a tumor to an agent that reduces the translation of a MYC dependent mRNA.

18. The method of claim 17 wherein the exposing is in vivo, ex vivo or in vitro.

19. A method for treating or correcting a metabolic or mitochondrial disease, or for promoting weight gain or weight loss comprising administering to a subject in need thereof an agent that reduces translation of MYC dependent mRNA.

20. The method of claim 19 wherein the agent binds to the RNA binding protein and reduces binding to the 5'UTR.

21. The method of claim 17 or 19 wherein the agent is an oligonucleotide, synthetic nucleotide, a peptide, or any agent comprising an aforementioned sequence or having the biological activity of an aforementioned sequence, wherein the agent can target a MYC dependent mRNA 5'UTR binding protein and reduce 5'UTR binding, mRNA translation, or the resulting levels of the protein encoded by the mRNA.

22. The method of claim 21 wherein the agent is an oligonucleotide selected from among GCTAAGTCA, TAACGGAAG, CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1), or is an oligonucleotide sequence comprising:

(1) at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G; or

(2) at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G; or

(3) at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position; or

(4) at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T; or

(5) at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2).

23. An isolated oligonucleotide selected from among GCTAAGTCA, TAACGGAAG, CAGCCTA, GGATCCAGA and TTGCTGTCTG (SEQ ID NO:1), or consists of sequence comprising:

(1) at the first position, G, C or T; at the second position, C, T, A or G; at the third position, T, C, G or A; at the fourth position, A, C, G or T; at the fifth position, A, C or G; at the sixth position, G; at the seventh position, T, A, G or C; at the eighth position, C, G, A or T; and at the ninth position, A, C, T or G; or

(2) at the first position, T, G, C or A; at the second position, A, G or T; at the third position, A; at the fourth position, C; at the fifth position, G or T; at the sixth position, G; at the seventh position, A, G or C; at the eighth position, A; and at the ninth position, G; or

(3) at the first position, C or A; at the second position, A; at the third position, G; at the fourth position, C or A; at the fifth position, C or G; at the sixth position, T or A; and at the seventh position; or

(4) at the first position, G or A; at the second position, C, G or T; at the third position, A or G; at the fourth position, T or A; at the fifth position, C or T; at the sixth position, C; at the seventh position, A, T or G; at the eighth position, G; and at the ninth position, A, G or T; or

(5) at the first position, T or C; at the second position, T; at the third position, G or C; at the fourth position, C, A or G; at the fifth position, T; at the sixth position, G or T; at the seventh position, T, G or A; at the eighth position, C, G or T; at the ninth position, T, G or A; and at the tenth position, G (SEQ ID NO:2).

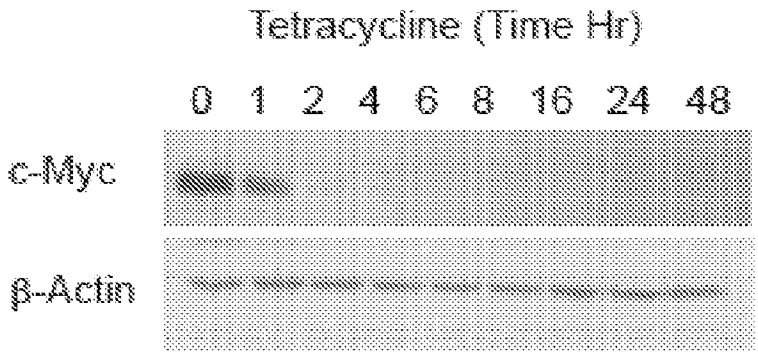


Fig. 1A

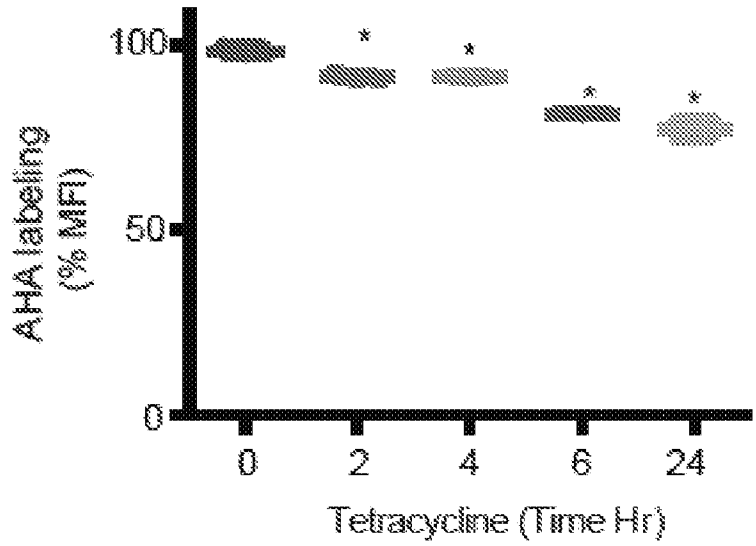


Fig. 1B

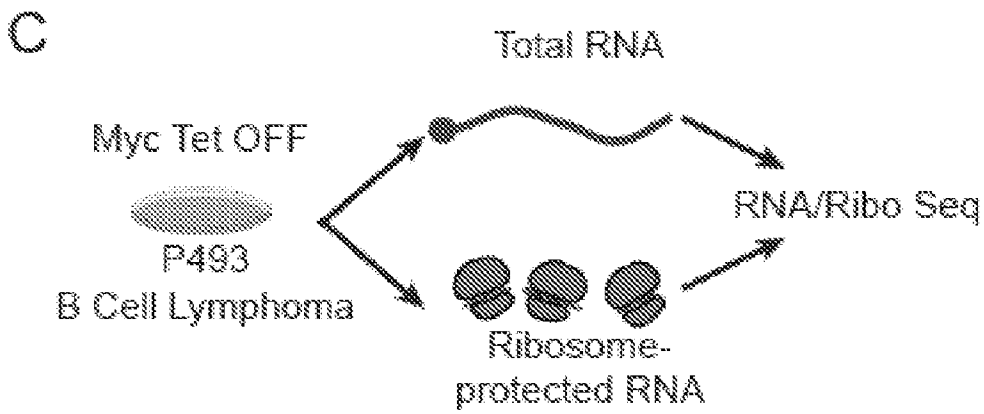


Fig. 1C

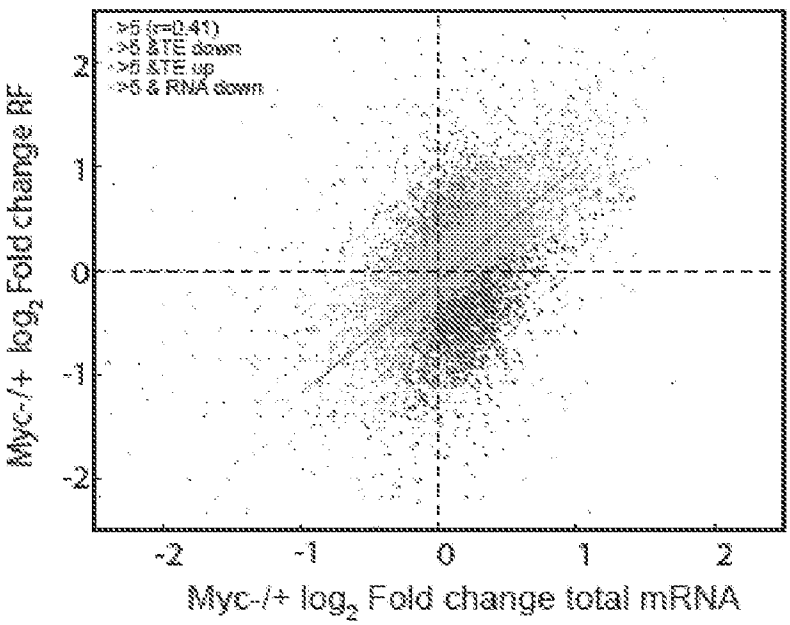

>5 (n=0.41)
>5 &TE down
>5 &TE up
>5 & RNA down
Myc-/+ log2 Fold change RE
Myc-/+ log2 Fold change total mRNA

Fig. 1D

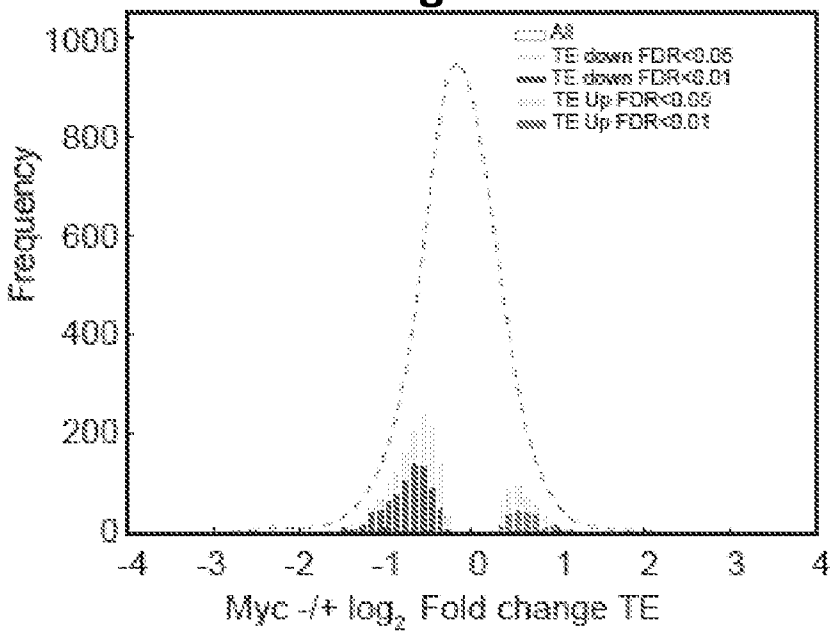

All
TE down FDR<0.05
TE down FDR<0.01
TE Up FDR<0.05
TE Up FDR<0.01
Frequency
Myc -/+ log2 Fold change TE

Fig. 1E

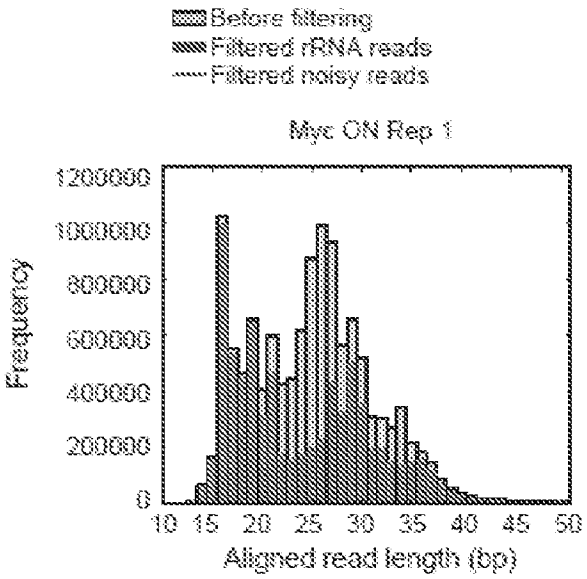


Fig. 2A

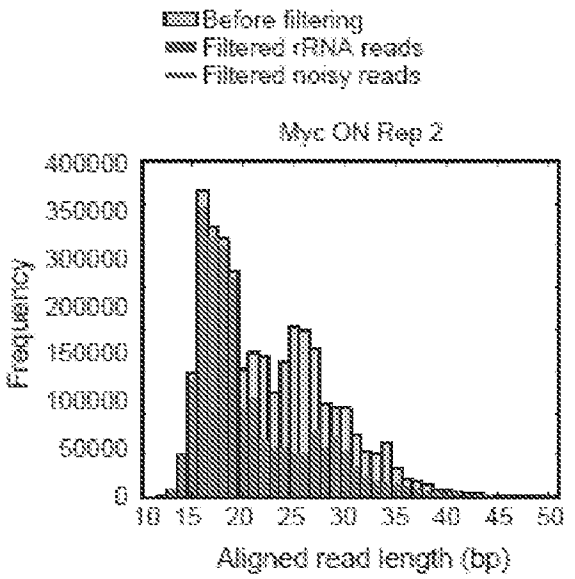


Fig. 2B

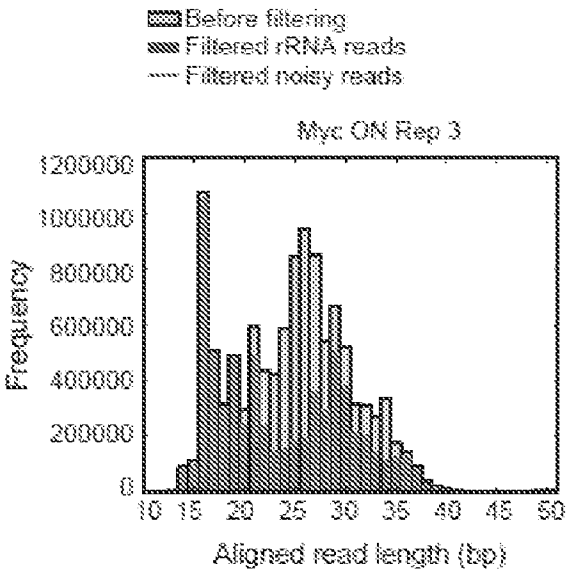


Fig. 2C

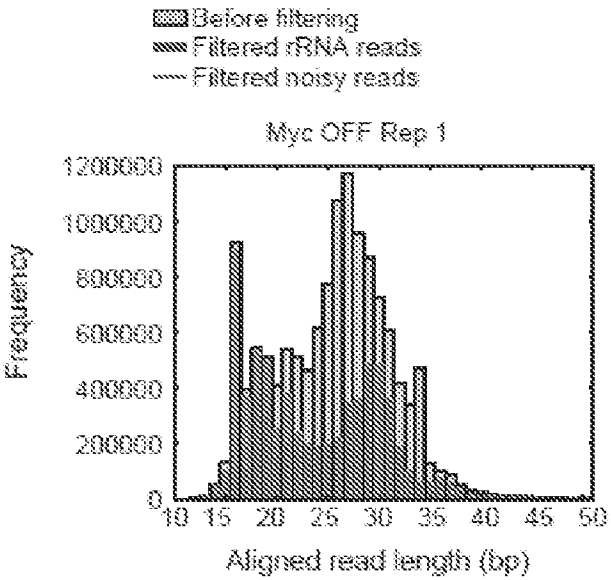


Fig. 2D

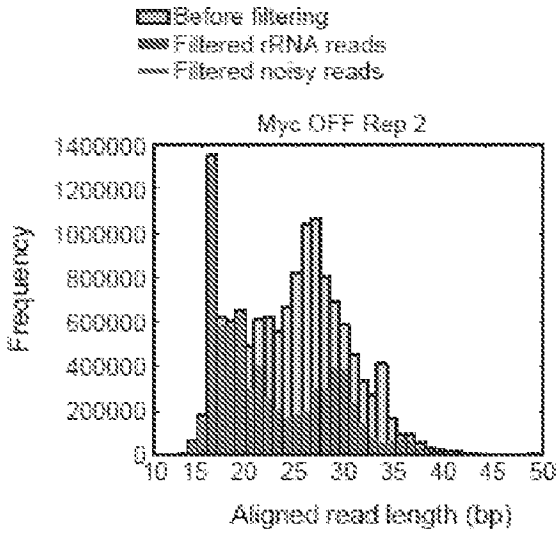


Fig. 2E

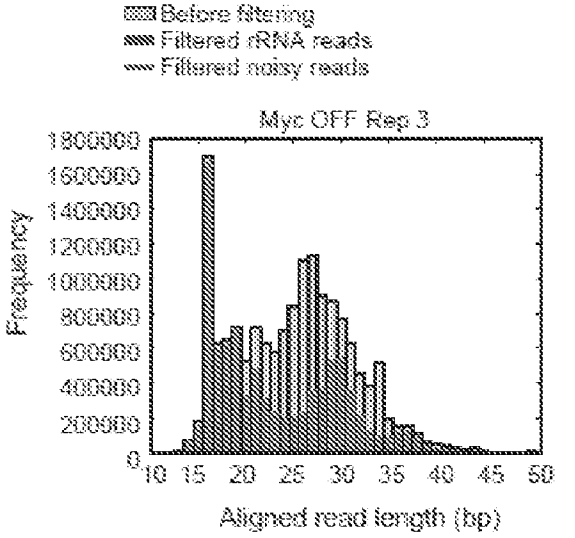


Fig. 2F

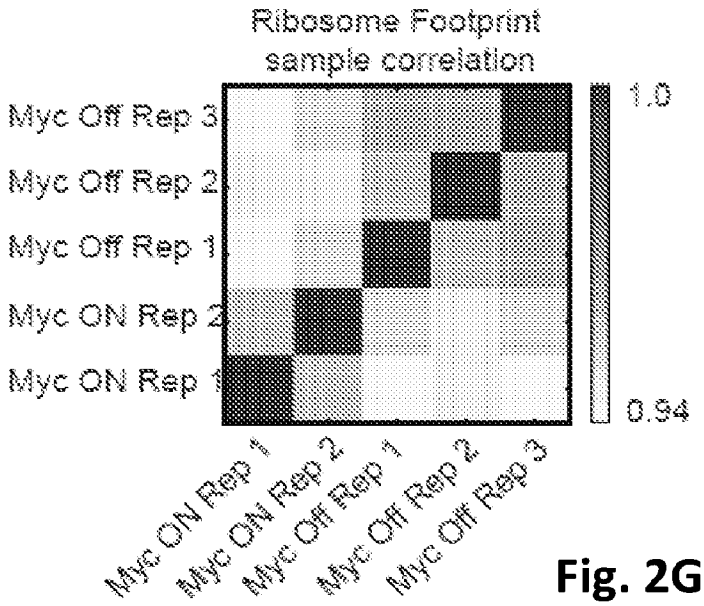


Fig. 2G

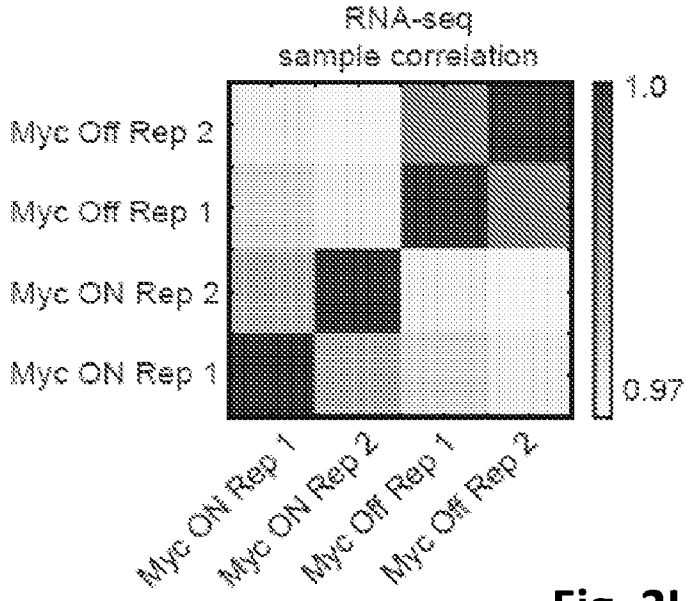


Fig. 2H

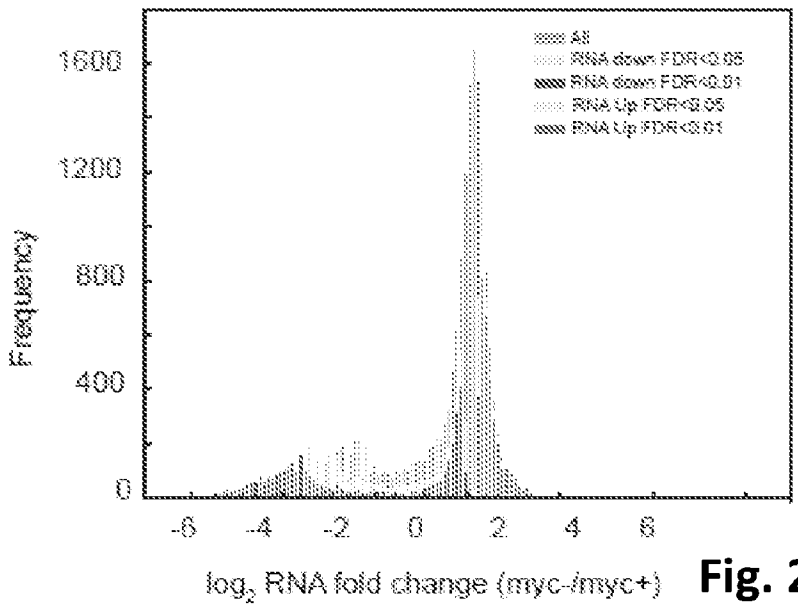


Fig. 2I

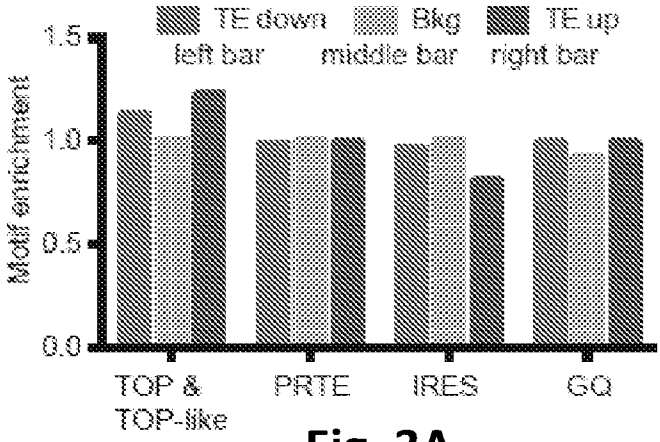


Fig. 3A

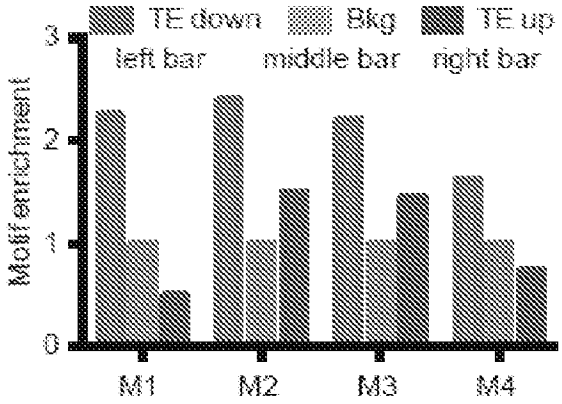


Fig. 3B

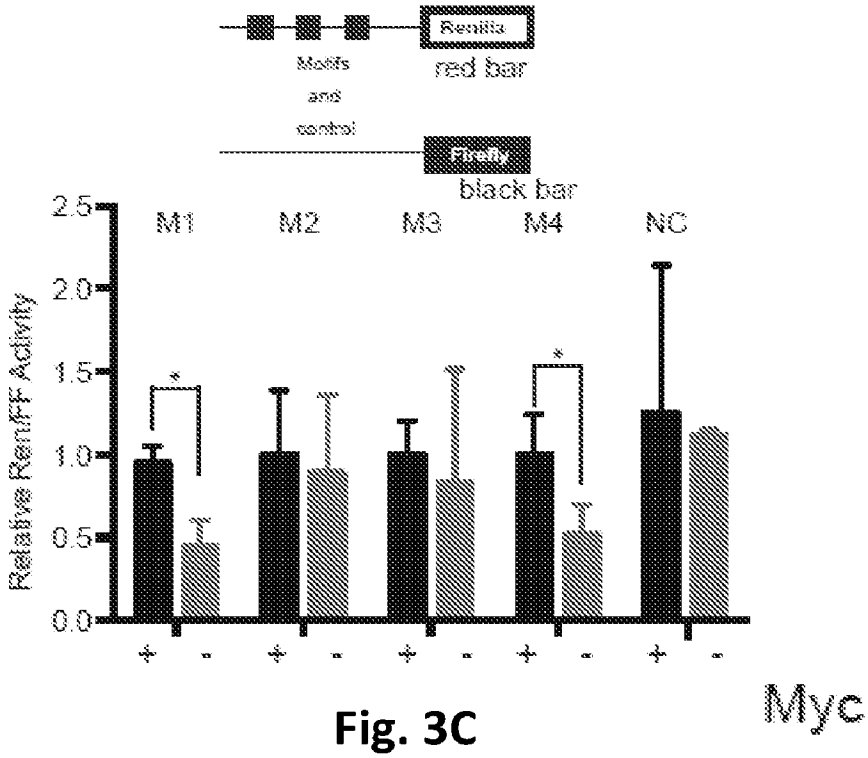


Fig. 3C

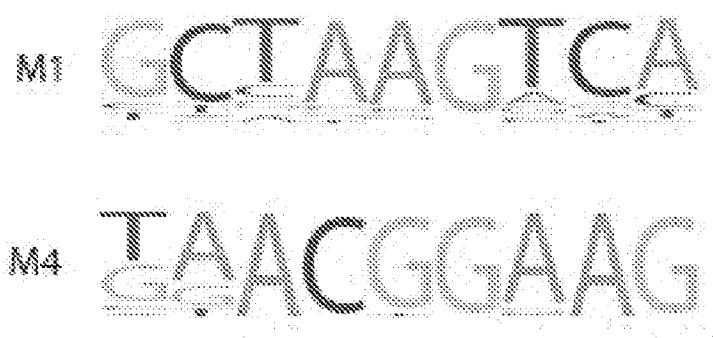


Fig. 3D

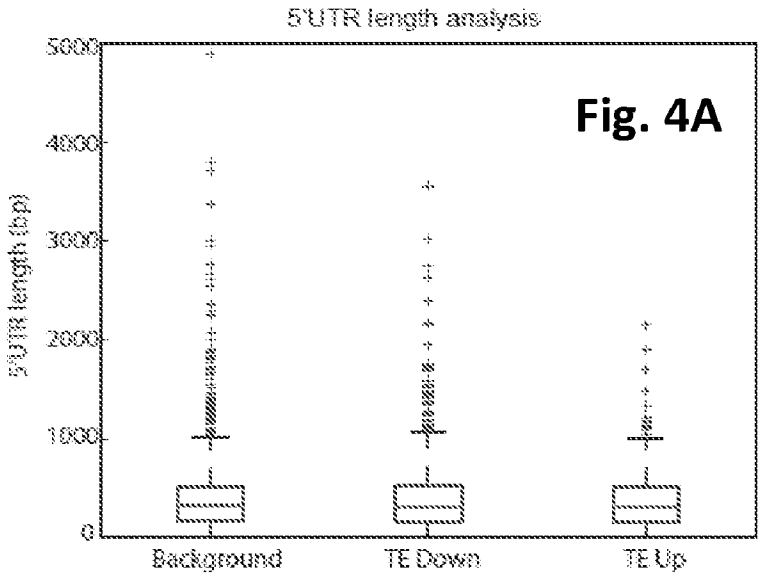


Fig. 4A

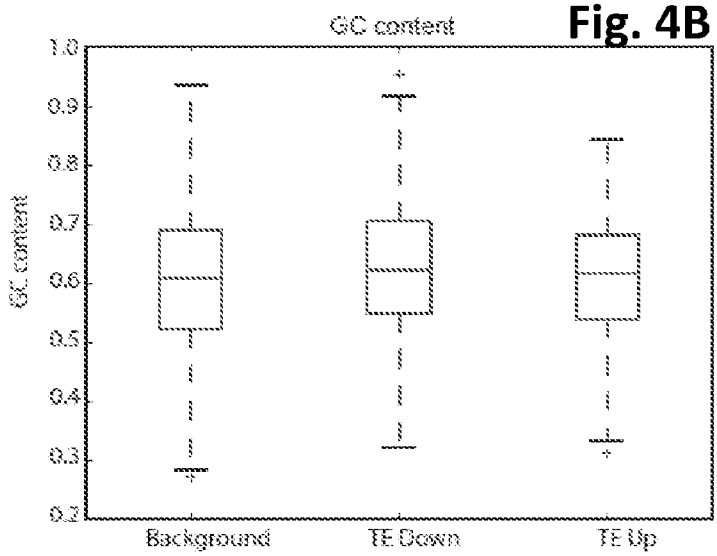


Fig. 4B

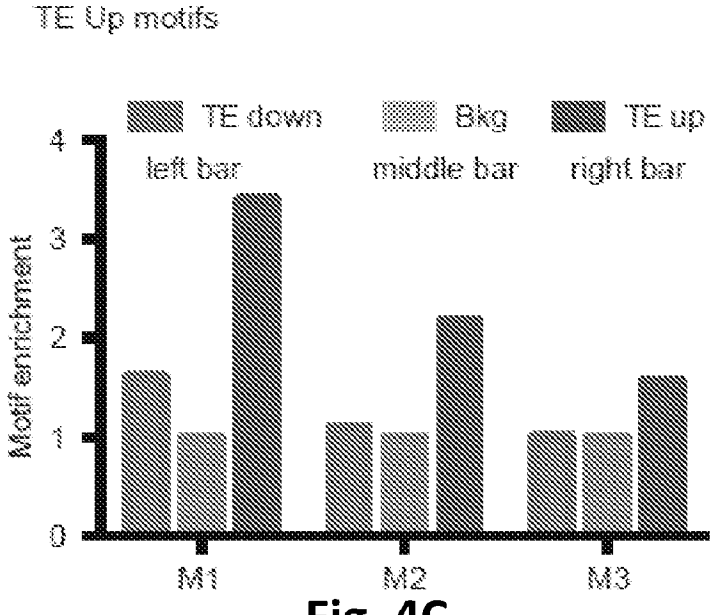


Fig. 4C

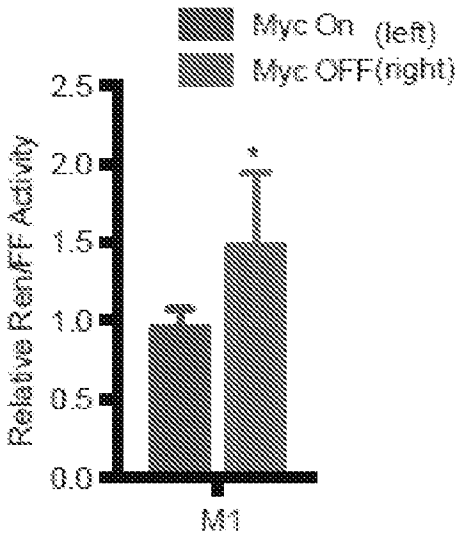


Fig. 4D

Fig. 4E

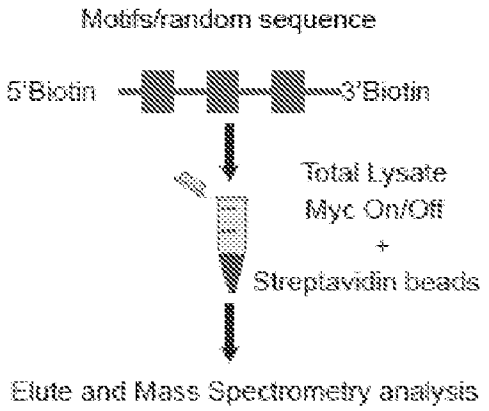


Fig. 5A

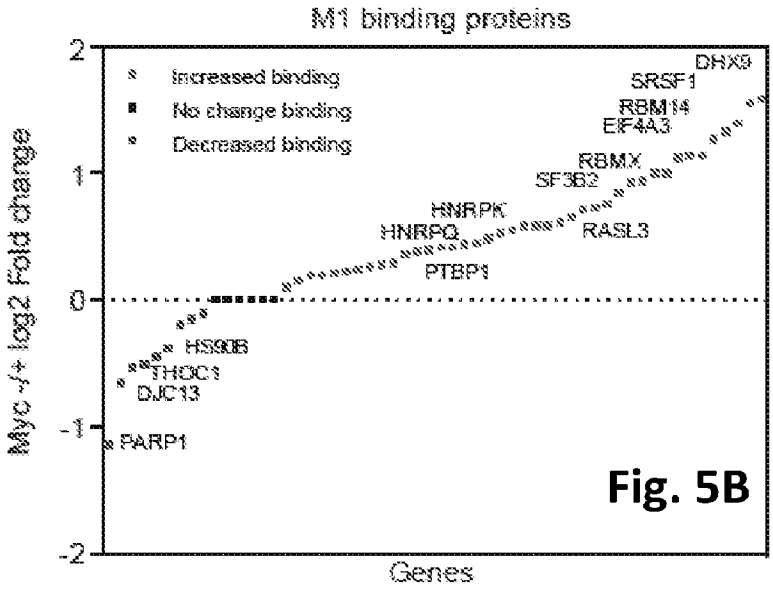


Fig. 5B

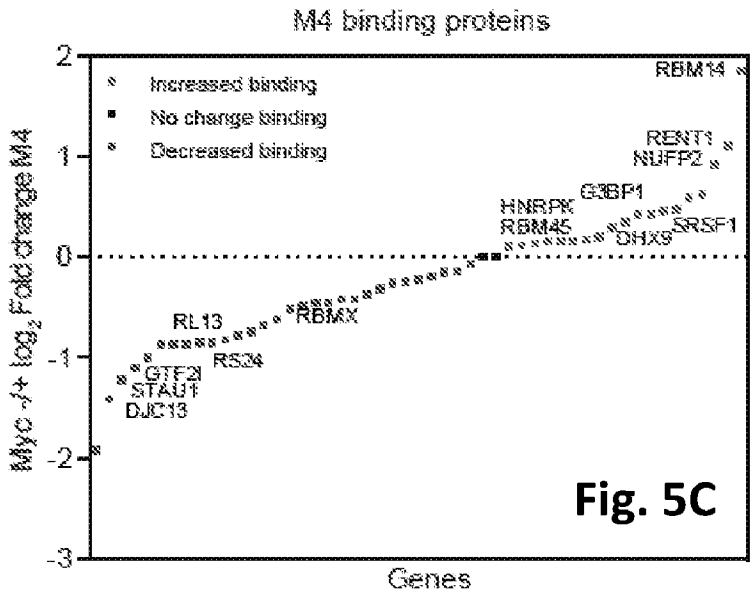


Fig. 5C

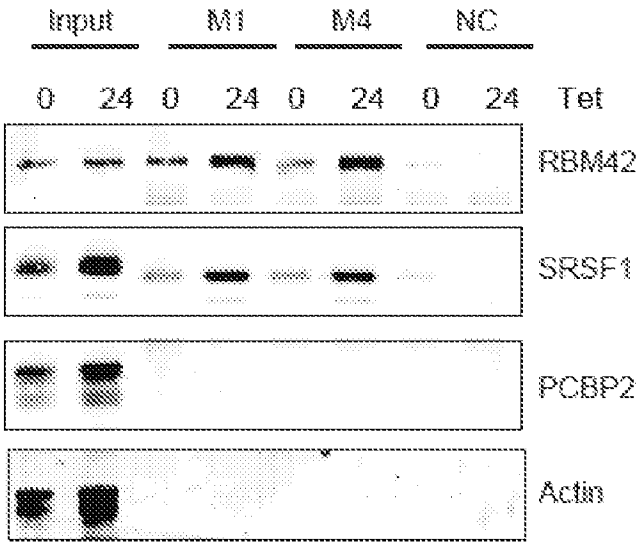


Fig. 5D

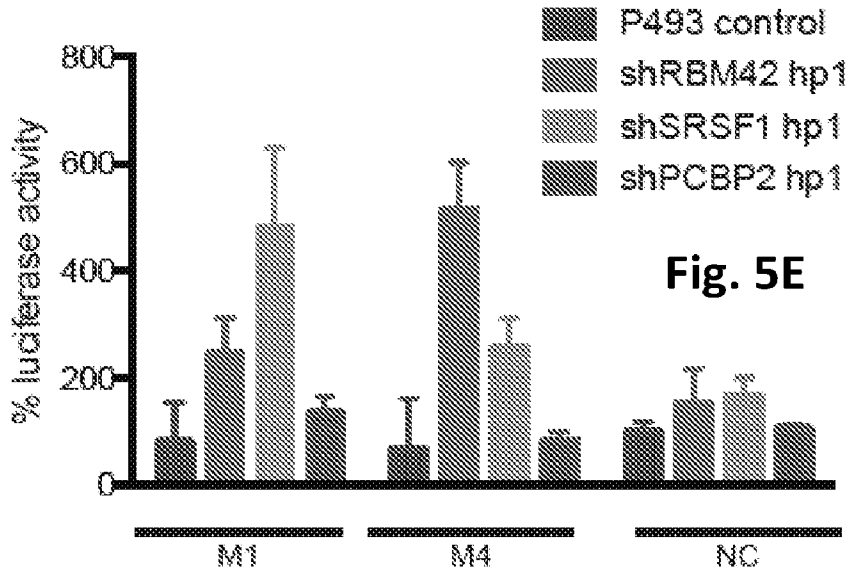


Fig. 5E

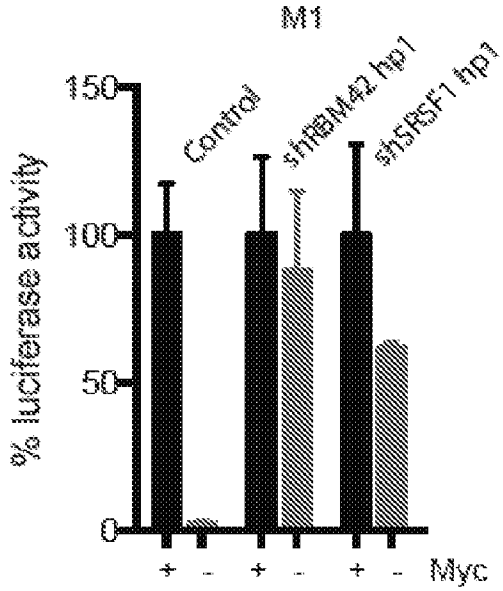


Fig. 5F

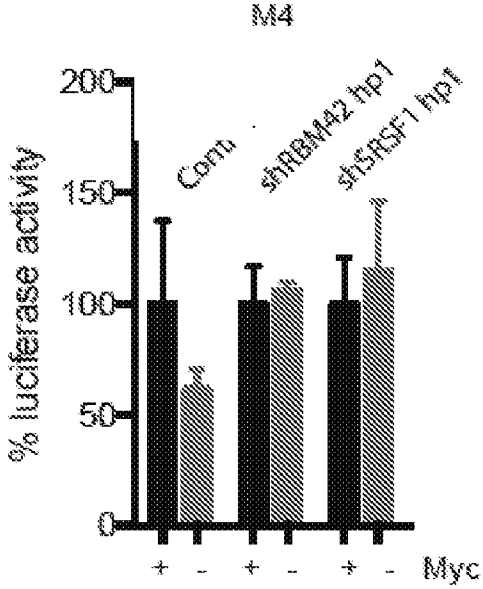


Fig. 5G

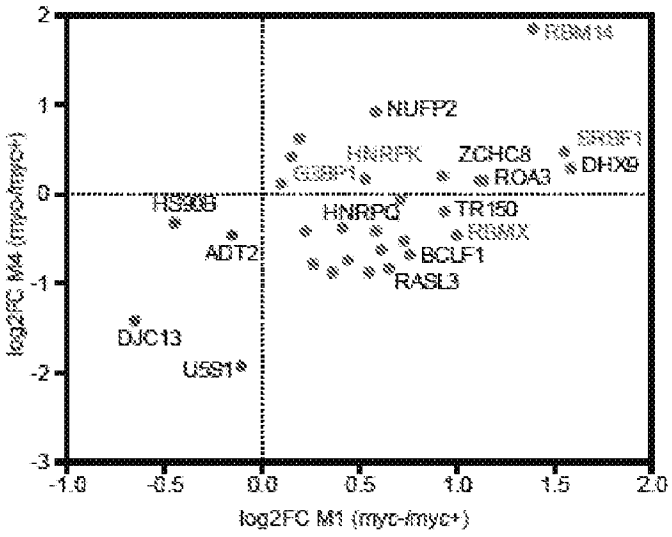


Fig. 6A

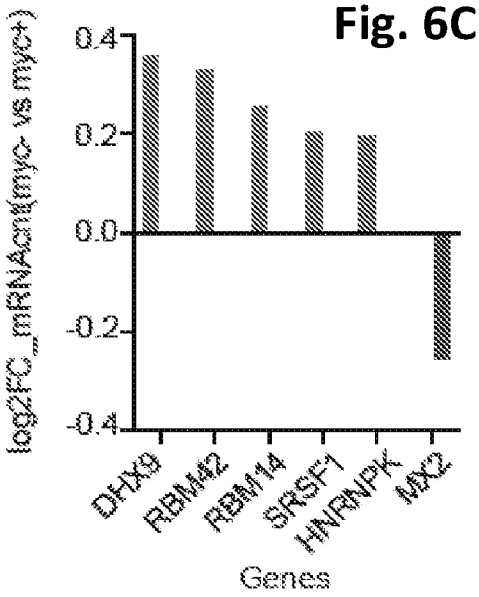


Fig. 6C

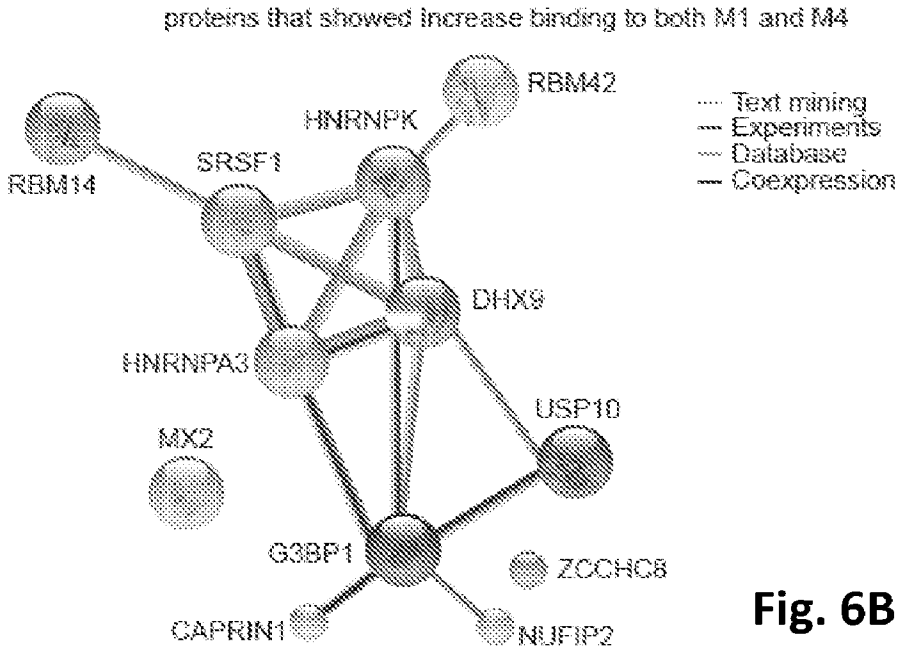


Fig. 6B

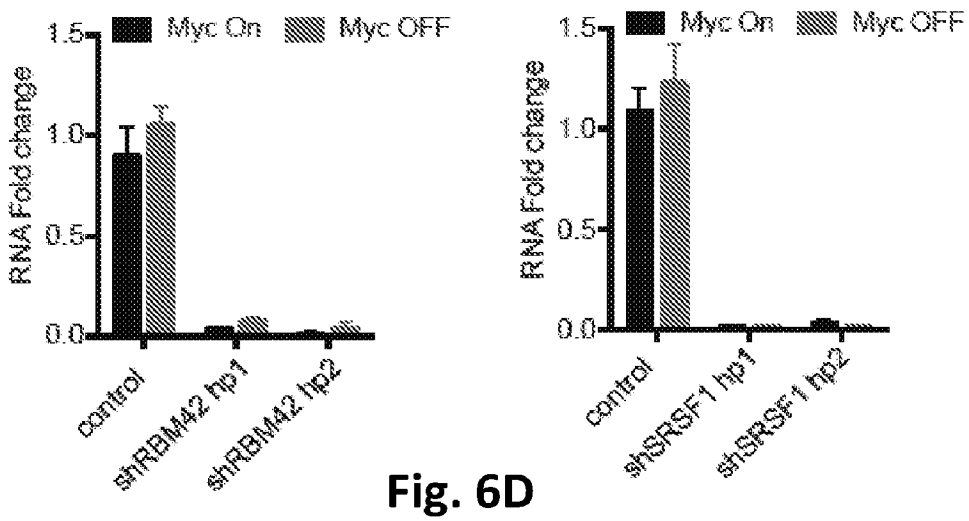


Fig. 6D

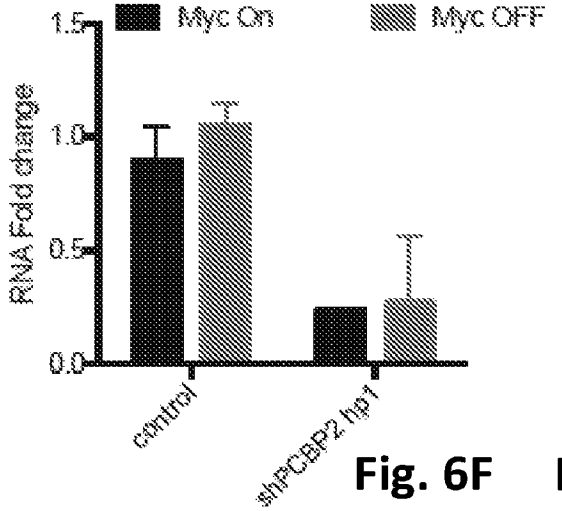


Fig. 6F

Fig. 6G

Fig. 6I

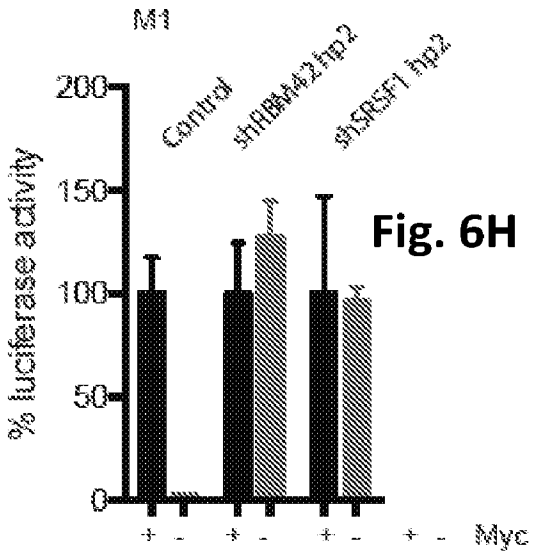
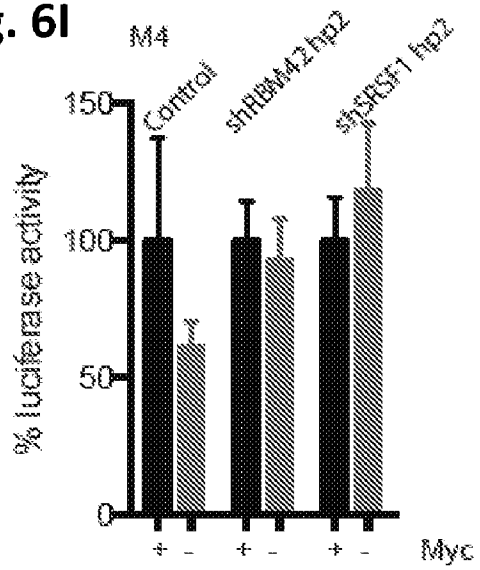


Fig. 6H



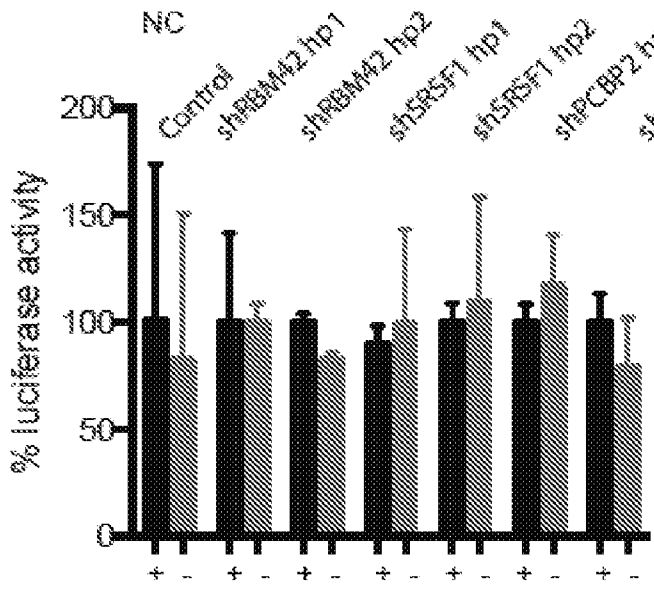


Fig. 6J

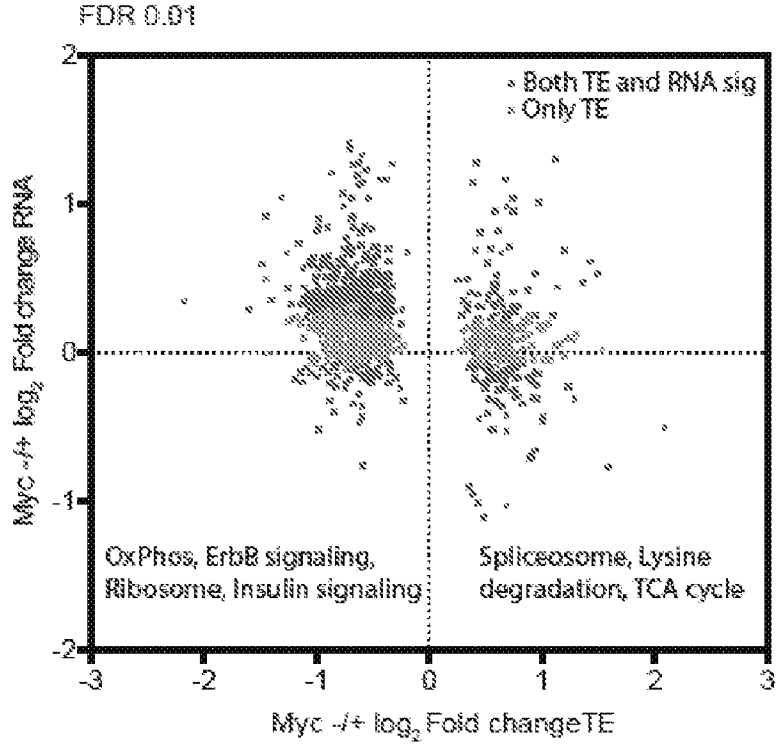


Fig. 7A

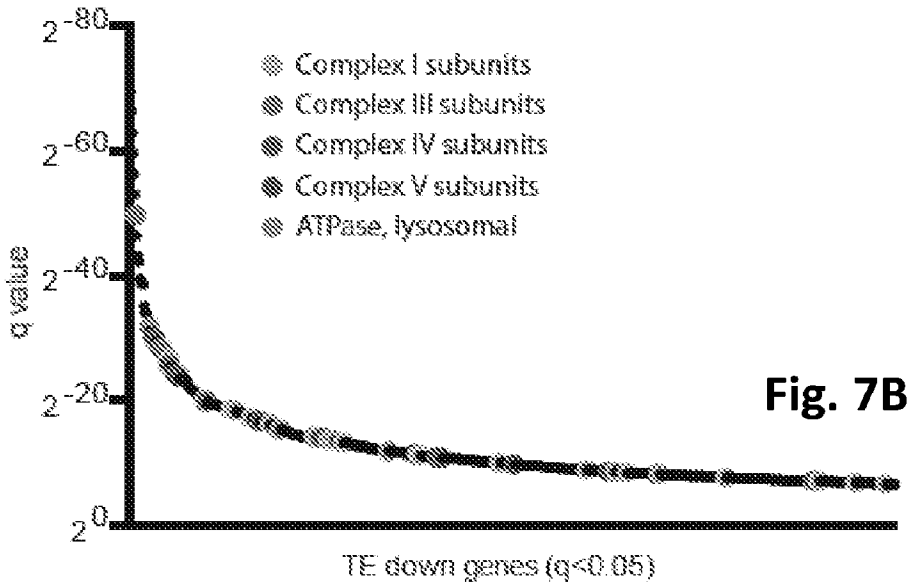


Fig. 7B

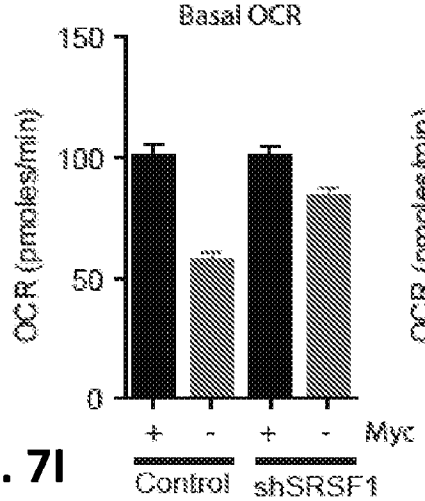


Fig. 7I

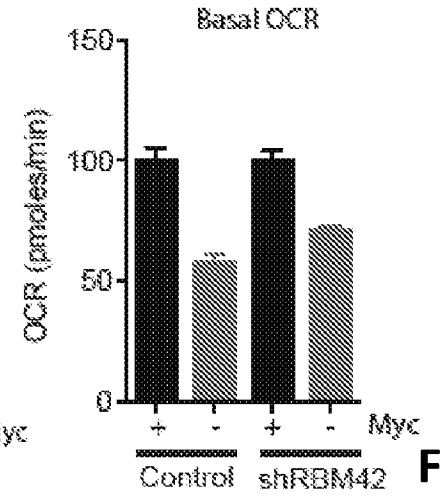


Fig. 7J

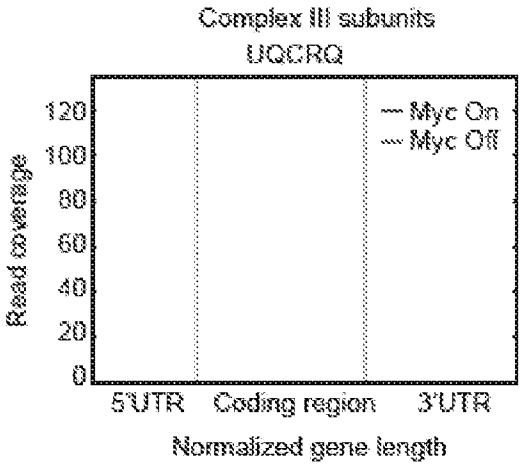


Fig. 7C

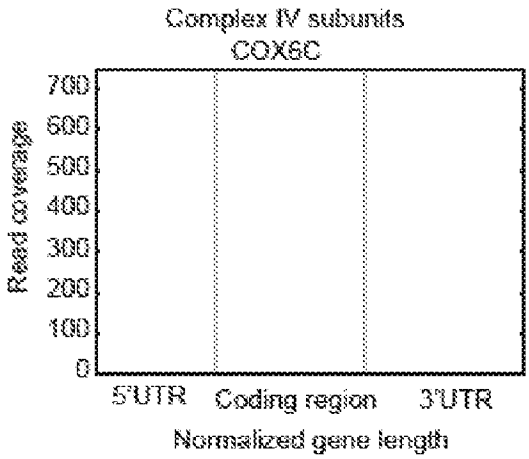


Fig. 7D

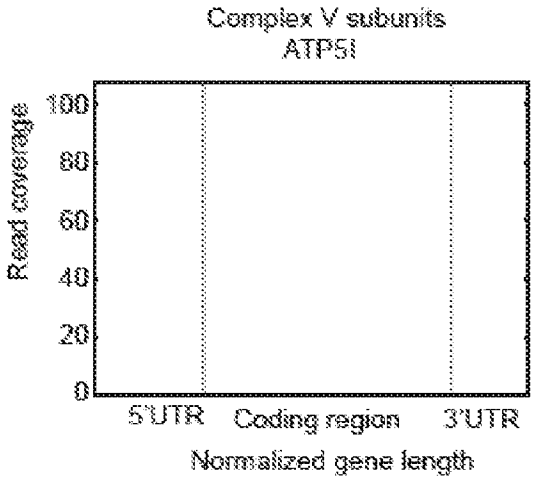


Fig. 7E

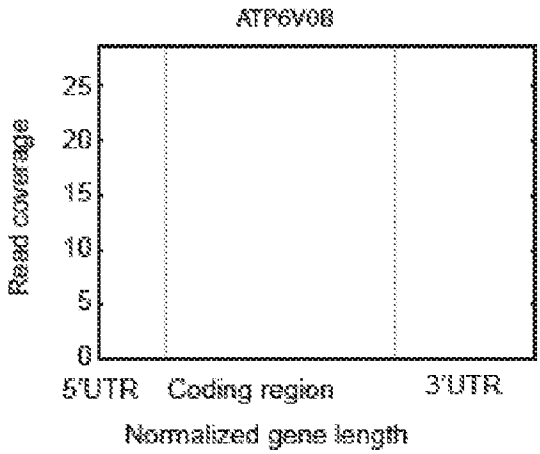


Fig. 7F

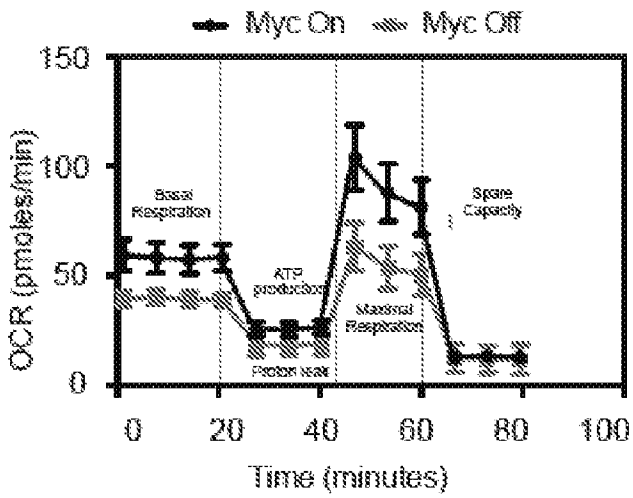


Fig. 7G

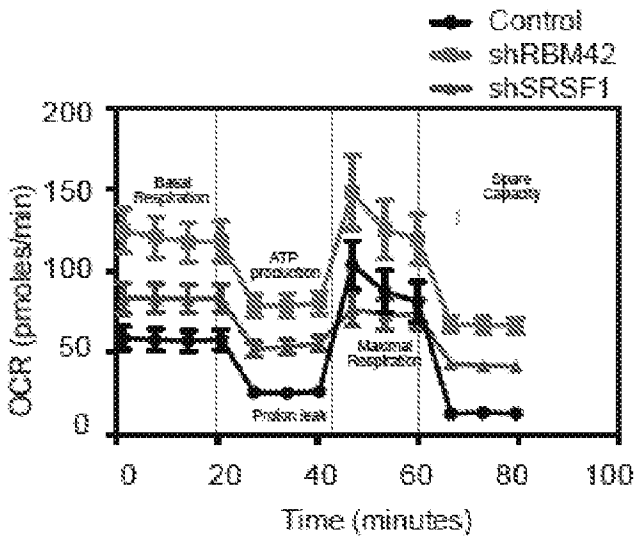


Fig. 7H

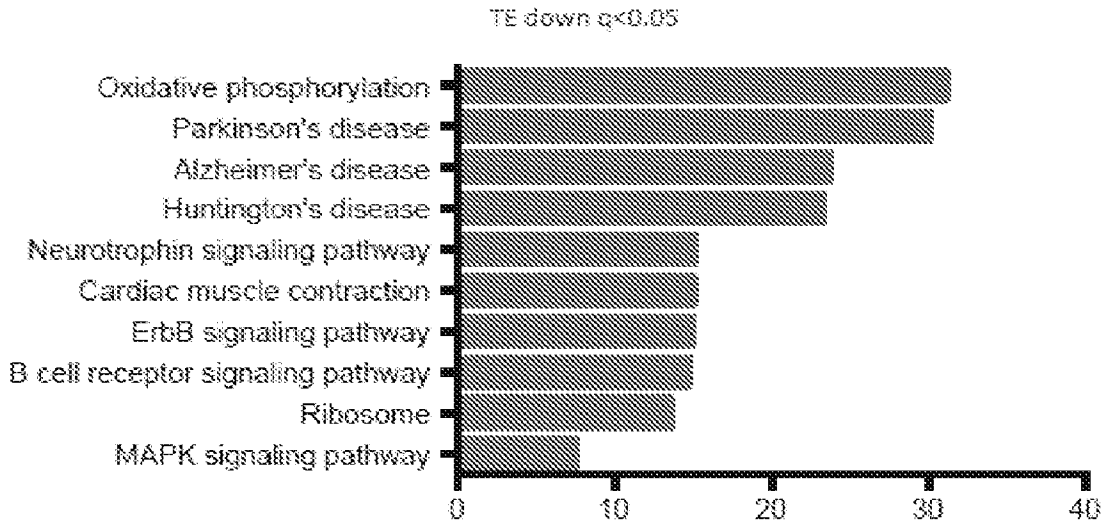


Fig. 8A

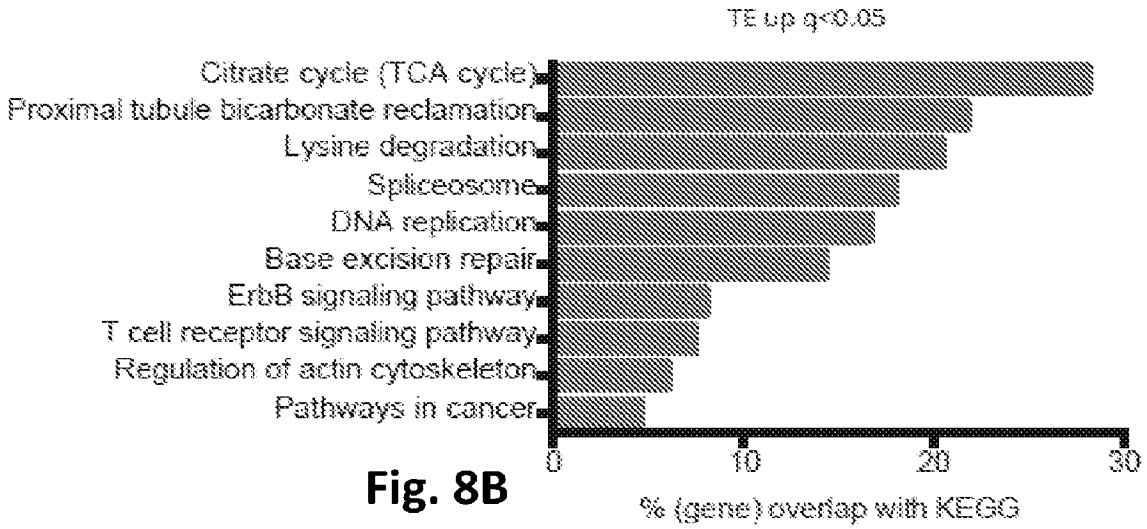


Fig. 8B

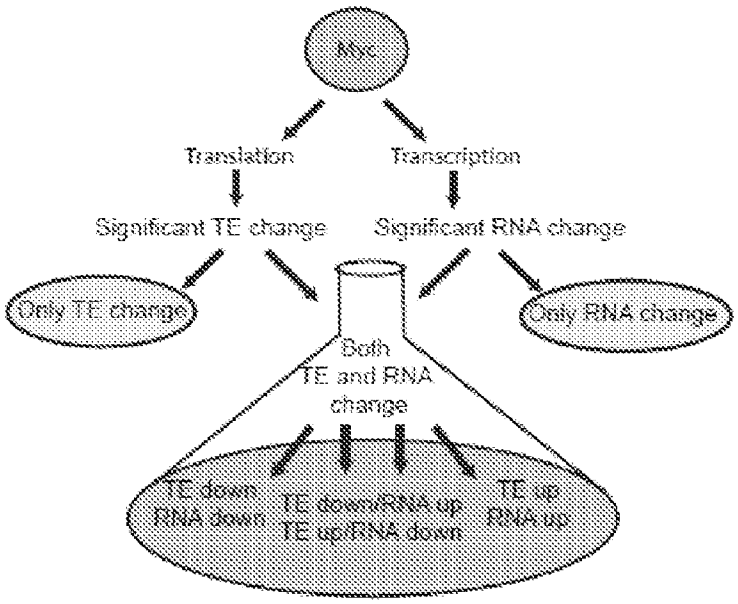


Fig. 8C

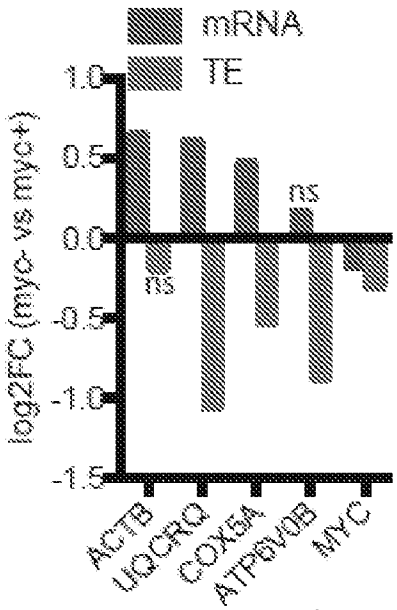


Fig. 8G

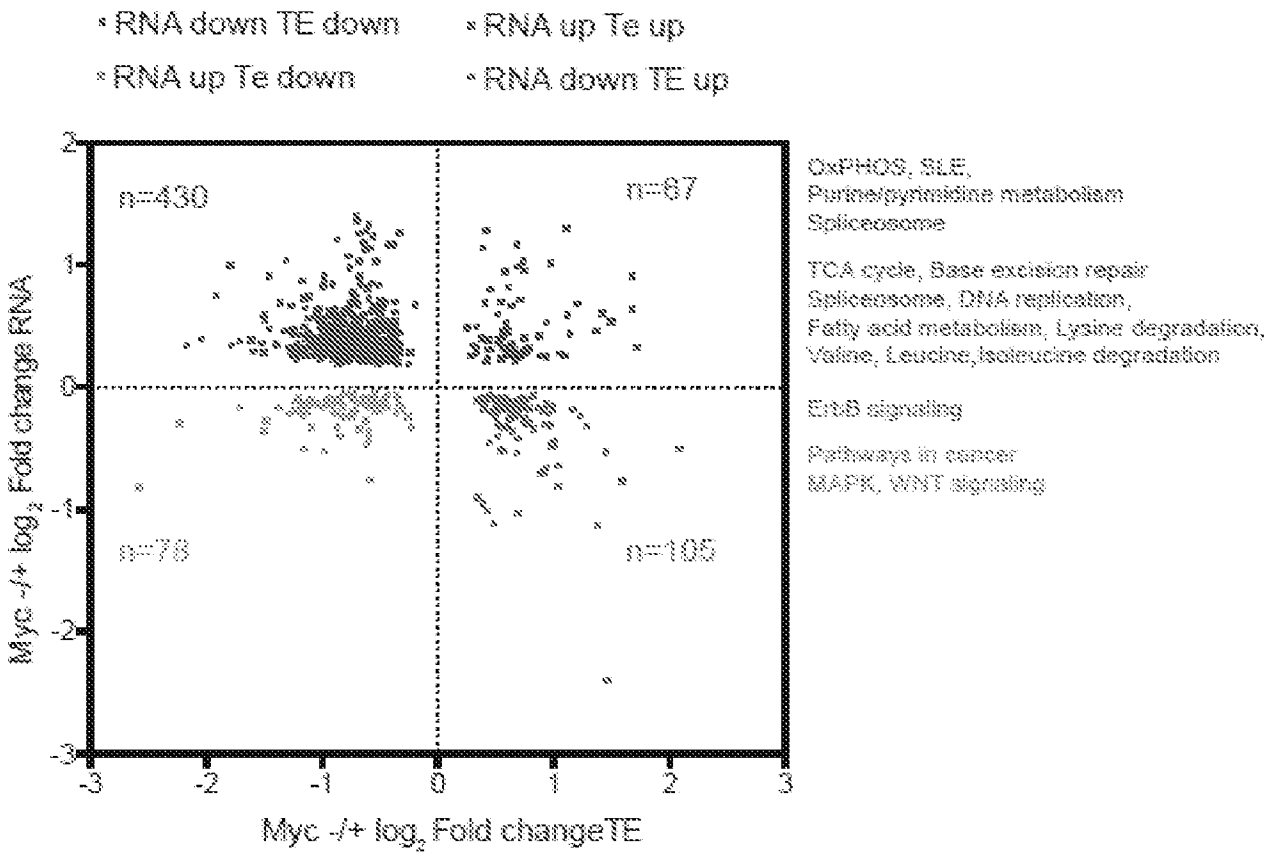


Fig. 8D

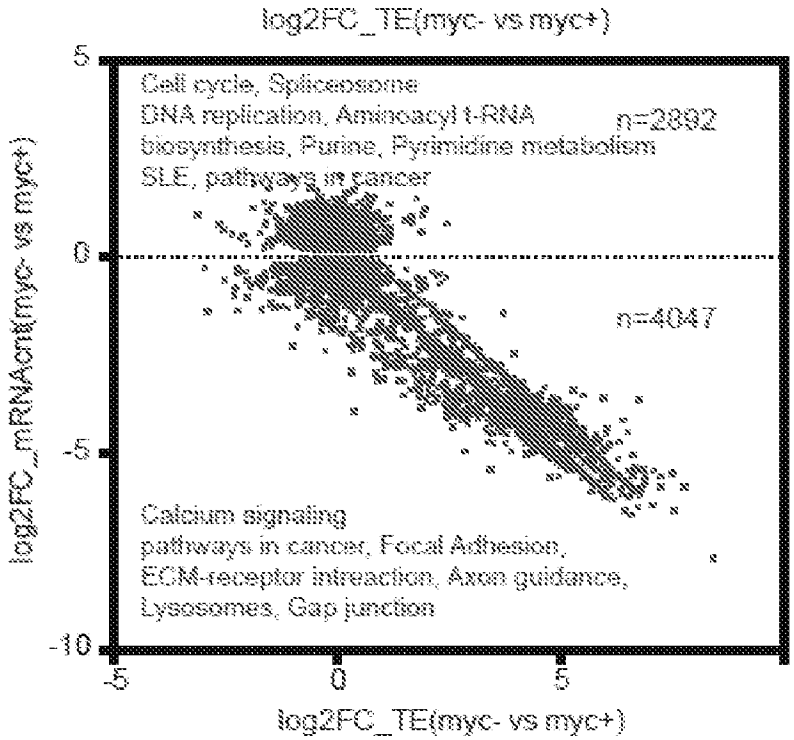


Fig. 8E

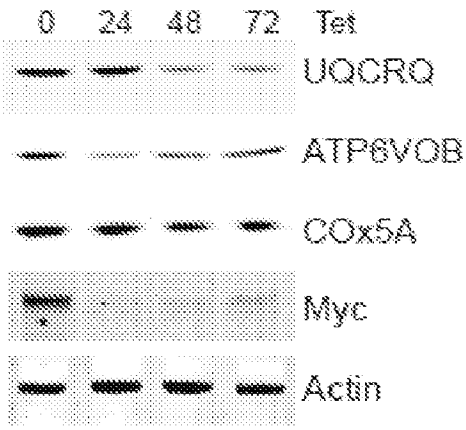


Fig. 8F