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(54) Title: NEW TREATMENTS INVOLVING MIRNA-193A

(57) Abstract: The invention relates to the use ofmiRNA-193a for regulating gene expression, particularly it relates to the use of miRNA-193a as a PTEN agonist. This allows the advantageous treatment of PTEN- deficient cancers. The invention further relates to compositions comprising the miRNA for use as a PTEN agonist.

New treatments involving miRNA-193a

Field of the invention

The invention relates to the use of miRNA-193a for regulating gene expression, particularly it relates to the use of miRNA-193a as a PTEN agonist. This allows the advantageous treatment of PTEN-deficient conditions such as various cancers. The invention further relates to compositions comprising the miRNA for use as a PTEN agonist.

Background art

MicroRNAs (miRNAs) are naturally occurring single-stranded, non-coding small RNA molecules that control gene expression by binding to complementary sequences in their target mRNAs, thereby inhibiting translation or inducing mRNA degradation. miRNAs have recently emerged as key regulators of gene expression during development and are frequently misexpressed in human disease states, for example in cancer. In fact, miRNAs can be used to silence specific cancer genes. Several miRNAs are reported to be effective modulators of cancer. For example, miRNA-193a has been described as effective in treating melanoma (WO2012005572).

Phosphatase and tensin homolog (PTEN) is 47-kDa protein and was first identified as a candidate tumour suppressor gene in 1997 after its positional cloning from a region of chromosome 10q23 known to exhibit loss in a wide spectrum of tumour types. Since then, mutations of PTEN have been detected in a variety of human cancers including breast, thyroid, glioblastoma, endometrial, and prostate cancer, and melanoma. Inherited mutations in this gene also predispose carriers to develop Cowden's disease, a heritable cancer risk syndrome, and several related conditions. PTEN is classified as a tumour suppressor because in various cancers its activity is lost by deletion, mutation, or through epigenetic changes. Molecular mechanistic studies of PTEN have provided insight into the basis for its involvement in tumour suppression. The PTEN protein has both protein phosphatase and lipid phosphatase activity. Although the tumour suppressive function of PTEN has mainly been attributed to its lipid phosphatase activity, a role for PTEN protein phosphatase activity in cell-cycle regulation and inhibition of cell invasion in vitro has been suggested as well. Loss of PTEN function seems to be responsible for many of the phenotypic features of PTEN-deficient melanoma, thus PTEN may serve as a potential target for drug development. Even when mutation of PTEN has minimal effects, it frequently contributes to tumorigenesis in the context of other genetic alterations (Aguissa-Toure et al., Cellular and Molecular Life Sciences 69: 1475-1491 (2012)).

PTEN agonists are known in the art, and their use in treating cancer has been described (WO2009126842). Their activity can stem from inhibition of mTOR. Known PTEN agonists include rapamycin (sirolimus) and its chemical analogues such as CCI-779 (temsirolimus), and RAD-001 (everolimus). Many PTEN agonists are small molecules (i.e., a compound having relatively low molecular weight, most often less than 500 or 600 kDa, or about 1000 kDa in the case of a macrolide such as rapamycin). Other agonists include monoclonal antibodies, and zinc finger proteins or nucleic acids encoding the same, engineered to bind to and activate transcription of PTEN (see WO 00/00388). Other PTEN agonists are described in US20070280918. Exemplary sequences for human PTEN and mTOR(FRAPI) are assigned UniProtKB/Swiss-Prot accession numbers P60484 and P42345.

A disadvantage of PTEN agonists is that they are associated with several adverse effects. For example, the PTEN agonist sirolimus is commonly (over 30% occurrence) associated with effects as diverse as peripheral edema, hypercholesterolemia, abdominal pain, headache, nausea, diarrhea, pain, constipation, hypertriglyceridemia, hypertension, increased creatinine, fever, urinary tract infection, anemia, arthralgia, and thrombocytopenia, in addition to diabetes-like symptoms, and even an increased risk for contracting skin cancers from exposure to UV radiation (see “"Rapamune Prescribing Information", United States Food and Drug Administration, Wyeth Pharmaceuticals, Inc. May 2015). The PTEN agonist temsirolimus is associated with fatigue, skin rash, mucositis, decreased haemoglobin, and decreased lymphocytes (Bellmunt et al., Annals of Oncology, 2008 DOI: 10.1093/annonc/mdn066).

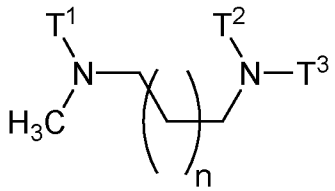
Accordingly, there is an ongoing need for alternative and improved PTEN agonists. There is an ongoing need for improved microRNA therapies for tumours, as well as an ongoing need for deeper mechanistic insight into microRNA treatment of tumours, which can open up new strategies for treatment.

Summary of the invention

The invention provides a miRNA-193a or a source thereof, for use in treating a condition associated with PTEN-deficiency. Preferably the miRNA-193a is a PTEN agonist. Preferably the miRNA-193a is a miRNA-193a molecule, an isomiR, or a mimic thereof, wherein it is preferably an oligonucleotide with a seed sequence comprising at least 6 of the 7 nucleotides of the seed sequence represented by SEQ ID NO: 22. Preferably the source of a miRNA is a precursor of a miRNA and is a nucleic acid of at least 50 nucleotides in length. Preferably, said miRNA shares at least 70% sequence identity with any one of SEQ ID NOs: 56, 121, or 122, and/or said miRNA is from 15-30 nucleotides in length, and/or said source of a miRNA is a precursor of said miRNA and shares at least 70% sequence identity with any one of SEQ ID NOs: 5 or 13. Preferably, the condition associated with PTEN deficiency is a PTEN-deficient cancer. Preferably, the PTEN-deficient cancer is a PTEN-deficient sarcoma, brain cancer, head and neck cancer, breast cancer, lung cancer, kidney cancer, liver cancer, colon cancer, ovarian cancer, melanoma, pancreatic cancer, thyroid cancer, hamartoma, tumour of the haematopoietic and lymphoid malignancy, or prostate cancer. Preferably, the miRNA-193a modulates expression of a gene selected from the group consisting of RPS6KB2, KRAS, PDGFRB, SOS2, TGFBR3, CASP9, INPPL1, PIK3R1, PTK2, CBL, PDPK1, CCND1, BCAR1, MAGI3, MDM2, YWHAZ, and MCL1, preferably from the group consisting of RPS6KB2, KRAS, PDGFRB, CASP9, INPPL1, PIK3R1, PTK2, CBL, PDPK1, CCND1, BCAR1, MAGI3, MDM2, YWHAZ, MCL1, more preferably selected from PDPK1 or INPPL1.

The invention further provides a composition comprising a miRNA-193a or a source thereof as defined above, for use as defined above. Preferably the composition further comprises a further miRNA or precursor thereof, wherein the further miRNA is selected from the group consisting of miRNA-323, miRNA-342, miRNA-520f, miRNA-520f-i3, miRNA-3157, and miRNA-7, or an isomiR thereof, or a mimic thereof. It preferably further comprises an additional pharmaceutically active compound, preferably selected from the group consisting of a PP2A methylating agent, an inhibitor of hepatocyte growth factor (HGF), an antibody, a PI3K inhibitor, an Akt inhibitor, an mTOR inhibitor, a binder of a T cell co-stimulatory molecule such as a binder of OX40, and a chemotherapeutic agent.

The invention further provides a nanoparticle composition, for use as defined above, the nanoparticle comprising a diamino lipid and a miRNA-193a or a source thereof as defined in any one of claims 1-8, wherein the diamino lipid is of general formula (I)



(I)

wherein

n is 0, 1, or 2, and

T^1, **T^2**, and **T^3** are each independently a C_{10}-C_{18} chain with optional unsaturations and with zero, one, two, three, or four substitutions, wherein the substitutions are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy.

Preferably the nanoparticles comprise 20-60 mol% of diamino lipid, and 0-40 mol% of a phospholipid, and 30-70 mol% of a sterol, and 0-10 mol% of a conjugate of a water soluble polymer and a lipophilic anchor.

The invention also provides an in vivo, in vitro, or ex vivo method for agonising PTEN, the method comprising the step of contacting a cell with a miRNA as defined above, or with a composition as defined above.

The invention also provides a method for treating a PTEN-deficient cancer, the method comprising the step of administering to a subject a miRNA-193a as defined above, or a composition as defined above.

Description of embodiments

Surprisingly, the inventors identified miRNA-193a as a PTEN agonist, allowing the use of miRNA-193a for treating diseases or conditions associated with PTEN-deficiency, particularly PTEN-deficient tumours. Accordingly, the invention provides a miRNA-193a or a source thereof, for use in treating a condition associated with PTEN-deficiency. Such a miRNA-193a or a source thereof is referred to hereinafter as a miRNA for use according to the invention, or a miRNA-193a for use according to the invention. Preferably, the miRNA for use according to the invention is a PTEN agonist.

As used herein, an "agonist of PTEN" or "PTEN agonist" refers to an agent that stimulates the production of PTEN mRNA in a cell, or stimulates expression of PTEN protein in a cell, or stimulates the activity of PTEN protein, or which can provide one or more of the functions of PTEN, e.g., in regulating the PTEN pathway or the PI3K/Akt/mTOR pathway. For example, PTEN is able to indirectly reduce the activity of mTOR (mammalian target of rapamycin) by downregulating the activity of Akt. An inhibitor of mTOR directly reproduces this particular role of PTEN - reduction of mTOR activity - so such an inhibitor is considered herein to be a PTEN agonist. This type of PTEN agonist will replace some but not necessarily all the functions of the tumour suppressor PTEN in a tumour cell with mutated, deleted, or dysfuctional PTEN, and may therefore cause the cell to revert to a more normal, less malignant phenotype. Insofar as a protein has more than one known form in a species due to natural allelic variation between individuals, an inhibitor can bind to and inhibit any, or all, of such known allelic forms, and preferably binds to and inhibits the wildtype, most common or first published allelic form.

miRNA, isomiR, mimic, or a source thereof

MicroRNAs (miRNAs) are small RNAs of 17-25 nucleotides, which function as regulators of gene expression in eukaryotes. miRNAs are initially expressed in the nucleus as part of long primary transcripts called primary miRNAs (pri-miRNAs). Inside the nucleus, pri-miRNAs are partially digested by the enzyme Drosha, to form 65-120 nucleotide-long hairpin precursor miRNAs (pre-miRNAs) that are exported to the cytoplasm for further processing by Dicer into shorter, mature miRNAs, which are the active molecules. In animals, these short RNAs comprise a 5' proximal "seed" region (generally nucleotides 2 to 8) which appears to be the primary determinant of the pairing specificity of the miRNA to the 3' untranslated region (3'-UTR) of a target mRNA.

Each of the definitions given below concerning a miRNA molecule, a miRNA mimic or a miRNA isomiR or a source of any of those is to be used for each of the identified miRNAs, molecules or mimics or isomiRs or sources thereof mentioned in this application: miRNA-193a, miRNA-323, miRNA-342, miRNA-520f, miRNA-520f-i3, miRNA-3157, and miRNA-7, or isomiRs or mimics or sources thereof. Preferred mature sequences (SEQ ID NOs: 51-57), seed sequences (SEQ ID NOs: 17-50, where SEQ ID NOs: 17-23 are seed sequences for canonical miRNAs and SEQ ID NOs: 24-50 are seed sequences for isomiRs), isomiR sequences (SEQ ID NOs: 58-125), or source sequences (RNA precursor as SEQ ID NOs: 1-8, or DNA encoding a RNA precursor as SEQ ID NOs: 9-16) of said miRNA molecule or mimic or isomiR thereof respectively are identified in the sequence listing.

In the context of this invention, a miRNA-193a refers to a miRNA-193a molecule (that is to the canonical oligonucleotide) or to an isomiR thereof or to a mimic thereof. Preferably, miRNA-193a is a miRNA-193a-3p, more preferably a miRNA-193a-3p molecule, isomiR, or mimic thereof, and comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NO: 22 and more preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more. For a miRNA-193a molecules (that is for the canonical miRNA) the preferred seed sequence is SEQ ID NO: 22. For an isomiR of miRNA-193a a preferred seed sequence is SEQ ID NO: 22.

A preferred mimic of miRNA-193a has a sense strand and an antisense strand, wherein the antisense strand comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NO: 22 and wherein the antisense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more, and wherein the antisense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 56, 121, 122, or 219, preferably 56 or 219, more preferably 219, and wherein the sense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 131, 196, 197, 206, or 218, more preferably 218, and wherein the sense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A mimic is a molecule which has a similar or identical activity with a miRNA molecule. In this context a similar activity is given the same meaning as an acceptable level of an activity. A mimic is, in a functional determination, opposed to an antagomir. Preferred mimics are synthetic oligonucleotides,

preferably comprising one or more nucleotide analogues such as locked nucleic acid monomers, and/or nucleotides comprising scaffold modifications and/or nucleotides comprising base modifications. A mimic can be a mimic for a miRNA or for an isomiR. Preferred mimics are mimics for a miRNA or for an isomiR. Preferred mimics are double stranded mimics.

Preferred mimics are double stranded oligonucleotides comprising a sense strand (also referred to as a passenger strand) and an antisense strand (also referred to as a guide strand). The canonical miRNA as it naturally occurs is defined herein as having an antisense sequence, because it is complementary to the sense sequence of naturally occurring targets. It follows that in a double stranded mimic as is a preferred mimic for use according to the invention, there are two strands, one of which is designated as a sense strand, and one of which is designated as an antisense strand. The antisense strand can have the same sequence as a miRNA, or as a precursor of a miRNA, or as an isomiR, or it can have the same sequence as a fragment thereof, or comprise the same sequence, or comprise the same sequence as a fragment thereof. The sense strand is at least partially reverse complementary to the antisense strand, to allow formation of the double stranded mimic. The sense strand is not necessarily biologically active per se, one of its important functions is to stabilize the antisense strand or to prevent its degradation or to facilitate its delivery. An examples of a sense strand for a mature miRNA is SEQ ID NO: 131. Examples of sense strands for isomiRs are SEQ ID NOs: 196 or 197.

A preferred mimic of miRNA-193a has a sense strand and an antisense strand, wherein the antisense strand comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NO: 22 and wherein the antisense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more, and wherein the antisense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 56, 121, 122, or 219, preferably 56, more preferably 219, and wherein the sense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 131, 196, 197, 206, or 218, more preferably 218, and wherein the sense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

In preferred embodiments an antisense strand comprises at least one modified nucleoside, preferably selected from the group consisting of a bridged nucleic acid nucleoside such as a locked nucleic acid (LNA) nucleoside, a 2'-O-alkylnucleoside such as a 2'-O-methylnucleoside, a 2'-fluoronucleoside, and a 2'-azidonucleoside, preferably a 2'-O-alkylnucleoside such as a 2'-O-methylnucleoside. It is preferred that such an at least one modified nucleoside replaces the first or the last RNA nucleoside, or replaces the second or second-to-last RNA nucleoside. In preferred embodiments at least two modified nucleosides replace the first two or the last two RNA nucleosides. More preferably both the first and the last RNA nucleosides are replaced, even more preferably both the first two and the last two. It is to be understood that the replacing modified nucleoside has the same pairing capacity as the nucleoside it replaces, preferably it has the same nucleobase. Preferably an antisense strand does not comprise modified nucleosides outside of the first two or the last two RNA nucleosides. In preferred embodiments, the last base of an antisense strand is a DNA nucleoside; more preferably the last two bases of an antisense strand are DNA nucleosides. Preferably the last one or two residues of an antisense strand form an overhang when the antisense strand forms a pair with the sense strand; more preferably the last two residues of an antisense strand form such an overhang. Preferably

an antisense sense does not comprise DNA nucleosides outside of the last two nucleosides, or outside of an overhang. Preferably a sense strand comprises only RNA nucleosides.

In preferred embodiments a sense strand comprises at least one modified nucleoside, preferably selected from the group consisting of a bridged nucleic acid nucleoside such as a locked nucleic acid (LNA) nucleoside, a 2'-O-alkylnucleoside such as a 2'-O-methylnucleoside, a 2'-fluoronucleoside, and a 2'-azidonucleoside, preferably a 2'-O-alkylnucleoside such as a 2'-O-methylnucleoside. It is preferred that such an at least one modified nucleoside replaces the first or the last RNA nucleoside, or replaces the second or second-to-last RNA nucleoside. In preferred embodiments at least two modified nucleosides replace the first two or the last two RNA nucleosides. More preferably both the first and the last RNA nucleosides are replaced, even more preferably both the first two and the last two. It is to be understood that the replacing modified nucleoside has the same pairing capacity as the nucleoside it replaces, preferably it has the same nucleobase. Preferably a sense strand does not comprise modified nucleosides outside of the first two or the last two RNA nucleosides. In preferred embodiments, the 3' prime end of the sense strand is elongated by a DNA nucleoside; more preferably the last two bases of a sense strand are DNA nucleosides, even more preferably the DNA nucleoside is deoxythymidine. Preferably the last one or two residues of a sense strand form an overhang when the sense strand forms a pair with the antisense strand; more preferably the last two residues of a sense strand form such an overhang. Preferably a sense strand does not comprise DNA nucleosides outside of the last two nucleosides, or outside of an overhang. In particularly preferred embodiments a mimic comprises an antisense strand that comprises only RNA nucleosides and a sense strand that comprises modifications as described above.

Preferably, the sense strand and the antisense strand do not fully overlap, having one, two, three, or four additional bases at their 3'-end, preferably having two additional bases at their 3'-end, forming a sticky end. Accordingly, in the corresponding antisense strand, the 3'-end one, two, three, or four bases preferably do not have a reverse complementary base in the sense strand, also forming a sticky end; more preferably the first two bases of a sense strand form a sticky end, not having complementary bases in the antisense strand. The sense strand is not necessarily biologically active, it serves primarily to increase the stability of the antisense strand. Examples of preferred sequences for sense/antisense pairs for mimics are SEQ ID NOs: 206 and 218 for sense strands, more preferably SEQ ID NO: 218 for sense strands, and SEQ ID NO: 219 for antisense strands. A preferred pair is SEQ ID NOs: 206 or 218 and SEQ ID NO: 219, more preferably SEQ ID NO: 218 and SEQ ID NO: 219.

In preferred embodiments, a mimic is a double stranded oligonucleotide comprising a sense strand and an antisense strand, wherein both strands have a length of 15 to 30 nucleotides, preferably of 17 to 27 nucleotides, wherein the antisense strand has 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or 100% sequence identity with any one of SEQ ID NOs: 56, 121, or 122, wherein the sense strand optionally has 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or 100% sequence identity with any one of SEQ ID NOs: 131, 196 or 197, preferably 131 or 196, wherein the sense strand and the antisense strand preferably can anneal to form said double stranded oligonucleotide, wherein optionally one or both ends of the oligonucleotide are sticky ends having an overlap of one, two, three, or four, preferably of two nucleotides, wherein the sense strand optionally comprises chemically modified nucleotides. Preferably, the two strands of a

double stranded mimic have the same length, or differ by one, two, three, four, five, or six nucleotides in length.

Within the whole text of the application unless otherwise indicated, a miRNA may also be named a miRNA molecule, a miR, an isomiR, or a mimic, or a source or a precursor thereof. Each sequence identified herein may be identified as being SEQ ID NO as used in the text of the application or as corresponding SEQ ID NO in the sequence listing. A SEQ ID NO as identified in this application may refer to the base sequence of said miRNA, isomiR, mimic, or source thereof such as a precursor. For all SEQ ID NOs, a skilled person knows that some bases can be interchanged. For example, each instance of T can be individually substituted by U, and vice versa. An RNA sequence provided for a mature miRNA can for example be synthesized as a DNA oligonucleotide using DNA nucleotides instead of RNA nucleotides. In such a case, thymine bases can be used instead of uracil bases. Alternately, thymine bases on deoxyribose scaffolds can be used. A skilled person understands that the base pairing behaviour is more important than the exact sequence, and that T and U are generally interchangeable for such purposes. Accordingly, a mimic can be either a DNA or an RNA molecule, or a further modified oligonucleotide as defined later herein.

In the context of the invention, a miRNA molecule or a mimic or an isomiR may be a synthetic or natural or recombinant or mature or part of a mature miRNA or a human miRNA or derived from a human miRNA as further defined in the part dedicated to the general definitions. A human miRNA molecule is a miRNA molecule which is found in a human cell, tissue, organ or body fluids (i.e. endogenous human miRNA molecule). A human miRNA molecule may also be a human miRNA molecule derived from an endogenous human miRNA molecule by substitution, deletion and/or addition of a nucleotide. A miRNA molecule or a mimic or an isomiR may be a single stranded or double stranded RNA molecule.

Preferably a miRNA molecule or a mimic or an isomiR thereof is from 6 to 30 nucleotides in length, preferably 12 to 30 nucleotides in length, preferably 15 to 28 nucleotides in length, more preferably said molecule has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

In a preferred embodiment, a miRNA molecule or a mimic or isomiR comprises at least 6 of the 7 nucleotides present in the seed sequence of said miRNA molecule or a mimic or isomiR thereof (SEQ ID NOs: 17-50). Preferably in this embodiment, a miRNA molecule or a mimic or isomiR is from 6 to 30 nucleotides in length and more preferably comprises at least 6 of the 7 nucleotides present in the seed sequence of said miRNA molecule or mimic or isomiR. Even more preferably a miRNA molecule or a mimic or isomiR is from 15 to 28 nucleotides in length and more preferably comprises at least 6 of the 7 nucleotides present in the seed sequence, even more preferably a miRNA molecule has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

In this context, to comprise at least 6 of the 7 nucleotides present in a seed sequence is intended to refer to a continuous stretch of 7 nucleotides that differs from the seed sequence in at most one

position. Alternately, this can refer to a continuous stretch of 6 nucleotides that differs from the seed sequence only through omission of a single nucleotide. Throughout the application, more preferred miRNA molecules, isomiRs, mimics, or precursors thereof comprise all 7 of the 7 nucleotides present in an indicated seed sequence, or in other words have 100% sequence identity with said seed sequences. Preferably, when comprised in a miRNA, isomiR, or mimic, a seed sequence starts at nucleotide number 1, 2, or 3, and ends at nucleotide number 7, 8, 9, 10, or 11; most preferably such a seed sequence starts at nucleotide number 2 and ends at nucleotide number 8.

The miRNA-193a for use according to the invention can be combined with a further miRNA selected from the group consisting of miRNA-323, miRNA-342, miRNA-520f, miRNA-520f-i3, miRNA-3157, and miRNA-7, or an isomiR thereof, or a mimic thereof

A preferred miRNA-323 is a miRNA-323-5p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 17 or 24-28 and more preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred mimic of miRNA-323 has a sense strand and an antisense strand, wherein the antisense strand comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 17 or 24-28 and wherein the antisense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more, and wherein the antisense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 51, 58-68, or 209 and wherein the sense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 126, 133-143, 201, or 208 and wherein the sense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred miRNA-342 is a miRNA-342-5p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 18 or 29-42 and more preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred mimic of miRNA-342 has a sense strand and an antisense strand, wherein the antisense strand comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 18 or 29-42 and wherein the antisense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more, and wherein the antisense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 52, 69-113, or 211 and wherein the sense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 127, 144-188, 202, or 210 and wherein the sense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred miRNA-520f is a miRNA-520f-3p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 19 or 43-44 and more preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred mimic of miRNA-520f has a sense strand and an antisense strand, wherein the antisense strand comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 19 or 43-44 and wherein the antisense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more, and wherein the antisense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 53, 114, 115, or 213 and wherein the sense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 128, 189, 190, 203, or 212, and wherein the sense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A further preferred miRNA-520f is a miRNA-520f-3p-i3 molecule or mimic thereof comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NO: 20 and more preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred mimic of miRNA-520f-3p-i3 has a sense strand and an antisense strand, wherein the antisense strand comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NO: 20 and wherein the antisense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more, and wherein the antisense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 54 or 215, and wherein the sense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 129, 204, or 214 and wherein the sense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred miRNA-3157 is a miRNA-3157-5p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 21 or 45-48 and more preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred mimic of miRNA-3157 has a sense strand and an antisense strand, wherein the antisense strand comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 21 or 45-48 and wherein the antisense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more, and wherein the antisense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 55, 116-120, or 217, and wherein the sense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 130, 191-195, 205, or 216, and wherein the sense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred miRNA-7 is a miRNA-7-5p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 23 or 50 and more preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

A preferred mimic of miRNA-7 has a sense strand and an antisense strand, wherein the antisense strand comprises at least 6 of the 7 nucleotides present in the seed sequence of SEQ ID NOs: 23 or 50 and wherein the antisense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13,

14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more, and wherein the antisense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 57, 123-125, or 221, and wherein the sense strand preferably has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 132, 198-200, 207, or 220, and wherein the sense strand preferably has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

Preferably, a miRNA molecule, isomiR, or mimic thereof has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more, comprises at least 6 of the 7 nucleotides present in a given seed sequence of any one of SEQ ID NOs: 17-50 and has at least 70% identity over the whole mature sequence of any one of SEQ ID NOs: 51-125. Preferably, identity is at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100%.

Alternatively, preferably, a miRNA molecule, isomiR, or mimic thereof has a length of not more than 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleotides, comprises at least 6 of the 7 nucleotides present in a given seed sequence of any one of SEQ ID NOs: 17-50 and has at least 70% identity over the whole mature sequence of any one of SEQ ID NOs: 51-125. Preferably, identity is at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100%.

In another preferred embodiment, an isomiR of a miRNA molecule has at least 70% identity over the whole isomiR sequence of any one of SEQ ID NOs: 58-125. Preferably, identity is at least 75%, 80%, 85%, 90%, 95% or higher. Preferably in this embodiment, an isomiR of a miRNA molecule or a mimic thereof has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 nucleotides or more.

Accordingly a preferred miRNA-323 molecule, isomiR, or mimic thereof is a miRNA-323-5p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence identified as SEQ ID NOs: 17, 24-28 and/or has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 51, 58-68 and/or has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleotides or more.

Accordingly a preferred miRNA-323 molecule, isomiR, or mimic thereof is a miRNA-323-5p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence identified as SEQ ID NOs: 17, 24-28 and/or has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 51, 58-68 and/or has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleotides or more.

Accordingly a preferred miRNA-342 molecule, isomiR, or mimic thereof is a miRNA-342-5p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence identified as SEQ ID NOs: 18, 29-42 and/or has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 52, 69-113 and/or has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleotides or more.

Accordingly a preferred miRNA-520f molecule, isomiR, or mimic thereof is a miRNA-520f-3p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence identified as SEQ ID NOs: 19, 43-44 and/or has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 53, 114-115 and/or has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleotides or more. A further preferred miRNA 520f molecule, isomiR, or mimic thereof is a miRNA-520f-3p-i3 molecule or a mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence identified as SEQ ID NO: 20 and/or has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NO: 54 and/or has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleotides or more.

Accordingly a preferred miRNA-3157 molecule, isomiR, or mimic thereof is a miRNA-3157-5p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence identified as SEQ ID NOs: 21, 45-48 and/or has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 55, 116-120 and/or has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleotides or more.

Accordingly a preferred miRNA-193a molecule, isomiR, or mimic thereof is a miRNA-193a-3p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence identified as SEQ ID NO: 22 and/or has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 56, 121-122 and/or has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleotides or more.

Accordingly a preferred miRNA-7 molecule, isomiR, or mimic thereof is a miRNA-7-5p molecule, isomiR, or mimic thereof and comprises at least 6 of the 7 nucleotides present in the seed sequence identified as SEQ ID NOs: 23 or 50 and/or has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity over SEQ ID NOs: 57, 123-125 and/or has a length of at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleotides or more.

Another preferred miRNA molecule, isomiR, or mimic thereof has at least 60% identity with a seed sequence of any one of SEQ ID NOs: 17-50, or with a mature sequence of any one of SEQ ID NOs: 51-57, or with a precursor sequence of any one of SEQ ID NOs: 1-16, preferably of any one of SEQ ID NOs: 1-8, or with a DNA encoding an RNA precursor of any one of SEQ ID NOs: 9-16, or with an isomiR sequence of any one of SEQ ID NOs: 58-125. Identity may be at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100%. Identity is preferably assessed on the whole SEQ ID NO as identified in a given SEQ ID NO. However, identity may also be assessed on part of a given SEQ ID NO. Part may mean at least 50% of the length of the SEQ ID NO, at least 60%, 70%, 80%, 90% or 100%.

A precursor sequence may result in more than one isomiR sequences depending on the maturation process - see for example miRNA-323 (mature sequence SEQ ID NO: 51) where in certain tissues multiple isomiRs have been identified (SEQ ID NOs: 58-68). IsomiRs of a miRNA molecule stem from the same precursor, and conversely a precursor can lead to multiple miRNA molecules, one of which is referred to as the canonical miRNA (such as miRNA-323-5p, SEQ ID NO: 51) and others being referred to as isomiRs (such as the oligonucleotide represented by SEQ ID NOs: 58-68). The difference between a canonical miRNA and its isomiRs can be said lie only in their prevalence – generally, the most prevalent molecule is called the canonical miRNA, while the others are isomiRs. Dependent on the type, environment, position in its life cycle, or pathological state of a cell, individual isomiRs or miRNAs can be expressed at different levels; expression can even differ between population groups or gender (Loher et al., Oncotarget (2014) DOI: 10.18632/oncotarget.2405).

The chemical structure of the nucleotides of a miRNA molecule or mimics or sources thereof, or of a sense strand or an antisense strand in a mimic of a miRNA or of an isomiR, may be modified to increase stability, binding affinity and/or specificity. Said sense strand or antisense strand may comprise or consists of a RNA molecule or preferably a modified RNA molecule. A preferred modified RNA molecule comprises a modified sugar. One example of such modification is the introduction of a 2'-O-methyl or 2'-O-methoxyethyl group or 2' fluoride group on the nucleic acid to improve nuclease resistance and binding affinity to RNA. Another example of such modification is the introduction of a methylene bridge connecting the 2'-O atom and the 4'-C atom of the nucleic acid to lock the conformation (Locked Nucleic Acid (LNA)) to improve affinity towards complementary single-stranded RNA. A third example is the introduction of a phosphorothioate group as linker between nucleic acid in the RNA-strand to improve stability against a nuclease attack. A fourth modification is conjugation of a lipophilic moiety on the 3' end of the molecule, such as cholesterol to improve stability and cellular delivery.

In a preferred embodiment, the first two bases of a sense strand of a mimic have modified sugars, preferably 2'-O-methyl modifications. In a preferred embodiment, the first two of the last four bases of a sense strand of a mimic have modified sugars, preferably 2'-O-methyl modifications. In a preferred embodiment, the first two bases and the first two of the last four bases of a sense strand of a mimic have modified sugars, preferably 2'-O-methyl modifications. In a preferred embodiment, the last two bases of a sense strand of a mimic have modified sugars, preferably 2'-O-methyl modifications. In a preferred embodiment, the first two and the last two bases of a sense strand of a mimic have modified sugars, preferably 2'-O-methyl modifications. In a preferred embodiment, the last two bases of a sense strand of a mimic are DNA bases. In a preferred embodiment, the first two bases and the first two of the last four bases of a sense strand of a mimic have modified sugars, preferably 2'-O-methyl modifications, and the last two bases of said sense strand are DNA bases. In a preferred embodiment, the first two bases of a sense strand of a mimic have modified sugars, preferably 2'-O-methyl modifications, and the last two bases of said sense strand are DNA bases. In a preferred embodiment, the first two of the last four bases of a sense strand of a mimic have modified sugars, preferably 2'-O-methyl modifications, and the last two bases of said sense strand are DNA bases.

A source of a miRNA molecule or a source of a mimic or an isomiR may be any molecule which is able to induce the production of a miRNA molecule or of a mimic or isomiR as identified herein and

which preferably comprises a hairpin-like structure and/or a double stranded nucleic acid molecule. The presence of a hairpin-like structure may be assessed using the RNAshapes program (Steffen P. et al 2006) using sliding windows of 80, 100 and 120 nt or more. The hairpin-like structure is usually present in a natural or endogenous source of a miRNA molecule whereas a double-stranded nucleic acid molecule is usually present in a recombinant or synthetic source of a miRNA molecule or of an isomiR or mimic thereof.

A source of a miRNA molecule or of a mimic or an isomiR may be a single stranded, a double stranded RNA or a partially double stranded RNA or may comprise three strands, an example of which is described in WO2008/10558. As used herein partially double stranded refers to double stranded structures that also comprise single stranded structures at the 5' and/or at the 3' end. It may occur when each strand of a miRNA molecule does not have the same length. In general, such partial double stranded miRNA molecule may have less than 75% double stranded structure and more than 25% single stranded structure, or less than 50% double stranded structure and more than 50% single stranded structure, or more preferably less than 25%, 20 % or 15% double stranded structure and more than 75%, 80%, 85% single stranded structure.

Alternatively, a source of a miRNA molecule or of a mimic or an isomiR thereof is a DNA molecule encoding a precursor of a miRNA molecule or a mimic or an isomiR thereof. Preferred DNA molecules in this context are SEQ ID NOs: 9-16. For the miRNA for use according to the invention, SEQ ID NO: 13 is preferred. The invention encompasses the use of a DNA molecule encoding a precursor of a miRNA molecule that has at least 70% identity with said SEQ ID NO: 13. Preferably, the identity is at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100%. Preferably in this embodiment, a DNA molecule has a length of at least 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 130, 150, 200, 250, 300, 350, 400 nucleotides or more and has at least 70% identity with a DNA sequence of SEQ ID NOs: 13.

The induction of the production of a given miRNA molecule or of a mimic or an isomiR is preferably obtained when said source is introduced into a cell using one assay as defined below. Cells encompassed by the present invention are later on defined.

A preferred source of a miRNA molecule or of a mimic or an isomiR thereof is a precursor thereof, more preferably a nucleic acid encoding said miRNA molecule or a mimic or an isomiR thereof. A preferred precursor is a naturally-occurring precursor. A precursor may be a synthetic or recombinant precursor. A synthetic or recombinant precursor may be a vector that can express a naturally-occurring precursor. In preferred embodiments, this aspect provides the miRNA for use according to the invention, wherein a source of a miRNA is a precursor of a miRNA and is a nucleic acid of at least 50 nucleotides in length. In preferred embodiments is provided the miRNA-193a or a source thereof for use according to the invention, wherein said miRNA shares at least 70% sequence identity with any one of SEQ ID NOs: 56, 121, or 122, and/or wherein said miRNA is from 15-30 nucleotides in length, and/or wherein said source of a miRNA is a precursor of said miRNA and shares at least 70% sequence identity with any one of SEQ ID NOs: 5 or 13. More preferably the miRNA-193a for use according to the invention shares at least 70% sequence identity with any one of SEQ ID NOs: 56, 121, or 122, and is from 15-30 nucleotides in length; more preferably said source of a miRNA-193a is a precursor of said miRNA-193a and shares at least 70% sequence identity with any one of SEQ ID NOs: 5 or 13.

A preferred precursor of a given miRNA molecule has a sequence represented by any one of SEQ ID NOs: 1-16. The invention encompasses the use of a precursor of a miRNA molecule or of an isomiR or mimic thereof that has at least 70% identity with said sequence. Preferably, identity is at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100%. Preferably in this embodiment, a DNA molecule has a length of at least 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 130, 150, 200, 250, 300, 350, 400 nucleotides or more and has at least 70% identity with a sequence represented by any one of SEQ ID NOs: 1-16. Preferably, in this embodiment, a precursor comprises a seed sequence that shares at least 6 of the 7 nucleotides with a seed sequence selected from the group represented by SEQ ID NOs: 17-50. More preferably, a precursor comprises a seed sequence selected from the group represented by SEQ ID NOs: 17-50. A more preferred precursor of a given miRNA molecule has a sequence represented by any one of SEQ ID NOs: 1-8. The invention encompasses the use of a precursor of a miRNA molecule or of an isomiR or mimic thereof that has at least 70% identity with said sequence. Preferably, identity is at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100%. Preferably in this embodiment, a DNA molecule has a length of at least 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 130, 150, 200, 250, 300, 350, 400 nucleotides or more and has at least 70% identity with a sequence represented by any one of SEQ ID NOs: 1-8. Preferably, in this embodiment, a precursor comprises a seed sequence that shares at least 6 of the 7 nucleotides with a seed sequence selected from the group represented by SEQ ID NOs: 17-50. More preferably, a precursor comprises a seed sequence selected from the group represented by SEQ ID NOs: 17-50.

Accordingly, a preferred source of a miRNA-323 molecule has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity with SEQ ID NOs: 1 or 9, preferably SEQ ID NO: 1, and optionally has a length of at least 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 130, 150, 200, 250, 300, 350, 400 nucleotides or more and optionally comprises a seed sequence that shares at least 6 of the 7 nucleotides of any one of SEQ ID NOs: 17 or 24-28. Such a source is a precursor of a miRNA-323 molecule and of miRNA-323 isomiRs.

Accordingly, a preferred source of a miRNA-342 molecule has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity with SEQ ID NOs: 2 or 10, preferably SEQ ID NO: 2, and optionally has a length of at least 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 130, 150, 200, 250, 300, 350, 400 nucleotides or more and optionally comprises a seed sequence that shares at least 6 of the 7 nucleotides of any one of SEQ ID NOs: 18 or 29-42. Such a source is a precursor of a miRNA-342 molecule and of miRNA-342 isomiRs.

Accordingly, a preferred source of a miRNA-520f molecule has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity with SEQ ID NOs: 3 or 11, preferably SEQ ID NO: 3, and optionally has a length of at least 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 130, 150, 200, 250, 300, 350, 400 nucleotides or more and optionally comprises a seed sequence that shares at least 6 of the 7 nucleotides of any one of SEQ ID NOs: 19, 20, 43, or 44. Such a source is a precursor of a miRNA-520f molecule and of miRNA-520f isomiRs such as miRNA-520f-3p-i3.

Accordingly, a preferred source of a miRNA-3157 molecule has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity with SEQ ID NOs: 4 or 12, preferably SEQ ID NO: 4, and optionally has a length of at least 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 130, 150, 200, 250, 300, 350, 400 nucleotides or more and optionally comprises a seed sequence that shares at least 6 of the 7

nucleotides of any one of SEQ ID NOs: 21 or 45-48. Such a source is a precursor of a miRNA-3157 molecule and of miRNA-3157 isomiRs.

Accordingly, a preferred source of a miRNA-193a molecule has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity with SEQ ID NOs: 5 or 13, preferably SEQ ID NO: 5, and optionally has a length of at least 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 130, 150, 200, 250, 300, 350, 400 nucleotides or more and optionally comprises a seed sequence that shares at least 6 of the 7 nucleotides of any one of SEQ ID NO: 22. Such a source is a precursor of a miRNA-193a molecule and of miRNA-193a isomiRs.

Accordingly, a preferred source of a miRNA-7 molecule has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identity with SEQ ID NOs: 6-8 or 14-16, preferably SEQ ID NOs: 6-8, and optionally has a length of at least 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 130, 150, 200, 250, 300, 350, 400 nucleotides or more and optionally comprises a seed sequence that shares at least 6 of the 7 nucleotides of any one of SEQ ID NOs: 23 or 50. Such a source is a precursor of a miRNA-7 molecule and of miRNA-7 isomiRs.

In this context, it is pointed that several precursors of a given mature miRNA molecule may lead to an identical miRNA molecule. For example, miRNA-7 may originate from precursor miRNA-7-1 or miRNA-7-2 or miRNA-7-3 (preferably identified as being SEQ ID NOs: 6, 8, or 8, respectively). Also in this context, it is pointed that several isomirs of a given mature miRNA molecule may lead to miRNA molecules with identical seed sequences. For example, mature miRNA-323-5p (SEQ ID NO: 51) and at least isomirs with SEQ ID NOs: 58 or 59 all share the same seed sequence (preferably identified as being SEQ ID NO: 17).

Preferred sources or precursors have been defined elsewhere herein. A preferred source includes or comprises an expression construct comprising a nucleic acid, i.e. DNA encoding said precursor of said miRNA, more preferably said expression construct is a viral gene therapy vector selected from gene therapy vectors based on an adenovirus, an adeno-associated virus (AAV), a herpes virus, a pox virus and a retrovirus. A preferred viral gene therapy vector is an AAV or Lentiviral vector. Other preferred vectors are oncolytic viral vectors. Such vectors are further described herein below. Alternatively, a source may be a synthetic miRNA molecule or a chemical mimic as further defined in the part dedicated to general definitions.

Conditions associated with PTEN-deficiency

The use according to the invention is use in treating a condition associated with PTEN-deficiency. Such a condition, or disease, is referred to herein as a PTEN-deficient condition. The invention provides this new medical use of miRNA-193a. This use can also be the use of the composition or miRNA in the manufacture of a medicament. Compositions are defined in a later section. Treatment preferably refers to preventing, ameliorating, reverting, curing and/or delaying a condition. When the PTEN-deficient condition is a PTEN-deficient tumour, preferred treatment can be obtaining an anti-tumour effect.

By the term "treating" and derivatives thereof as used herein, is meant therapeutic therapy. In reference to a particular condition, treating means: (1) to ameliorate the condition or one or more of the biological manifestations of the condition; (2) to interfere with (a) one or more points in the biological

cascade that leads to or is responsible for the condition or (b) one or more of the biological manifestations of the condition; (3) to alleviate one or more of the symptoms, effects or side effects associated with the condition or one or more of the symptoms, effects or side effects associated with the condition or treatment thereof; (4) to slow the progression of the condition or one or more of the biological manifestations of the condition and/or (5) to cure said condition or one or more of the biological manifestations of the condition by eliminating or reducing (preferably to undetectable levels) one or more of the biological manifestations of the condition for a period of time considered to be a state of remission for that manifestation without additional treatment over the period of remission. One skilled in the art will understand the duration of time considered to be remission for a particular disease or condition. Prophylactic therapy is also contemplated. The skilled artisan will appreciate that "prevention" is not always an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a condition or biological manifestation thereof, or to delay the onset of such condition or biological manifestation thereof. Prophylactic therapy is appropriate, for example, when a subject is considered at high risk for developing cancer, such as when a subject has a strong family history of cancer or when a subject has been exposed to a carcinogen, or when PTEN-deficiency is diagnosed in a patient.

T cell-mediated immunotherapies are promising cancer treatments. However, many patients still fail to respond to these therapies. The molecular determinants of immune resistance are poorly understood. Loss of PTEN in tumour cells in preclinical models of melanoma inhibits T cell-mediated tumour killing and decreases T-cell trafficking into tumours. In patients (e.g., subjects), PTEN loss correlates with decreased T-cell infiltration at tumour sites, reduced likelihood of successful T-cell expansion from resected tumours, and inferior outcomes with PD-1 inhibitor therapy. PTEN loss in tumour cells increased the expression of immunosuppressive cytokines, resulting in decreased T-cell infiltration in tumours, and inhibited autophagy, which decreased T cell-mediated cell death. Treatment with a selective RI3Kb (PI3Kb) inhibitor can improve the efficacy of both anti-PD-1 and anti-CTLA-4 antibodies in murine models. These findings demonstrate that PTEN loss promotes immune resistance and support the rationale to explore combinations of immunotherapies and PI3K- AKT pathway inhibitors. See Peng et al., Cancer Discovery 6:202-216 (2016).

The PI3K pathway plays a critical role in cancer by regulating several critical cellular processes, including proliferation and survival. One of the most common ways that this pathway is activated in cancer is by loss of expression of the tumour suppressor PTEN, which is a lipid phosphatase that dampens the activity of PI3K signalling. Loss of PTEN corresponds with increased activation of the PI3K-AKT pathway in multiple tumour types. Loss of PTEN is not universal in cancer – for example, it occurs in up to 30% of melanomas.

As used herein, "PTEN deficient" or "PTEN deficiency" preferably refers to a condition caused by or exacerbated by a deficiency of the tumour suppressor function of PTEN, e.g., loss of expression of the PTEN tumour suppressor. Such deficiency preferably includes mutation in the PTEN gene, reduction or absence of PTEN protein when compared to PTEN wild-type, or mutation or absence of other genes that cause suppression of PTEN function. It more preferably includes PTEN activity or expression lost by deletion, mutation, or through epigenetic changes. Multiple mechanisms exist for the regulation of PTEN, including transcription, mRNA stability, miRNA targeting, translation, and protein stability. PTEN

is transcriptionally silenced by promoter methylation in PTEN-deficient endometrial, gastric, lung, thyroid, breast and ovarian tumours, as well as glioblastoma. Mutations resulting in the loss of function or reduced levels of PTEN, as well as PTEN deletions or alteration are found in several sporadic tumours. See Aguissa-Toure et al., Cellular and Molecular Life Sciences 69: 1475-1491 (2012). A skilled person knows how to determine whether a condition such as a cancer is PTEN deficient. PTEN deficiency can be determined by methods such as Q-PCR or ELISA or immunohistochemistry. Human PTEN qPCR primer pairs are commercially available, e.g., from Sino Biological and Genecopoeia. A PTEN (Human) ELISA kit is commercially available, e.g., from BioVision and Abeam. An immunohistochemistry protocol is provided, e.g., in Sakr et al., Appl. Immunohistochem. Mol. Morphol. 18:371-374 (2010). PTEN antibodies are commercially available, e.g., from Abeam and Sino Biological. For reference, the human PTEN mRNA sequence is NCBI Accession No. NM_000314.4; the protein sequence is NCBI Accession No. AAH05821.1.

PTEN-deficient conditions are known in the art, and as described above the PTEN-deficient nature of a condition can be readily established using routine assays. Examples of conditions of which PTEN-deficient variants exist are cancer, autism, macrocephaly, benign tumours, and non-cancerous neoplasia. Preferred conditions of which PTEN-deficient variants exist are cancer, benign tumours, and non-cancerous neoplasia, which are herein collectively referred to as PTEN-deficient tumours. Examples of non-cancerous neoplasia are hamartoma such as those occurring in Bannayan-Zonana syndrome, Bannayan–Riley–Ruvalcaba syndrome, Proteus syndrome, Proteus-like syndrome, Cowden disease, PTEN hamartoma tumour syndrome (PHTS), and Lhermitte-Duclos disease. A most highly preferred PTEN-deficient tumour is a PTEN-deficient cancer.

A preferred PTEN-deficient condition is a tumour, in other words a preferred use according to the invention is in treating a PTEN-deficient tumour, more preferably a PTEN-deficient cancer. Generally, as used herein, reference to treatment of cancer is intended to refer to treatment of PTEN-deficient cancer. Unless otherwise indicated, an anti-tumour effect is preferably assessed or detected before treatment and after at least one week, two weeks, three weeks, four weeks, one month, two months, three months, four months, five months, six months or more in a treated subject. An anti-tumour effect is preferably identified in a subject as:

- an inhibition of proliferation or a detectable decrease of proliferation of tumour cells or a decrease in cell viability of tumour cells or melanocytes, and/or
- an increase in the capacity of differentiation of tumour cells, and/or
- an increase in tumour cell death, which is equivalent to a decrease in tumour cell survival, and/or
- a delay in occurrence of metastases and/or of tumour cell migration, and/or
- an inhibition or prevention or delay of the increase of a tumour weight or growth, and/or
- a prolongation of patient survival of at least one month, several months or more (compared to those not treated or treated with a control or compared with the subject at the onset of the treatment), and/or
- a decrease in tumour size or volume.

In the context of the invention, a patient may survive and may be considered as being disease free. Alternatively, the disease or condition may have been stopped or delayed or regressed. An inhibition

of the proliferation of tumour cells may be at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75% or more. Proliferation of cells may be assessed using known techniques. An decrease in cell viability of tumour cells or melanocytes may be a decrease of at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75% or more. Such decrease may be assessed 4 days after transfection with a given miRNA molecule, equivalent or source thereof. Cell viability may be assessed via known techniques such as the MTS assay.

Treatment of tumour or cancer can be the reduction of tumour volume or a decrease of tumour cell viability. Reduction of tumour volume can be assessed using a calliper. A decrease of tumour volume or cell viability or survival may be at least a decrease of at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. An induction of apoptosis in tumour cells or an induction of tumour cell death may be at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. Tumour cell viability or survival or death may be assessed using techniques known to the skilled person. Tumour cell viability and death may be assessed using routine imaging methods such as MRI, CT or PET, and derivatives thereof, or in biopsies. Tumour cell viability may be assessed by visualising the extension of the lesion at several time points. A decrease of 10%,15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more of the lesion observed at least once will be seen as a decrease of tumour cell viability.

An inhibition of the proliferation of tumour cells may be at least 1%, 5%, 10%, 15%, 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. Proliferation of cells may be assessed using known techniques as a standard proliferation assay. Such a proliferation assay may use of vital stains such as Cell Titer Blue (Promega). This includes a substrate molecule that is converted into a fluorescent molecule by metabolic enzymes. The level of fluorescence then reflects the number of living and metabolically active cells. Alternatively, such proliferation assay may determine the mitotic index. The mitotic index is based on the number of tumour cells under proliferation stage compared to the number of total tumour cells. The labelling of proliferative cells can be performed by using the antibody Ki-67 and immunohistochemistry staining. An inhibition of the proliferation of tumours cells may be seen when the mitotic index is reduced by at least 20%, at least 30%, at least 50% or more (as described in Kearsley J.H., et al, 1990, PMID: 2372483).

A delay in occurrence of metastases and/or of tumour cell migration may be a delay of at least one week, one month, several months, one year or longer. The presence of metastases may be assessed using MRI, CT or Echography or techniques allowing the detection of circulating tumour cells (CTC). Examples of the latter tests are CellSearch CTC test (Veridex), an EpCam-based magnetic sorting of CTCs from peripheral blood.

In certain embodiments, an inhibition or a decrease of a tumour weight or a delayed tumour growth or an inhibition of a tumour growth may be of at least 1%, 5%, 10%, 15%, 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. Tumour weight or volume tumour growth may be assessed using techniques known to the skilled person. The detection of tumour growth or the detection of the proliferation of tumour cells may be assessed in vivo by measuring changes in glucose utilization by positron emission tomography with the glucose analogue 2-[^{18}F]-fluor-2-deoxy-D-glucose (FDG-PET) or [^{18}F]-3'-fluoro-3'-deoxy-L-thymidine PET. An ex vivo alternative may be staining of a tumour biopsy with Ki67. An increase in the capacity of differentiation of tumour cells may be assessed using a specific differentiation marker and following the presence of such marker on cells treated. Preferred markers or

parameters are p16, Trp-1 and PLZF, c-Kit, MITF, Tyrosinase, and Melanin. This may be done using RT-PCR, western blotting or immunohistochemistry. An increase of the capacity of differentiation may be at least a detectable increase after at least one week of treatment using any of the identified techniques. Preferably, the increase is of 1%, 5%, 10%, 15%, 20%, 25%, or more, which means that the number of differentiated cells within a given sample will increase accordingly. In certain embodiments, tumour growth may be delayed at least one week, one month, two months or more. In a certain embodiment, an occurrence of metastases is delayed at least one week, two weeks, three weeks, four weeks, one months, two months, three months, four months, five months, six months or more.

In preferred embodiments, the PTEN-deficient tumour is a PTEN-deficient sarcoma, brain cancer, head and neck cancer, breast cancer, lung cancer, kidney cancer, liver cancer, colon cancer, ovarian cancer, melanoma, pancreatic cancer, thyroid cancer, hamartoma, tumour of the haematopoietic and lymphoid malignancy, or prostate cancer. In other more preferred embodiments, the PTEN-deficient tumour is a PTEN-deficient sarcoma, brain cancer, head and neck cancer, breast cancer, lung cancer, kidney cancer, liver cancer, colon cancer, ovarian cancer, pancreatic cancer, thyroid cancer, hamartoma, tumour of the haematopoietic and lymphoid malignancy, or prostate cancer. In other more preferred embodiments, the PTEN-deficient tumour is a PTEN-deficient sarcoma, brain cancer, head and neck cancer, ovarian cancer, thyroid cancer, or hamartoma. In other more preferred embodiments, the PTEN-deficient tumour is a PTEN-deficient lung cancer (preferably non small cell lung cancer), liver cancer (preferably hepatocellular carcinoma), breast cancer (preferably triple-negative breast cancer), and melanoma (preferably melanoma with an activating BRAF mutation). In other more preferred embodiments, the PTEN-deficient tumour is a PTEN-deficient lung cancer (preferably non small cell lung cancer), liver cancer (preferably hepatocellular carcinoma), or breast cancer (preferably triple-negative breast cancer).

Further examples of cancers that are suitable for treatment according to the invention include, but are not limited to, both primary and metastatic forms of head and neck, breast, lung, colon, ovary, and prostate cancers. Preferably the cancer is selected from: brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumour, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumour of bone, thyroid, lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, AML, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia, malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumour) and testicular cancer. Preferred hamartoma are Bannayan-Zonana

syndrome, Bannayan–Riley–Ruvalcaba syndrome, Proteus syndrome, Proteus-like syndrome, Cowden disease, PTEN hamartoma tumour syndrome (PHTS), and Lhermitte-Duclos disease.

Additionally, examples of a cancer to be treated (when PTEN-deficient) include Barret's adenocarcinoma; billiary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central nervous system tumours including primary CNS tumours such as glioblastomas, astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and secondary CNS tumours (i.e., metastases to the central nervous system of tumours originating outside of the central nervous system); colorectal cancer including large intestinal colon carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell carcinoma of the head and neck; hematologic cancers including leukemias and lymphomas such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma and erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma; prostate cancer; renal cancer; sarcoma; skin cancers including melanomas; and thyroid cancers.

In preferred embodiments the cancer is selected from the group consisting of: brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, colon cancer, head and neck cancer, kidney cancer, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma and thyroid cancer. In other preferred embodiments the cancer is selected from the group consisting of: ovarian, breast cancer, pancreatic cancer and prostate cancer. In other preferred embodiments the cancer is non-small cell lung carcinoma (NSCLC), small cell lung cancer (SCLC), bladder cancer or metastatic hormone-refractory prostate cancer. In other preferred embodiments the cancer is breast cancer, thyroid cancer, glioblastoma, endometrial cancer, prostate cancer, or melanoma. In other preferred embodiments the cancer is breast cancer, thyroid cancer, glioblastoma, endometrial cancer, or prostate cancer.

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant cancer such as sorafenib-resistant cancer.

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of carcinoma. More perferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant carcinoma such as sorafenib-resistant carcinoma.

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of hepatocellular carcinoma (HCC). More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant HCC such as hepatocellular carcinoma (HCC) that is resistant to receptor tyrosine kinase inhibitors such as VEGF receptor inhibitors, for example axitinib, cediranib, lenvatinib, nintedanib, pazopanib, regorafenib, semaxanib, sorafenib, sunitinib, tivozanib, toceranib, or vandetanib, preferably sorafenib.

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of non-small-cell lung carcinoma (NSCLC). More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant NSCLC such as NSCLC that is resistant to platinum-based cell-cycle nonspecific antineoplastic agents (for example carboplatin,

cisplatin, dicycloplatin, nedaplatin, oxaliplatin, or satraplatin, preferably cisplatin or carboplatin), or that is resistant to taxanes (for example cabazitaxel, docetaxel, larotaxel, ortataxel, paclitaxel, or tesetaxel, preferably paclitaxel or docetaxel, more preferably paclitaxel), or that is resistant to pyrimidine-based antimetabolites (for example fluorouracil, capecitabine, doxifluridine, tegafur, carmofur, floxuridine, cytarabine, gemcitabine, azacitidine, or decitabine, preferably gemcitabine), or that is resistant to vinca alkaloids (for example vinblastine, vincristine, vinflunine, vindesine, or vinorelbine, preferably vinorelbine), or that is resistant to folic acid antimetabolites (aminopterin, methotrexate, pemetrexed, pralatrexate, or raltitrexed, preferably pemetrexed).

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of triple-negative breast cancer (TNBC). More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant TNBC such as anthracyclin-resistant TNBC, for example TNBC resistant to aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, amrubicin, pirarubicin, valrubicin, or zorubicin, preferably to doxorubicin.

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of melanoma. More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant melanoma such as melanoma that is resistant to nonclassical cell-cycle nonspecific antineoplastic agents (for example procarbazine, dacarbazine, temozolomide, altretamine, mitobronitol, or pipobroman, preferably dacarbazine or temozolomide), or that is resitant to taxanes (for example cabazitaxel, docetaxel, larotaxel, ortataxel, paclitaxel, or tesetaxel, preferably paclitaxel such as albumin-bound paclitaxel), or that is resistant to platinum-based cell-cycle nonspecific antineoplastic agents (for example carboplatin, cisplatin, dicycloplatin, nedaplatin, oxaliplatin, or satraplatin, preferably cisplatin or carboplatin), or that is resistant to vinca alkaloids (for example vinblastine, vincristine, vinflunine, vindesine, or vinorelbine, preferably vinblastine). In other preferred embodiments, the miRNA for use according to the invention is not for use in the treatment of melanoma.

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of pancreas cancer. More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant pancreas cancer such as pancreas cancer that is resitant to taxanes (for example cabazitaxel, docetaxel, larotaxel, ortataxel, paclitaxel, or tesetaxel, preferably paclitaxel such as albumin-bound paclitaxel), or that is resistant to pyrimidine-based antimetabolites (for example fluorouracil, capecitabine, doxifluridine, tegafur, carmofur, floxuridine, cytarabine, gemcitabine, azacitidine, or decitabine, preferably fluorouracil or gemcitabine), or that is resistant to topoisomerase inhibitors (for example camptothecin, cositecan, belotecan, gimatecan, exatecan irinotecan, lurtotecan, silatecan, topotecan, rubitecan, preferably irinotecan).

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of colon cancer. More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant colon cancer such as colon cancer that is resistant to pyrimidine-based antimetabolites (for example fluorouracil, capecitabine, doxifluridine, tegafur, carmofur, floxuridine, cytarabine, gemcitabine, azacitidine, or decitabine, preferably fluorouracil or capecitabine), or that is resistant to topoisomerase inhibitors (for example camptothecin, cositecan, belotecan, gimatecan, exatecan irinotecan, lurtotecan, silatecan, topotecan, rubitecan, preferably irinotecan), or that is resistant to platinum-based cell-cycle nonspecific antineoplastic agents (for example carboplatin,

cisplatin, dicycloplatin, nedaplatin, oxaliplatin, or satraplatin, preferably oxaliplatin), or that is resistant to trifluridine or tipiracil, or a combination of trifluridine and tipiracil.

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of renal cell cancer (RCC). More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant RCC such as RCC that is resistant to receptor tyrosine kinase inhibitors such as VEGF receptor inhibitors, for example axitinib, cediranib, lenvatinib, nintedanib, pazopanib, regorafenib, semaxanib, sorafenib, sunitinib, tivozanib, toceranib, or vandetanib, preferably suntinib, sorafenib, or pazopanib, more preferably sorafenib.

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of head and neck cancer (HNSCC). More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant HNSCC such as HNSCC that is resistant to taxanes (for example cabazitaxel, docetaxel, larotaxel, ortataxel, paclitaxel, or tesetaxel, preferably paclitaxel or docetaxel), or that is resistant to pyrimidine-based antimetabolites (for example fluorouracil, capecitabine, doxifluridine, tegafur, carmofur, floxuridine, cytarabine, gemcitabine, azacitidine, or decitabine, preferably fluorouracil), or that is resistant to folic acid antimetabolites (aminopterin, methotrexate, pemetrexed, pralatrexate, or raltitrexed, preferably methotrexate), or that is resistant to platinum-based cell-cycle nonspecific antineoplastic agents (for example carboplatin, cisplatin, dicycloplatin, nedaplatin, oxaliplatin, or satraplatin, preferably cisplatin), or that is resistant to anthracyclins (for example aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, amrubicin, pirarubicin, valrubicin, or zorubicin, preferably doxorubicin), or that is resistant to intercalating crosslinking agents (for example actinomycin, bleomycin, mitomycins, plicamycin, preferably bleomycin or mitomycin).

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of prostate cancer. More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant prostate cancer such as prostate cancer that is resistant to taxanes (for example cabazitaxel, docetaxel, larotaxel, ortataxel, paclitaxel, or tesetaxel, preferably docetaxel), or that is resistant to anthracenediones (for example mitoxantrone or pixantrone, preferably mitoxantrone), or that is resistant to alkylating antineoplastic agents (for example estrogen-based alkylating antineoplastic agents such as alestramustine, atrimustine, cytestrol acetate, estradiol mustard, estramustine, estromustine, stilbostat; or phenestrol, preferably estramustine).

In preferred embodiments, the miRNA for use according to the invention is for use in the treatment of tumours of the haematopoietic and lymphoid malignancies. More preferably, the miRNA for use according to the invention is for use in the treatment of chemotherapy-resistant tumours of the haematopoietic and lymphoid malignancies such as myeloma that is resistant to bortezomib, or that is resistant to lenalidomide, or such as lymphoma that is resistant to CHOP or to rituximab, such as resistance to cyclophosphamide or to anthracyclines such as hydroxydaunorubicin or to oncovin or to prednisone, or such as leukemia resistant to vincristine, anthracyclines such as doxorubicine, L-asparaginase, cyclophosphamide, methotrexate, 6-mercaptopurine, chlorambucil, cyclophosphamide, corticosteroids such as prednisone or prednisolone, fludarabine, pentostatin, or cladribine. Treatment of chemotherapy-resistant cancer such as sorafenib-resitant cancer as described herein can be as second line treatment when chemotherapy such as sorafenib treatment has been found to be ineffective, or to be less effective than anticipated or desired.

Solid tumours are often epithelial in origin (i.e. carcinomas). A loss of epithelial cell markers (e.g. E-cadherin) and gain of mesenchymal cell markers (e.g. N-cadherin and Vimentin) is known for patient tumour samples, including prostate cancer. Cancer cells can dedifferentiate through this so-called Epithelial to Mesenchymal Transition (EMT). During EMT, intercellular cell junctions are broken down, thereby giving tumour cells the ability to migrate and invade into the surrounding tissue or through blood vessel walls. Such phenotypic changes play a major role in dissemination of the disease and ultimately lead to disease progression, which is often associated with poor prognosis for the patients.

Loss of E-cadherin expression is considered as a molecular hallmark of EMT. EMT in tumour cells results from a transcriptional reprogramming of the cell. In particular the transcriptional repression of the E-cadherin (CDH1) gene promoter has been shown to trigger the EMT phenotype. The E-cadherin protein is one of the most important cadherin molecules mediating cell-cell contacts in epithelial cells/tissues. CDH1 is repressed by binding of the transcriptional repressors, SNAI1, SNAI2, TCF3, TWIST, ZEB1, ZEB2 or KLF8, to three so-called E-boxes in the CDH1 proximal promoter region. Inhibiting the binding of these repressors to the CDH1 promoter can revert EMT, also called mesenchymal to epithelial transition (MET), and inhibits tumour cell invasion and tumour progression.

In preferred embodiments, the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of a disease or a condition associated with EMT, when such a disease or condition is associated with PTEN-deficiency. Herein the miRNA is preferably combined with a miRNA-518b molecule, miRNA-520f molecule, or a miRNA-524 molecule; or an isomiR or mimic thereof, or a precursor thereof. The disease or condition associated with EMT is preferably a cancer, more preferably a bladder or prostate cancer. This use is preferably by inducing a mesenchymal to epithelial transition.

In preferred embodiments, the composition for use according to the invention (compositions for use according to the invention are defined later herein) or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by downregulating the immunosuppressive tumour microenvironment. In related preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by preventing or reducing evasion of host immunity by a tumour. Such use is preferably for preventing, inhibiting, or reducing adenosine generation, for example by inhibiting or reducing activity of cell surface ectoenzymes such as those that dephosphorylate ATP to produce adenosine. Such use is more preferably for reducing NT5E expression and/or reducing ENTPD1 expression and/or inhibiting adenosine generation. More preferably, the composition for use according to the invention or the miRNA for use according to the invention is for reducing NT5E expression. More preferably, this composition for use according to the invention or this miRNA for use according to the invention is for reducing ENTPD1 expression. More preferably, this composition for use according to the invention or this miRNA for use according to the invention is for inhibiting adenosine generation. In even more preferred embodiments, this composition for use according to the invention or this miRNA for use according to the invention is for reducing cancer cell migration, preferably for reducing adenosine-induced cancer cell migration, most preferably for reducing adenosine-induced cancer cell migration associated with NT5E expression. Reduction of NT5E or ENTPD1 expression is preferably assessed by

luciferase assay or by RT-PCR. Reduction of cancer cell migration is preferably assessed by in vitro transwell assays.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by promoting or increasing G2/M arrest in cancer cells, preferably in liver cancer cells, in lung cancer cells, in pancreatic cancer cells, in carcinoma cells, or in melanoma cells, more preferably in liver cancer cells, in carcinoma cells, or in melanoma cells, even more preferably in hepatocellular carcinoma cells or in melanoma cells. Such use is preferably for reducing the expression or activity of factors that regulate cell division and/or proliferation by associating with the cytoskeleton, such as MPP2 and/or STMN1. Such use is preferably for promoting or increasing factors that bind and/or sequester cyclin-dependent kinases, such as YWHAZ and/or CCNA2. Preferably, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by reducing the expression or activity of at least one of MPP2, STMN1, YWHAZ, and CCNA2, more preferably by reducing the expression or activity of at least YWHAZ or STMN1, even more preferably of at least YWHAZ, most preferably of each of MPP2, STMN1, YWHAZ, and CCNA2. Increase in G2/M arrest is preferably an increase as compared to untreated cells, and is preferably an increase of at least 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50% or more. It is preferably assessed by DNA staining followed by microscopy imaging to determine nucleus intensity based on DNA content. Reduction of the expression or activity of at least one of MPP2, STMN1, YWHAZ, and CCNA2 is preferably assessed using RT-PCR.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by decreasing or reducing cancer cell migration, cancer cell adhesion, or cancer cell proliferation, or by increasing or promoting cancer cell apoptosis. These cancer cells are preferably lung cancer cells, liver cancer cells, breast cancer cells, melanoma cells, or carcinoma cells, more preferably lung cancer cells, liver cancer cells, breast cancer cells, or melanoma cells, even more preferably lung cancer cells such as A549 and H460, liver cancer cells such as Hep3B and Huh7, breast cancer cells such as BT549, and skin cancer cells such as A2058. In more preferred embodiments this use in treatment, prevention, delay, or amelioration of cancer is by decreasing expression or activity of at least one gene selected from the group consisting of FOXRED2, ERMP1, NT5E, SHMT2, HYOU1, TWISTNB, AP2M1, CLSTN1, TNFRSF21, DAZAP2, C1QBP, STARD7, ATP5SL, DCAF7, DHCR24, DPY19L1, AGPAT1, SLC30A7, AIMP2, UBP1, RUSC1, DCTN5, ATP5F1, CCDC28A, SLC35D2, WSB2, SEC61A1, MPP2, FAM60A, PITPNB, and POLE3, even more preferably from the group consisting of NT5E and TNFRSF21; preferably the use as described above for apoptosis, cell migration, adhesion, and proliferation is use for apoptosis, cell migration, adhesion, and/or proliferation associated with at least one of these genes. Expression is preferably assessed by RT-PCR.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by increasing or promoting apoptosis of cancer cells, preferably by increasing or promoting apoptosis associated with at least one gene selected from the group consisting of KCNMA1, NOTCH2, TNFRSF21, YWHAZ, CADM1, NOTCH1, CRYAA, ETS1, AIMP2, SQSTM1, ZMAT3, TGM2, CECR2, PDE3A, STRADB, NIPA1, MAPK8, TP53INP1, PRNP, PRT1, GCH1, DHCR24, TGFB2, NET1, PHLDA2, and TPP1, more

preferably from the group consisting of NOTCH2, TNFRSF21, YWHAZ, ETS1, TGFB2, and MAPK8. Expression or activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by decreasing or inhibiting angiogenesis, preferably angiogenesis associated with cancer cells, more preferably by decreasing or inhibiting angiogenesis associated with at least one gene selected from the group consisting of CRKL, CTGF, ZMIZ1, TGM2, ELK3, LOX, UBP1, PLAU, CYR61, and TGFB2, even more preferably CRKL, TGFB2 or PLAU, most preferably PLAU. Expression or activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by modulating the unfolded protein response in cancer cells, more preferably by modulating the unfolded protein response associated with at least one gene selected from the group consisting of ERMP1, NCEH1, SEC31A, CLSTN1, FOXRED2, SEPN1, EXTL2, HYOU1, SLC35D1, SULF2, PTPLB, HHAT, ERAP2, FAF2, DPM3, PDZD2, SEC61A1, DHCR24, IDS, MOSPD2, DPM, PRNP, and AGPAT1. Expression or activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention. Modulation of the unfolded protein response is preferably an inhibition or reduction of the unfolded protein response.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by decreasing or inhibiting chemotaxis of cancer cells, more preferably by decreasing or inhibiting chemotaxis associated with at least one gene selected from the group consisting of CXCL1, RAC2, CXCL5, CYR61, PLAUR, KCNMA1, ABI2, and HPRT1, most preferably PLAUR. Expression or activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by decreasing or inhibiting protein transport in cancer cells, more preferably by decreasing or inhibiting protein transport associated with at least one gene selected from the group consisting of STON2, RAB11FIP5, SRP54, YWHAZ, SYNRG, GCH1, THBS4, SRP54, TOMM20, SEC31A, TPP1, SLC30A7, TGFB2, AKAP12, AP2M1, ITGB3, GNAI3, SORL1, KRAS, SLC15A1, SEC61A1, APPL1, LRP4, PLEKHA8, STRADB, SCAMP4, HFE, CADM1, ZMAT3, ARF3, VAMP8, NUP50, DHCR24, RAB11FIP5, ATP6V1B2, SQSTM1, and WNK4, even more preferably YWHAZ, TGFB2, or KRAS, most preferably YWHAZ. Expression or activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by decreasing or inhibiting nucleoside metabolism in cancer cells, more preferably by decreasing or inhibiting nucleoside metabolism associated with at least one gene selected from the group consisting of NUDT3, NUDT15, NUDT21, DERA, NT5E, GCH1, and HPRT1, most preferably NT5E. Expression or

activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by decreasing or inhibiting glycosylation of cancer cells, more preferably by decreasing or inhibiting glycosylation associated with at least one gene selected from the group consisting of SLC35D1, ST3GAL5, SULF2, LAT2, GALNT1, NCEH1, ST3GAL4, CHST14, B3GNT3, DPM3, GALNT13, DHCR24, NUDT15, IDH2, PPTC7, HPRT1, EXTL2, SEC61A1, ERAP2, and GALNT14. Expression or activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by decreasing or inhibiting oncogenesis, more preferably by decreasing or inhibiting oncogenesis associated with at least one gene selected from the group consisting of CCND1, CBL, CXCL1, CRKL, MAX, KCNMA1, TBL1XR1, GNAI3, YWHAZ, RAC2, ETS1, PTCH1, MAPK8, LAMC2, PIK3R1, CDK6, CBL, APPL1, GNAI3, PDE3A, TGFB2, ABI2, MAX, ITGB3, LOX, CXCL5, ARPC5, PPARGC1A, and THBS4, even more preferably selected from CRKL, TGFB2, YWHAZ, ETS1, MAPK8, and CDK6, most preferably from YWHAZ, ETS1, MAPK8, and CDK6. Expression or activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by decreasing or inhibiting dysfunctional wound healing, more preferably by decreasing or inhibiting dysfunctional wound healing associated with at least one gene selected from the group consisting of NOTCH2, KCNMA1, CXCL1, ITGB3, PLAU, CCND1, ZMIZ1, ELK3, YWHAZ, IL11, PLAUR, LOX, CTGF, and TGFB2, even more preferably selected from TGFB2, NOTCH2, PLAU, YWHAZ, and PLAUR, most preferably from NOTCH2, PLAU, YWHAZ, and optionally PLAUR. Expression or activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer by increasing or promoting immune activation, preferably immune activation associated with an immune response against cancer, more preferably by increasing or promoting immune activation associated with at least one gene selected from the group consisting of NOTCH2, LAT2, CRKL, LRRC8A, YWHAZ, PIK3R1, IRF1, TGFB2, IL11, UNG, CDK6, and HPRT1, even more preferably selected from CRKL, TGFB2, NOTCH2, YWHAZ, and CDK6, most preferably from NOTCH2, YWHAZ, and CDK6. Expression or activity of the gene is preferably reduced by the composition for use according to the invention or by the miRNA for use according to the invention.

The invention also provides a T-cell obtained from a subject treated with a miRNA for use according to the invention or with a composition for use according to the invention. Such a T-cell can be for use in the treatment of cancer as described elsewhere herein. In its use, the T-cell is preferably previously obtained from a subject treated with a miRNA for use according to the invention or with a composition for use according to the invention. The T-cell is preferably from a human subject. It is preferably for use as a vaccine, or for preventing recurrence or metastasis of cancer.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of a cancer associated with at least one gene selected from the group consisting of CDK6, EIF4B, ETS1, IL17RD, MCL1, MAPK8, NOTCH2, NT5E, PLAU, PLAUR, TNFRSF21, and YWHAZ, more preferably selected from NOTCH2, NT5E, PLAU, PLAUR, and YWHAZ.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of a cancer associated with at least one gene selected from the group consisting of CDK4, CDK6, CRKL, NT5E, HMGB1, IL17RD, KRAS, KIT, HDAC3, RTK2, TGFB2, TNFRSF21, PLAU, NOTCH1, NOTCH2, and YAP1. These genes have known involvement in anti-tumour immunity.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of a cancer associated with at least one gene selected from the group consisting of ETS1, YWHAZ, MPP2, PLAU, CDK4, CDK6, EIF4B, RAD51, CCNA2, STMN1, and DCAF7. These genes are involved in regulation of the cell cycle.

In preferred embodiments, the composition for use according to the invention or the miRNA for use according to the invention is for use in treatment, prevention, delay, or amelioration of cancer, wherein a preferred cancer is a cancer selected from the group consisting of colon cancer such as colon carcinoma, lung cancer such as lung carcinoma, melanoma, lymphoma such as reticulum cell sarcoma, pancreas cancer such as pancreatic adenocarcinoma, liver cancer such as hepatocarcinoma or hepatoma, breast cancer such as breast carcinoma, prostate cancer, kidney cancer such as renal adenocarcinoma, carcinoma such as adenocarcinoma or colon, lung, liver, pancreas, kidney, or breast carcinoma, and adenocarcinoma such as pancreatic or renal adenocarcinoma. A more preferred cancer is a cancer selected from the group consisting of colon cancer such as colon carcinoma, lung cancer such as lung carcinoma, melanoma, lymphoma such as reticulum cell sarcoma, pancreas cancer such as pancreatic adenocarcinoma, liver cancer such as hepatocarcinoma, breast cancer such as breast carcinoma, prostate cancer, carcinoma such as adenocarcinoma or colon, lung, liver, pancreas, or breast carcinoma, and adenocarcinoma such as pancreatic adenocarcinoma. An even more preferred cancer is a cancer selected from the group consisting of colon cancer such as colon carcinoma, lung cancer such as lung carcinoma, melanoma, lymphoma such as reticulum cell sarcoma, and carcinoma such as colon or lung carcinoma.

In further preferred embodiments, the miRNA for use according to the invention is for use in the treatment of cancer wherein the composition is combined with a further chemotherapeutic agent such as sorafenib. This is referred to hereinafter as a combination according to the invention. A combination according to the invention is preferably for use as described above for the composition for use according to the invention.

A combination according to the invention is a combination comprising a composition for use according to the invention or the miRNA for use according to the invention and comprising a chemotherapeutic agent such as a kinase inhibitor drug suitable for the treatment of cancer, for example such as a combination comprising a composition for use according to the invention and comprising

sorafenib, or for example comprising a miRNA for use according to the invention and comprising sorafenib.

Suitable chemotherapeutic agents are kinase inhibitor drugs such as sorafenib or B-raf inhibitors or MEK inhibitors or RNR inhibitors or AURKB inhibitors. A preferred B-raf inhibitor is vemurafenib and/or dabrafenib. A preferred MEK inhibitor is trametinib and/or selumetinib. A preferred RNR inhibitor is selected from the group consisting of gemcitabine, hydroxyurea, clolar clofarabine and triapine

B-raf inhibitors are compounds that specifically inhibit the B-raf protein, for which a mutated form of the BRAF gene encodes. Several mutations of the BRAF gene are known to cause melanoma, and specific compounds have been developed which inhibit the mutated form of the B-raf protein. B-raf inhibitors are known in the art and include, but are not limited to vemurafenib, dabrafenib, trametinib, GDC-0879, PLX-4720, sorafenib, SB590885, PLX4720, XL281 and RAF265. B-raf inhibitors are e.g. described in Wong K.K., et al. One B-raf inhibitor may be used or together with other B-raf inhibitors in a combination according to the invention. Preferred B-raf inhibitors to be used in the present invention are vemurafenib, dabrafenib or a mixture of vemurafenib and dabrafenib. Vemurafenib is also known as RG7204 or N-(3-{[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl}-2,4-difluorophenyl)propane-1-sulfonamide, and marketed as Zelboraf. Dabrafenib is also known as N-{3-[5-(2-aminopyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide.

MEK inhibitors are compounds that specifically inhibit a MEK protein. Several MEK inhibitors are known in the art and include, but are not limited to trametinib (GSK1120212), selumetinib (AZD-6244), XL518, CI-1040, PD035901. Trametinib is also known as N-(3-(3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl)acetamide. Selumetinib is also known as: 6-(4-bromo-2-chlorophenylamino)-7-fluoro-N-(2-hydroxyethoxy)-3-methyl-3Hbenzo[d]imidazole-5-carboxamide. MEK inhibitors are e.g. described in Wong, K.K. (PMID: 19149686). One MEK inhibitor may be used or together with other MEK inhibitors in a combination according to the invention. Several MEK inhibitors is synonymous with several distinct MEK inhibitors. Prefered MEK inhibitors to be used in the present invention are trametinib and/or selumetinib.

RNR and/or AURKB inhibitors are compounds that specifically inhibit RNR and/or AURKB proteins. RNR is a ribonucleotide reductase (RNR) and as such is the only enzyme responsible for the de novo conversion of ribonucleoside diphosphate (NDP) to deoxyribonucleoside diphosphate (dNDP) (Zhou et al. 2013). RNR is the key regulator of intracellular dNTP supply. Maintenance of a balanced dNTP pool is a fundamental cellular function because the consequences of imbalance in the substrates for DNA synthesis and repair include mutagenesis and cell death. Human RNR is composed of a subunits (RRM1) that contain the catalytic site and two binding sites for enzyme regulators and b subunits (RRM2) with a binuclear iron cofactor that generates the stable tyrosyl radical necessary for catalysis. An inhibitor of RNR may inhibit RRM1 and/or RRM2. Preferred RNR inhibitors are selected from the group consisting of gemcitabine, hydroxyurea, clolar clofarabine and triapine.

AURKB (Aurora B kinase) is a protein that functions in the attachment of the mitotic spindle to the centromere. Chromosomal segregation during mitosis as well as meiosis is regulated by kinases and phosphatases. The Aurora kinases associate with microtubules during chromosome movement and

segregation. In cancerous cells, over-expression of these enzymes causes unequal distribution of genetic information, creating aneuploid cells, a hallmark of cancer.

A chemotherapeutic agent is a drug that is able to induce or promote an anti-cancer effect as defined herein. A preferred chemotherapeutic agent is a kinase inhibitor or an RNR inhibitor or an AURKB inhibitor. Examples of such inhibitors are compounds that specifically inhibit the RNR and/or the AURKB proteins. To evaluate the ability of a therapeutic compound to inhibit RNR and/or AURKB proteins, one can perform western blotting with RNR (RRM1 and/or RRM2) or AURKB protein as read-out. Cells are plated in 6-well plates and treated for 72 hours at 0.01, 0.1 and 1 μM of said compound. After treatment cells are scraped into a lysis buffer as a RIPA lysis buffer. Equal amounts of protein extracts are separated by using 10% SDS PAGE, and then transferred to a polyvinylidene difluoride membrane. After blocking for 1 hour in a Tris-buffered saline containing 0.1% Tween 20 and 5% nonfat milk, the membrane is probed with a RNR (i.e. RRM1 and/or RRM2) and/or a AURKB primary antibody, followed by a secondary antibody conjugated to horseradish peroxidase for chemiluminescent detection on film. Tubulin is used as loading control. A preferred RRM2 antibody used is from Santa Cruz (product# sc-10846) and/or a preferred AURKB antibody is from Cell Signalling (product# 3094). The evaluation of the therapeutic ability of said RNR and/or AURKB inhibitor may also be assessed at the RNA level by carrying out a Nothern blot or by PCR.

Preferred combinations according to the invention comprise:

i) a composition for use according to the invention or a miRNA for use according to the invention, and

ii) at least one chemotherapeutic agent selected from the group consisting of

a. receptor tyrosine kinase inhibitors such as VEGF receptor inhibitors, for example axitinib, cediranib, lenvatinib, nintedanib, pazopanib, regorafenib, semaxanib, sorafenib, sunitinib, tivozanib, toceranib, or vandetanib, preferably suntinib, sorafenib, or pazopanib, more preferably sorafenib;

b. platinum-based cell-cycle nonspecific antineoplastic agents, for example carboplatin, cisplatin, dicycloplatin, nedaplatin, oxaliplatin, or satraplatin, preferably cisplatin or carboplatin or oxaliplatin;

c. taxanes, for example cabazitaxel, docetaxel, larotaxel, ortataxel, paclitaxel, or tesetaxel, preferably paclitaxel or docetaxel, more preferably paclitaxel or docetaxel;

d. pyrimidine-based antimetabolites, for example fluorouracil, capecitabine, doxifluridine, tegafur, carmofur, floxuridine, cytarabine, gemcitabine, azacitidine, or decitabine, preferably fluorouracil or gemcitabine or capecitabine;

e. vinca alkaloids, for example vinblastine, vincristine, vinflunine, vindesine, or vinorelbine, preferably vinorelbine or vinblastine;

f. folic acid antimetabolites, aminopterin, methotrexate, pemetrexed, pralatrexate, or raltitrexed, preferably pemetrexed or methotrexate;

g. anthracyclins, for example aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, amrubicin, pirarubicin, valrubicin, or zorubicin, preferably to doxorubicin;

h. nonclassical cell-cycle nonspecific antineoplastic agents, for example procarbazine, dacarbazine, temozolomide, altretamine, mitobronitol, or pipobroman, preferably dacarbazine or temozolomide;

i. taxanes, for example cabazitaxel, docetaxel, larotaxel, ortataxel, paclitaxel, or tesetaxel, preferably paclitaxel such as albumin-bound paclitaxel;
j. topoisomerase inhibitors, for example camptothecin, cositecan, belotecan, gimatecan, exatecan irinotecan, lurtotecan, silatecan, topotecan, rubitecan, preferably irinotecan;
k. trifluridine or tipiracil, or a combination of trifluridine and tipiracil;
l. intercalating crosslinking agents, for example actinomycin, bleomycin, mitomycins, plicamycin, preferably bleomycin or mitomycin;
m. anthracenediones, for example mitoxantrone or pixantrone, preferably mitoxantrone; and
n. alkylating antineoplastic agents, for example estrogen-based alkylating antineoplastic agents such as alestramustine, atrimustine, cytestrol acetate, estradiol mustard, estramustine, estromustine, stilbostat; or phenestrol, preferably estramustine.

In preferred embodiments, a composition for use according to the invention or a miRNA for use according to the invention is for use in the treatment of cancer, wherein the composition increases the immune response to cancer cells. This may mean that it initiates an immune response in cases where no immune response was present.

In more preferred embodiments for increasing immune response, the composition for use according to the invention or a miRNA for use according to the invention is for increasing the production of immune system activating cytokines, such as IL-2. Preferably, cytokine production is increased by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more, and is preferably detected through FACS. Immune system activating cytokines are increased in a 4T1 mouse model for triple negative breast cancer (TNBC) after one week of treatment. The increase in cytokines leads to increased immune suppression of cancers, and can lead to immune suppression or partial immune suppression of cancers that would otherwise not be susceptible to immune suppression. In preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for increasing T-cell function, such as increasing production of IFNγ and IL-2.

In more preferred embodiments for increasing immune response, the composition for use according to the invention or a miRNA for use according to the invention is for decreasing regulatory T cell population. Regulatory T cells (Tregs) are immunosuppressive T regulatory cells, and decreasing Tregs increases the immune response to a cancer. Preferably, Tregs are decreased by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. Decrease of Tregs can be determined via the determination of FOXP3 or LAG3. This effect is preferably in parallel with increased cytokine production as described above.

Recruitment of CD8+ T effector cells is increased in a 4T1 mouse model for triple negative breast cancer (TNBC) after two weeks of treatment, and T-cell function is induced, while Treg population is decreased. Accordingly, in preferred embodiments for increasing immune response, the composition for use according to the invention or a miRNA for use according to the invention is for increasing T-cell frequency. Preferably, such an increase is by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. Such an increase can be determined by measuring CD8. In preferred embodiments for increasing immune response, the composition for use according to the invention or a miRNA for use according to the invention is for inducing T-cell function, preferably for inducing T-cell function by inducing IFNγ production. Most preferably, the composition for use according to the invention

or a miRNA for use according to the invention is for increasing T-cell frequency and simultaneously inducing T-cell function, preferably while simultaneously decreasing regulatory T cell population. Tumours with decreased Tregs and with increased CD8+ T effector cells are referred to as 'hot' tumours, which are tumours that do not have an immunosuppressed microenvironment. Conversely, tumours in an immunosuppressed microenvironment are referred to as 'cold' tumours.

Additionally, compositions according to the invention can reduce expression of immune suppressive target genes such as ENTPD1 (CD39) or TIM-3. Such a reduction is preferably by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. TIM-3 or ENTPD1 expression can be determined via qPCR. ENTPD1 is an ectonucleotidase that catalyses the hydrolysis of γ- and β-phosphate residues of triphospho- and diphosphonucleosides to the monophosphonucleoside derivative. It has an immune suppressive role through its generation of high amounts of adenosine. Reduction of ENTPD1 expression increases the immune response to tumour cells. TIM-3 is also known as hepatitis A virus cellular receptor 2 (HAVCR2), and is an immune checkpoint, an inhibitory receptor acting as an immune-suppressive marker. TIM-3 is mainly expressed on activated CD8+ T cells and suppresses macrophage activation. Reduction of TIM-3 expression increases the immune response to tumour cells. In preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for reducing expression of ENTPD1 or of TIM-3 or for reducing expression of ENTPD1 and TIM-3.

The positive effect of compositions according to the invention and miRNA for use according to the invention on the immune system as it relates to tumour cells and cancer cells leads to the invention being suitable for preventing the growth of new tumours, preventing metastasis, or reducing the growth of tumours that have been removed in size, for example through surgery. For example treatment with a composition for use according to the invention reduces the regrowth of surgically excised tumours, and reduces metastasis of such tumours, increasing survival in affected subjects. A tumour from which metastases derive is referred to as a primary tumour. Moreover, subjects with a particular tumour type that had been treated with a composition for use according to the invention or with a miRNA for use according to the invention show limited tumour take when re-challenged with new tumour cells of the same type that had already been treated. After the limited tumour take, the tumour fully regresses. When challenged with a different tumour type, the tumour fully takes, but also subsequently regresses entirely.

Accordingly, in preferred embodiments the compositions according to the invention and miRNA for use according to the invention are for use as a medicament for preventing, reducing, or delaying cancer or metastatic cancer. In this context, preferred cancers are breast cancer, carcinoma, and liver cancer, more preferably breast cancer and liver cancer.

Accordingly, in preferred embodiments the compositions according to the invention and miRNA for use according to the invention are for use as a cancer vaccine, preferably for use as a cancer vaccine for the prevention or treatment of cancer. Such vaccines are preferably for preventing or reducing regrowth or recurrence of primary tumours. Preferably, regrowth is reduced by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. In another use, such vaccines are preferably for reducing or treating metastatic cancer. Preferably, metastatic cancer is reduced by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more, or motility of cancer cells is reduced by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or

more. In this context, preferred cancers are breast cancer, carcinoma, and liver cancer, more preferably breast cancer and liver cancer.

Accordingly, in preferred embodiments the compositions according to the invention and miRNA for use according to the invention are for use as a medicament, wherein the medicament is for the prevention, reduction, or treatment of metastatic cancer, preferably wherein the primary tumour has been surgically excised or has regressed, more preferably wherein the primary tumour has been surgically excised. Preferably, metastatic cancer is reduced by by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. In this context, preferred cancers are breast cancer, carcinoma, and liver cancer, more preferably breast cancer and liver cancer.

Accordingly, in preferred embodiments the compositions according to the invention and miRNA for use according to the invention are for use as a medicament, wherein the medicament is for the prevention, reduction, or treatment of regrowth or recurrence of a cancer after surgical excision. Preferably, regrowth or recurrence is reduced by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. In this context, preferred cancers are breast cancer, carcinoma, and liver cancer, more preferably breast cancer and liver cancer.

Accordingly, in preferred embodiments the compositions according to the invention and miRNA for use according to the invention are for use as a medicament, wherein the medicament is for the prevention, reduction, or treatment of regrowth or recurrence of a cancer after said cancer has regressed or has been successfully treated. Preferably, regrowth or recurrence is reduced by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. In this context, preferred cancers are breast cancer, carcinoma, and liver cancer, more preferably breast cancer and liver cancer.

In preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for inhibiting proliferation of tumour cells. Compositions according to the invention can reduce K-RAS and MCL1 expression, leading to a reduced proliferation of tumour cells. K-RAS, also known as KRAS, K-ras, Ki-ras, is a proto-oncogene known in the art. MCL1 is also known as induced myeloid leukaemia cell differentiation protein Mcl-1. It can enhance cancer cell survival by inhibiting apoptosis. Both K-RAS and MCL1 enhance proliferation of cancer cells. In preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for reducing expression of K-RAS or of MCL1 or for reducing expression of K-RAS and MCL1. In preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for reducing expression of K-RAS and MCL1 and ENTPD1 and TIM-3.

Inhibition of proliferation is preferably via induction of apoptosis. Compositions according to the invention induce apoptosis in cancer cells through caspase activation and PARP inactivation through PARP cleavage. Preferred caspase activation is activation of caspase 3/7. PARP is also known as poly (ADP-ribose) polymerase and refers to a family of proteins involved in programmed cell death. It is cleaved in vivo by caspase 3 and by caspase 7, which triggers apoptosis. Cleavage of PARP can be determined through blotting techniques, and caspase activation can be assayed by determining PARP cleavage through blotting, or by qPCR. In preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for inducing apoptosis in cancer cells. In preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for activating caspase 3 and caspase 7. In preferred embodiments, the composition

for use according to the invention or a miRNA for use according to the invention is for inactivating PARP. Preferably, PARP is inactivated by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. Inactivation of PARP can be monitored by blotting techniques, detecting the smaller fragments of the uncleaved enzyme. Preferably, caspase activity is increased by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more.

In further preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for reducing expression of at least one of the genes selected from the group consisting of K-RAS, MCL1, ENTPD1, TIM-3, c-Kit, CyclinD1, and CD73. c-Kit is a proto-oncogene also known as tyrosine-protein kinase Kit or CD117, and codes for a receptor tyrosine kinase protein. Cyclin D1 overexpression correlates with early cancer onset and tumour progression. CD73 is also known as 5'-nucleotidase (5'-NT), and as ecto-5'-nucleotidase. The enzyme encoded by CD73 is ecto-5-prime-nucleotidase (5-prime-ribonucleotide phosphohydrolase; EC 3.1.3.5) and catalyzes the conversion at neutral pH of purine 5-prime mononucleotides to nucleosides, the preferred substrate being AMP. Expression of such genes is preferably reduced by 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more, which can for example be determined via qPCR techniques.

In preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for regulating the adenosine A2A receptor pathway. The adenosine A2A receptor, also known as ADORA2A, is an adenosine receptor that can suppress immune cells. The activity of compositions according to the invention in reducing expression of CD73 and/or of ENTPD1, as described above, interferes with the A2A receptor pathway, reducing immune suppression. This leads to an anti-tumour effect because tumour cells ability to escape immune surveillance is reduced. In preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for increasing the susceptibility of tumour cells to immune surveillance. Such an increase preferably leads to a reduction of tumour volume of 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more. In more preferred embodiments, the composition for use according to the invention or a miRNA for use according to the invention is for increasing the susceptibility of tumour cells to immune surveillance, while increasing recruitment of CD8+ T effector cells, preferably while decreasing Tregs, such as through reducing expression of LAG3 or of FoxP3, or of both. Increased susceptibility to immune surveillance preferably leads to reduced tumour volume.

The inventors have found that miRNA-193a modulates several pathways and genes. This activity of miRNA-193a can be used for treating conditions associated with those pathways or genes. Accordingly, in preferred embodiments is provided the miRNA-193a or a source thereof for use according to the invention, wherein the miRNA-193a modulates expression of a gene selected from the group consisting of RPS6KB2, KRAS, PDGFRB, SOS2, TGFBR3, CASP9, INPPL1, PIK3R1, PTK2, CBL, PDPK1, CCND1, BCAR1, MAGI3, MDM2, YWHAZ, and MCL1, preferably from the group consisting of RPS6KB2, KRAS, PDGFRB, CASP9, INPPL1, PIK3R1, PTK2, CBL, PDPK1, CCND1, BCAR1, MAGI3, MDM2, YWHAZ, MCL1, more preferably selected from PDPK1 or INPPL1. This modulation is preferably downregulation. In preferred embodiments PDPK1 is modulated, preferably downregulated by the miRNA. In preferred embodiments INPPL1 is modulated, preferably downregulated by the miRNA.

Modulation is defined elsewhere herein. Upregulation refers to an increased expression, which can refer to an increased transcription, production of mRNA, translation, production of gene product, and/or activity of gene product. Downregulation refers to a decreased expression, can refer to a decreased transcription, production of mRNA, translation, production of gene product, and/or activity of gene product. Preferably, upregulation and downregulation refer to transcription of production of mRNA. In other preferred embodiments upregulation and downregulation refer to activity of gene product. Upregulation and downregulation are preferably as compared to a reference, such as to a healthy cell, or such as to an untreated cell, when cultivated under otherwise identical conditions. For example, when miRNA-193a is used for downregulation of INPPL1 in a cell, then miRNA-193a preferably decreases INPPL1 expression in that cell as compared to a cell (of the same type) that has not been contacted with miRNA-193a. The change in expression is preferably at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, 100, 125, 150, 200, 250% or more, more preferably at least 50% or more, even more preferably at least 100% or more. In case of downregulation, optionally there is no longer any detectable expression after downregulation.

The invention provides a miRNA-193a molecule, isomiR, mimic, or source thereof as described herein, or a miRNA-193a for use in treating a condition associated with PTEN-deficiency such as for use as a PTEN agonist, wherein the miRNA-193a molecule, isomiR, mimic, or source thereof is for upregulation of a gene selected from the group consisting of STAT3, TMEM2, PEG10, GCC2, RFX5, CPEB2, UNKL, RNF44, PGM2L1, NACC2, TDG, IFT81, CAMK2N1, BDNF, KANK1, CPS1, HDHD1, THBD, SEMA4G, SAMD4A, RP11-438N16.1, C2orf69, TPRG1L, CHIC1, HOXC13, DYRK1B, RASA2, CELSR3, ADM, KLHDC3, ABCC5, PNKD, MOK, PBXIP1, NUAK2, CLDN2, PHLPP2, CPOX, ZNF76, MBLAC2, VTN, CDH1, RMND5A, SCML1, LMBR1L, TGFBR2, ENTPD7, LZTFL1, C7orf60, ZNF558, CTNNBIP1, SNN, IFT140, RALGAPA1, WIPI1, C8orf58, PDCD4, RPL26, HOXA10, RP11-443N24.1, EIF4EBP2, RECK, ZNF614, HBP1, PRICKLE4, WDR25, DNMT3B, GNAZ, PER2, LMLN, SARM1, C17orf97, AC011841.1, CCNG1, ANKRD46, SYNGR3, TPPP3, KIAA0513, UBE2Q2P6, FAM227A, NEK11, KLHDC7A, ARID3A, CROT, PER1, F3, FAM217B, AK7, FRAT2, FOS, STX1B, APH1B, FER1L4, SAMD15, C3orf67, SKIDA1, SESN3, CTD-2366F13.1, SESN1, PADI1, C9orf9, ZBTB3, CCAT1, LATS2, RP11-553L6.5, JHDM1D-AS1, ZNF438, CEBPD, CTB-171A8.1, TEF, CYP1A1, LIN28B, DPY19L1P1, ZNF138, LINC00886, KLF9, LRRIQ1, LRRC46, C5orf55, YOD1, RP11-339B21.14, RP11-504P24.8, ZNF77, GABPB1, SLC25A42, NPR1, LIPT1, TMEM91, ROPN1L, VIL1, TJP3, SDCBP2-AS1, CLEC2B, RPS6KL1, LRRC6, DFNB59, USH1G, GPR157, C7orf63, CTD-3065J16.9, MIR210HG, ADRB1, GXYLT2, SLC2A3, WDR65, TSNAXIP1, ATP2A1, PHYHIP, OSCP1, C12orf55, RP11-706O15.7, RGS9BP, MSH5, RP11-498C9.12, LRRC29, MPZL3, TTC40, RP11-195F19.9, R3HDML, 43347, SNORA5C, RP11-214N9.1, COL6A3, MAOB, RP11-86H7.7, KCNJ16, DHRS9, ALOX5AP, ISM2, LYPD3, NPHS1, DBNDD2, GLT8D2, SELPLG, RP11-263K19.6, RP13-131K19.2, SERPINA5, TCP10L, AC018816.3, RP11-318A15.2, ZMYND10, RP11-576C2.1, GPR132, CTD-2292M16.8, HOXD11, CDH16, CCDC148, ZNF404, ZMIZ1-AS1, RP13-631K18.3, FAR2P1, C10orf107, RP1-121G13.3, RP5-1157M23.2, C2orf62, CSPG4P8, RP11-108K14.4, EEF1DP2, RP11-12A20.7, PSG1, ARMC12, CDH8, RP11-309L24.9, ALS2CR12, POU5F1P3, DNM1P35, TAF7L, RAPSN, RFPL3S, RNF223, AURKC, TRBV20OR9-2, C6orf165, RP11-699L21.1, CXorf58, DNAAF1, RP11-167N4.2, XAGE1B, TMEM88, TMEM229B, COL5A1, RRM2, MAZ, LTV1, KLHDC3, RNF44,

C9orf69, LMNB1, GRPEL2, DICER1, ZMYND19, ERGIC2, H2AFX, LATS2, SLC35E1, MORC2, PUS7, DDX19A, C2orf69, WDR37, RFC4, TMUB1, GSG2, CTXN1, CPA4, FBXO10, EIF4EBP2, EIF5A2, GMNN, HDHD1, E2F8, ARID3A, MZF1, SPATA33, GNB1L, C6orf120, CEBPD, TMC7, ZNRF2, MAPK15, INTU, ASB13, ZNF107, SCML2, LMLN, AK4, ZNF367, HIC2, SKP2, DPF1, KPNA5, KRT10, ZNF724P, C14orf79, CIPC, C17orf97, SUV420H2, AC012146.7, SCAI, SFXN5, TOR2A, LHPP, ZNF680, RP11-296I10.6, CDK5R1, LINC00116, CDC25A, TTLL7, FAM227A, RP11-313J2.1, NKIRAS1, EIF4A1, KIF17, FER1L4, HMGA2, BOP1, THRB, FAM86B1, NRARP, KIAA1407, CTD-2583A14.11, GPR157, C17orf89, EPB41L4B, SLC2A3, ZNF257, RP11-263K19.4, ZNF487, ZNF846, RP11-305E6.4, DYNC2LI1, NEURL2, MORN1, DUSP2, PBX4, NCALD, ZNF2, YOD1, AC006115.3, RP4-717I23.3, RP4-635E18.8, RP11-384K6.2, RP11-242D8.1, C20orf24, RORA, C4orf48, NKX2-5, IRAK1BP1, ZNF695, RP4-758J24.5, GPR75, DENND2C, NR6A1, MIR210HG, AC005224.2, LIPE, NPIPA1, GPS2, LPAR2, AOC3, HS6ST1P1, HOXC-AS2, NIM1K, MRPL45P2, RP11-254B13.1, RP11-524H19.2, PDF, DTX2P1, TAS2R14, CBWD3, ZNF19, FGF14-AS2, CTC-251D13.1, NKD2, TTC18, AC007551.3, SNAP91, IPO4, C9orf163, FSIP1, CTC-546K23.1, DRP2, AP006216.11, RND1, CTC-462L7.1, RP11-517B11.2, BAIAP3, RMRP, RP11-795F19.5, DIO2, RP11-69E11.4, RP1-63G5.5, SCNN1A, PCDH17, ZNF595, EFCAB6, SENP3-EIF4A1, ZEB2-AS1, C5orf66, LRGUK, AP001468.1, RP5-940J5.6, SLCO5A1, CATSPER3, COL5A2, SLC6A6, RHOB, GOLGA4, DCAF6, CPS1, TRIML2, RFX5, LATS2, CDKN1A, POMT2, DCAF4, HMOX1, SUCO, OPN3, MNT, DICER1, PDCD4, ATXN7L3B, C9orf69, YOD1, CLIP4, KDM5B, TSPYL2, RABL5, CASP7, ELOVL4, C3orf49, THNSL1, TCTN2, CYBRD1, WDR19, UBXN11, TIGD1, ZNF33B, FBXW9, SPATA2, SNN, CCDC113, LZTFL1, DYNLL1-AS1, AMDHD1, TLDC1, FRAT2, CALCOCO1, PIK3R3, CROT, IFT81, PLD1, IFT140, LINC01139, EXOC6B, HOXC13, BTG2, RABL2A, GABPB1, SOX6, HDHD1, TPPP, NDRG4, TRANK1, NPHP1, ZNF287, C6orf120, ODF2L, TEF, LMBR1L, APH1B, AC006273.5, SESN3, YPEL5, ANKRD46, CCNG2, DUSP18, ABCA1, FAM229A, MXD4, MPZL3, SUV420H2, RNF44, HIST1H2AC, LDHD, IQCG, RP11-280G9.1, RP11-356J5.12, SLC15A5, ZNF354C, CTD-2270L9.4, USP49, RAB36, GRK5, CTXN1, RP11-420G6.4, DYNC2LI1, TTC30A, ARL17B, DNAJB5, CREBRF, RP11-115D19.1, AP001372.2, LINC01021, DENND2C, CHIC1, ZBTB3, THRB, BBS12, SPEF2, RBKS, ZNF385A, AKAP6, RAD51-AS1, RPS17, LINC00319, SRP14-AS1, SAMD15, DNAJC3-AS1, RIBC1, NEK10, FBXO10, RP4-717I23.3, RP11-108K14.4, RP11-253M7.1, FAM227A, HIST1H2BC, KLF9, CPEB3, RP11-545E17.3, CASC2, PIH1D2, C17orf97, SLC2A3, NME5, C7orf63, SEC31B, HIST1H4H, LMLN, SLC46A3, KLHDC9, OSCP1, C9orf9, ZNF599, C2orf70, C4orf48, ZNF606, HOGA1, FGGY, MDH1B, LRRC46, RP11-235E17.6, FAM160A1, RP11-299G20.2, HLA-DMA, RP11-144N1.1, HBP1, LINC00668, LRRC48, KCNH3, ZNF347, RGCC, YPEL2, RP11-504P24.2, AC016700.5, CFHR3, RP11-175K6.1, AL773604.8, RN7SKP97, CPT1C, CDS1, ZNF876P, RP11-43F13.3, RP11-315O6.1, RPL9P8, FANK1, RP5-1092A3.4, RP4-740C4.6, HYDIN, PTCHD4, SLC9A9, HIC1, C5, CCDC30, LRRIQ1, CETN4P, KLHDC1, STK32A, CCDC146, RBM44, CTB-51J22.1, RSPH1, FBXO15, RP11-159N11.4, AK8, RP11-467H10.1, CTC-203F4.2, PIK3IP1, RP11-465N4.4, TLL2, ZNF410, RP11-526A4.1, KIAA2022, RP11-417E7.1, RP11-290L1.2, PRKXP1, ZMYND10, THBS4, CCL26, ENO4, RN7SL441P, RP11-1000B6.5, CDKL2, TPRXL, AC007551.3, WDR63, RP5-940J5.6, ARMC3, MT-CO3, DPP9, NCAPD2, CLPTM1, KPNA2, TMEM245, ACSL4, RNF4, ASNA1, MINK1, PON2, RACGAP1, TMEM194A, ELK4, CEP192, ABCA1, TGFBR2, SRPR, HBP1, PNKD, TNFRSF10B, TRIM71, NRBP1, TRMT61A, ENTPD7, WDR90, KPNA5, ZNF542, C1orf109, M6PR, TSEN2, PHF1, LRRC14, MVK, PIGW, CASP7, ZNF680, TBC1D17, LIN28B, MRPL24,

GNS, NR6A1, CTXN1, C2CD2, GOLGA1, TPRG1L, NHLRC3, NAB2, YOD1, API5P1, CREBL2, GABPB1, KLHL17, RAB23, DYNC2LI1, BRMS1L, ATP8B1, FAM206A, ZNF837, POLD3, ZNF470, ZNF138, COG6, UNKL, TCTN2, DCAF6, SPATA2, PIGL, WDR5B, DNAH1, ZNF626, SCN1B, CROT, TTC30B, DCAF4, C2orf69, RP11-500C11.3, TMEM160, TECPR2, RRAS, CDS1, C20orf24, CHIC1, ZNF862, TPGS1, VAMP1, BANF1P3, CDK5R1, CHD9, C14orf79, MTND2P28, RPL4P5, TEF, KCTD13, SENP8, DNAH5, SFR1, IQCC, NR4A2, PFKFB4, DYNLL1-AS1, ZNF808, GREB1L, AC133528.2, DNAH6, KCNK1, FDXACB1, RP11-620J15.3, RNF32, C17orf82, GPX2, RP11-294O2.2, DUSP19, NIPSNAP3B, GNAS-AS1, RP11-66N24.3, C2orf27A, LINC01003, ZNF396, GEMIN8P4, RHOH, LINC00476, CDKL2, BEGAIN, RP11-566J3.4, RPS17L, RP11-111M22.2, PDLIM3, CPEB1, SPNS1, RP5-890E16.2, SH3RF3-AS1, RP11-411B10.4, RP11-254B13.1, CTC-360G5.9, DIO3OS, RP13-766D20.2, FRZB, MIR4519, GFRA3, RP11-347C18.3, SOCS2-AS1, AC105760.2, RBPMS-AS1, LCA5L, ANKRD20A5P, RP11-336K24.12, RP11-37C7.3, IL9RP3, BCO2, RN7SL832P, CTD-3203P2.1, C11orf94, RP11-545E17.3, RP3-329A5.8, C3orf18, DDX11-AS1, ALX3, RN7SKP97, SPG20OS, CYP2C8, TMEM150C, RP11-417L19.4, RP11-152F13.7, RP11-196G11.4, CYP2W1, ATF3, HERPUD1, FAM127A, SEMA4B, JUND, TBC1D17, LZTFL1, TPRG1L, PNRC1, STX4, PNPLA6, PLXNA3, SYNGR2, SESN3, YPEL2, APH1B, BTG2, SLC39A13, CPEB2, SLC2A14, LZTS3, CELSR3, LMBR1L, PPFIA3, C1orf216, ARRDC3, PDCD4, ZNF493, SOCS2, MTMR9, ZNF117, PCSK1N, MT1M, C9orf69, PHLPP2, SPATA2, CROT, ITGB8, NR6A1, ZNF616, MT1F, LMLN, ZNF449, ADCK1, TCTN2, DET1, DUSP8, MPP3, DNAJB5, FAM211B, MT1X, RABL2B, C17orf107, SPA17, CXCL12, BAIAP2-AS1, LINC00847, DYNC2LI1, CAPN12, DZANK1, THBS3, C12orf36, DCAF4, TMEM27, OCA2, ZNF699, RP11-284F21.10, C14orf79, MXD4, CCDC176, NRBP2, C19orf54, ZFP41, HSD17B3, PCSK4, RP11-235E17.6, GPC2, ARMCX1, CTSK, ZNF596, CLIP3, TUBA1A, CSPG4P11, RP11-284F21.7, DNAH1, AC005154.6, LIN37, RP11-923I11.7, RFTN2, GS1-124K5.11, PCDHA4, ANKRD42, CTHRC1, ZNF25, DYRK1B, ATL1, LINC00884, ZNF23, AQPEP, CTC-429P9.5, CARD9, CCT6P3, SNORA33, C14orf28, C17orf97, RNA28S5, RDH5, SPEF2, CCDC40, NEK10, RP5-1112D6.4, RP11-498D10.6, B3GNT9, LINC00886, RNF112, CCDC113, AC079922.3, RP11-522I20.3, ZNF793, TINCR, LIN28A, ZNF404, CTD-2540F13.2, MAP3K14-AS1, SLC35E2, MST1R, RP11-390F4.6, TTLL3, H1FX-AS1, ZIC4, METTL25, PFKP, ZNF490, RBFADN, TSNAXIP1, TRIM29, EIF3CL, NEK11, RP11-73K9.2, ALKBH6, PHYHIP, ZNF214, HM13-IT1, PRRX1, RPS17, AC074212.5, ARMC3, DNAAF3, RP11-554A11.9, LINC00865, EFCAB13, ZNF701, RP11-552M11.8, PCDHGC4, PNPLA7, SPACA6P, RPS17L, RP11-48B3.4, AC005076.5, AC008174.3, PCDHB6, CCDC81, SH2D4B, CASP16, SRD5A2, RP11-254B13.1, RP11-1105G2.3, CTB-152G17.6, SAMD15, PRKG2, NUGGC, NOXO1, EPS8L1, LINC00086, RP11-1391J7.1, TTC18, MYLK2, ODF3L2, SOCS2-AS1, ASIC3, AC117395.1, ABCA9, ACOT12, ST6GALNAC1, FAM65B, CPNE7, RGS16, RP4-798A10.2, LINC00894, AC012442.6, PRKG1-AS1, CTAGE8, CTD-2015H6.3, CCDC71L, C9orf163, TBC1D3F, CTD-2083E4.4, LINC00176, USP3-AS1, and NRG3. This use is preferably for treatment of cancer, such as for treatment of PTEN-deficient cancer, wherein the cancer is preferably associated with lowered or insufficient expression of said gene. These genes were found to be upregulated by miRNA-193a in Example 1.2.1.

In more preferred embodiments, it is for upregulation of a gene selected from the group consisting of STAT3, TMEM2, PEG10, GCC2, RFX5, CPEB2, UNKL, RNF44, PGM2L1, NACC2, TDG, IFT81, CAMK2N1, BDNF, KANK1, CPS1, HDHD1, THBD, SEMA4G, SAMD4A, RP11-438N16.1, C2orf69, TPRG1L, CHIC1, HOXC13, DYRK1B, RASA2, CELSR3, ADM, KLHDC3, ABCC5, PNKD,

MOK, PBXIP1, NUAK2, CLDN2, PHLPP2, CPOX, ZNF76, MBLAC2, VTN, CDH1, RMND5A, SCML1, LMBR1L, TGFBR2, ENTPD7, LZTFL1, C7orf60, ZNF558, CTNNBIP1, SNN, IFT140, RALGAPA1, WIPI1, C8orf58, PDCD4, RPL26, HOXA10, RP11-443N24.1, EIF4EBP2, RECK, ZNF614, HBP1, PRICKLE4, WDR25, DNMT3B, GNAZ, PER2, LMLN, SARM1, C17orf97, AC011841.1, CCNG1, ANKRD46, SYNGR3, TPPP3, KIAA0513, UBE2Q2P6, FAM227A, NEK11, KLHDC7A, ARID3A, CROT, PER1, F3, FAM217B, AK7, FRAT2, FOS, STX1B, APH1B, FER1L4, SAMD15, C3orf67, SKIDA1, SESN3, CTD-2366F13.1, SESN1, PADI1, C9orf9, ZBTB3, CCAT1, LATS2, RP11-553L6.5, JHDM1D-AS1, ZNF438, CEBPD, CTB-171A8.1, TEF, CYP1A1, LIN28B, DPY19L1P1, ZNF138, LINC00886, KLF9, LRRIQ1, LRRC46, C5orf55, YOD1, RP11-339B21.14, RP11-504P24.8, ZNF77, GABPB1, SLC25A42, NPR1, LIPT1, TMEM91, ROPN1L, VIL1, TJP3, SDCBP2-AS1, CLEC2B, RPS6KL1, LRRC6, DFNB59, USH1G, GPR157, C7orf63, CTD-3065J16.9, MIR210HG, ADRB1, GXYLT2, SLC2A3, WDR65, TSNAXIP1, ATP2A1, PHYHIP, OSCP1, C12orf55, RP11-706O15.7, RGS9BP, MSH5, RP11-498C9.12, LRRC29, MPZL3, TTC40, RP11-195F19.9, R3HDML, 43347, SNORA5C, RP11-214N9.1, COL6A3, MAOB, RP11-86H7.7, KCNJ16, DHRS9, ALOX5AP, ISM2, LYPD3, NPHS1, DBNDD2, GLT8D2, SELPLG, RP11-263K19.6, RP13-131K19.2, SERPINA5, TCP10L, AC018816.3, RP11-318A15.2, ZMYND10, RP11-576C2.1, GPR132, CTD-2292M16.8, HOXD11, CDH16, CCDC148, ZNF404, ZMIZ1-AS1, RP13-631K18.3, FAR2P1, C10orf107, RP1-121G13.3, RP5-1157M23.2, C2orf62, CSPG4P8, RP11-108K14.4, EEF1DP2, RP11-12A20.7, PSG1, ARMC12, CDH8, RP11-309L24.9, ALS2CR12, POU5F1P3, DNM1P35, TAF7L, RAPSN, RFPL3S, RNF223, AURKC, TRBV20OR9-2, C6orf165, RP11-699L21.1, CXorf58, DNAAF1, RP11-167N4.2, XAGE1B, TMEM88, and TMEM229B, even more preferably it is for upregulation of all of these genes. This use is preferably for treatment of lung cancer, such as for treatment of PTEN-deficient lung cancer, wherein the lung cancer is preferably associated with lowered or insufficient expression of said gene. These genes were found to be upregulated by miRNA-193a in A549 cells (Example 1.2.1).

In other more preferred embodiments, it is for upregulation of a gene selected from the group consisting of COL5A1, RRM2, MAZ, LTV1, KLHDC3, RNF44, C9orf69, LMNB1, GRPEL2, DICER1, ZMYND19, ERGIC2, H2AFX, LATS2, SLC35E1, MORC2, PUS7, DDX19A, C2orf69, WDR37, RFC4, TMUB1, GSG2, CTXN1, CPA4, FBXO10, EIF4EBP2, EIF5A2, GMNN, HDHD1, E2F8, ARID3A, MZF1, SPATA33, GNB1L, C6orf120, CEBPD, TMC7, ZNRF2, MAPK15, INTU, ASB13, ZNF107, SCML2, LMLN, AK4, ZNF367, HIC2, SKP2, DPF1, KPNA5, KRT10, ZNF724P, C14orf79, CIPC, C17orf97, SUV420H2, AC012146.7, SCAI, SFXN5, TOR2A, LHPP, ZNF680, RP11-296I10.6, CDK5R1, LINC00116, CDC25A, TTLL7, FAM227A, RP11-313J2.1, NKIRAS1, EIF4A1, KIF17, FER1L4, HMGA2, BOP1, THRB, FAM86B1, NRARP, KIAA1407, CTD-2583A14.11, GPR157, C17orf89, EPB41L4B, SLC2A3, ZNF257, RP11-263K19.4, ZNF487, ZNF846, RP11-305E6.4, DYNC2LI1, NEURL2, MORN1, DUSP2, PBX4, NCALD, ZNF2, YOD1, AC006115.3, RP4-717I23.3, RP4-635E18.8, RP11-384K6.2, RP11-242D8.1, C20orf24, RORA, C4orf48, NKX2-5, IRAK1BP1, ZNF695, RP4-758J24.5, GPR75, DENND2C, NR6A1, MIR210HG, AC005224.2, LIPE, NPIPA1, GPS2, LPAR2, AOC3, HS6ST1P1, HOXC-AS2, NIM1K, MRPL45P2, RP11-254B13.1, RP11-524H19.2, PDF, DTX2P1, TAS2R14, CBWD3, ZNF19, FGF14-AS2, CTC-251D13.1, NKD2, TTC18, AC007551.3, SNAP91, IPO4, C9orf163, FSIP1, CTC-546K23.1, DRP2, AP006216.11, RND1, CTC-462L7.1, RP11-517B11.2, BAIAP3, RMRP, RP11-795F19.5, DIO2, RP11-69E11.4, RP1-63G5.5, SCNN1A, PCDH17, ZNF595, EFCAB6, SENP3-EIF4A1, ZEB2-AS1, C5orf66, LRGUK, AP001468.1, RP5-940J5.6, SLCO5A1, and CATSPER3, even more

preferably it is for upregulation of all of these genes. This use is preferably for treatment of breast cancer, more preferably of triple negative breast cancer, wherein the breast cancer is preferably associated with lowered or insufficient expression of said gene. These genes were found to be upregulated by miRNA-193a in BT549 cells (Example 1.2.1).

In other more preferred embodiments, it is for upregulation of a gene selected from the group consisting of COL5A2, SLC6A6, RHOB, GOLGA4, DCAF6, CPS1, TRIML2, RFX5, LATS2, CDKN1A, POMT2, DCAF4, HMOX1, SUCO, OPN3, MNT, DICER1, PDCD4, ATXN7L3B, C9orf69, YOD1, CLIP4, KDM5B, TSPYL2, RABL5, CASP7, ELOVL4, C3orf49, THNSL1, TCTN2, CYBRD1, WDR19, UBXN11, TIGD1, ZNF33B, FBXW9, SPATA2, SNN, CCDC113, LZTFL1, DYNLL1-AS1, AMDHD1, TLDC1, FRAT2, CALCOCO1, PIK3R3, CROT, IFT81, PLD1, IFT140, LINC01139, EXOC6B, HOXC13, BTG2, RABL2A, GABPB1, SOX6, HDHD1, TPPP, NDRG4, TRANK1, NPHP1, ZNF287, C6orf120, ODF2L, TEF, LMBR1L, APH1B, AC006273.5, SESN3, YPEL5, ANKRD46, CCNG2, DUSP18, ABCA1, FAM229A, MXD4, MPZL3, SUV420H2, RNF44, HIST1H2AC, LDHD, IQCG, RP11-280G9.1, RP11-356J5.12, SLC15A5, ZNF354C, CTD-2270L9.4, USP49, RAB36, GRK5, CTXN1, RP11-420G6.4, DYNC2LI1, TTC30A, ARL17B, DNAJB5, CREBRF, RP11-115D19.1, AP001372.2, LINC01021, DENND2C, CHIC1, ZBTB3, THRB, BBS12, SPEF2, RBKS, ZNF385A, AKAP6, RAD51-AS1, RPS17, LINC00319, SRP14-AS1, SAMD15, DNAJC3-AS1, RIBC1, NEK10, FBXO10, RP4-717I23.3, RP11-108K14.4, RP11-253M7.1, FAM227A, HIST1H2BC, KLF9, CPEB3, RP11-545E17.3, CASC2, PIH1D2, C17orf97, SLC2A3, NME5, C7orf63, SEC31B, HIST1H4H, LMLN, SLC46A3, KLHDC9, OSCP1, C9orf9, ZNF599, C2orf70, C4orf48, ZNF606, HOGA1, FGGY, MDH1B, LRRC46, RP11-235E17.6, FAM160A1, RP11-299G20.2, HLA-DMA, RP11-144N1.1, HBP1, LINC00668, LRRC48, KCNH3, ZNF347, RGCC, YPEL2, RP11-504P24.2, AC016700.5, CFHR3, RP11-175K6.1, AL773604.8, RN7SKP97, CPT1C, CDS1, ZNF876P, RP11-43F13.3, RP11-315O6.1, RPL9P8, FANK1, RP5-1092A3.4, RP4-740C4.6, HYDIN, PTCHD4, SLC9A9, HIC1, C5, CCDC30, LRRIQ1, CETN4P, KLHDC1, STK32A, CCDC146, RBM44, CTB-51J22.1, RSPH1, FBXO15, RP11-159N11.4, AK8, RP11-467H10.1, CTC-203F4.2, PIK3IP1, RP11-465N4.4, TLL2, ZNF410, RP11-526A4.1, KIAA2022, RP11-417E7.1, RP11-290L1.2, PRKXP1, ZMYND10, THBS4, CCL26, ENO4, RN7SL441P, RP11-1000B6.5, CDKL2, TPRXL, AC007551.3, WDR63, RP5-940J5.6, and ARMC3, even more preferably it is for upregulation of all of these genes. This use is preferably for treatment of lung cancer, such as for treatment of PTEN-deficient lung cancer, wherein the lung cancer is preferably associated with lowered or insufficient expression of said gene. These genes were found to be upregulated by miRNA-193a in H460 cells (Example 1.2.1).

In other more preferred embodiments, it is for upregulation of a gene selected from the group consisting of MT-CO3, DPP9, NCAPD2, CLPTM1, KPNA2, TMEM245, ACSL4, RNF4, ASNA1, MINK1, PON2, RACGAP1, TMEM194A, ELK4, CEP192, ABCA1, TGFBR2, SRPR, HBP1, PNKD, TNFRSF10B, TRIM71, NRBP1, TRMT61A, ENTPD7, WDR90, KPNA5, ZNF542, C1orf109, M6PR, TSEN2, PHF1, LRRC14, MVK, PIGW, CASP7, ZNF680, TBC1D17, LIN28B, MRPL24, GNS, NR6A1, CTXN1, C2CD2, GOLGA1, TPRG1L, NHLRC3, NAB2, YOD1, API5P1, CREBL2, GABPB1, KLHL17, RAB23, DYNC2LI1, BRMS1L, ATP8B1, FAM206A, ZNF837, POLD3, ZNF470, ZNF138, COG6, UNKL, TCTN2, DCAF6, SPATA2, PIGL, WDR5B, DNAH1, ZNF626, SCN1B, CROT, TTC30B, DCAF4, C2orf69, RP11-500C11.3, TMEM160, TECPR2, RRAS, CDS1, C20orf24, CHIC1, ZNF862, TPGS1, VAMP1, BANF1P3, CDK5R1, CHD9, C14orf79, MTND2P28, RPL4P5, TEF, KCTD13, SENP8, DNAH5, SFR1, IQCC, NR4A2, PFKFB4, DYNLL1-AS1, ZNF808, GREB1L, AC133528.2, DNAH6, KCNK1, FDXACB1, RP11-

620J15.3, RNF32, C17orf82, GPX2, RP11-294O2.2, DUSP19, NIPSNAP3B, GNAS-AS1, RP11-66N24.3, C2orf27A, LINC01003, ZNF396, GEMIN8P4, RHOH, LINC00476, CDKL2, BEGAIN, RP11-566J3.4, RPS17L, RP11-111M22.2, PDLIM3, CPEB1, SPNS1, RP5-890E16.2, SH3RF3-AS1, RP11-411B10.4, RP11-254B13.1, CTC-360G5.9, DIO3OS, RP13-766D20.2, FRZB, MIR4519, GFRA3, RP11-347C18.3, SOCS2-AS1, AC105760.2, RBPMS-AS1, LCA5L, ANKRD20A5P, RP11-336K24.12, RP11-37C7.3, IL9RP3, BCO2, RN7SL832P, CTD-3203P2.1, C11orf94, RP11-545E17.3, RP3-329A5.8, C3orf18, DDX11-AS1, ALX3, RN7SKP97, SPG20OS, CYP2C8, TMEM150C, RP11-417L19.4, RP11-152F13.7, RP11-196G11.4, and CYP2W1, even more preferably it is for upregulation of all of these genes. This use is preferably for treatment of liver cancer, such as for treatment of PTEN-deficient liver cancer, wherein the liver cancer is preferably associated with lowered or insufficient expression of said gene. These genes were found to be upregulated by miRNA-193a in HEP38 cells (Example 1.2.1).

In other more preferred embodiments, it is for upregulation of a gene selected from the group consisting of ATF3, HERPUD1, FAM127A, SEMA4B, JUND, TBC1D17, LZTFL1, TPRG1L, PNRC1, STX4, PNPLA6, PLXNA3, SYNGR2, SESN3, YPEL2, APH1B, BTG2, SLC39A13, CPEB2, SLC2A14, LZTS3, CELSR3, LMBR1L, PPFIA3, C1orf216, ARRDC3, PDCD4, ZNF493, SOCS2, MTMR9, ZNF117, PCSK1N, MT1M, C9orf69, PHLPP2, SPATA2, CROT, ITGB8, NR6A1, ZNF616, MT1F, LMLN, ZNF449, ADCK1, TCTN2, DET1, DUSP8, MPP3, DNAJB5, FAM211B, MT1X, RABL2B, C17orf107, SPA17, CXCL12, BAIAP2-AS1, LINC00847, DYNC2LI1, CAPN12, DZANK1, THBS3, C12orf36, DCAF4, TMEM27, OCA2, ZNF699, RP11-284F21.10, C14orf79, MXD4, CCDC176, NRBP2, C19orf54, ZFP41, HSD17B3, PCSK4, RP11-235E17.6, GPC2, ARMCX1, CTSK, ZNF596, CLIP3, TUBA1A, CSPG4P11, RP11-284F21.7, DNAH1, AC005154.6, LIN37, RP11-923I11.7, RFTN2, GS1-124K5.11, PCDHA4, ANKRD42, CTHRC1, ZNF25, DYRK1B, ATL1, LINC00884, ZNF23, AQPEP, CTC-429P9.5, CARD9, CCT6P3, SNORA33, C14orf28, C17orf97, RNA28S5, RDH5, SPEF2, CCDC40, NEK10, RP5-1112D6.4, RP11-498D10.6, B3GNT9, LINC00886, RNF112, CCDC113, AC079922.3, RP11-522I20.3, ZNF793, TINCR, LIN28A, ZNF404, CTD-2540F13.2, MAP3K14-AS1, SLC35E2, MST1R, RP11-390F4.6, TTLL3, H1FX-AS1, ZIC4, METTL25, PFKP, ZNF490, RBFADN, TSNAXIP1, TRIM29, EIF3CL, NEK11, RP11-73K9.2, ALKBH6, PHYHIP, ZNF214, HM13-IT1, PRRX1, RPS17, AC074212.5, ARMC3, DNAAF3, RP11-554A11.9, LINC00865, EFCAB13, ZNF701, RP11-552M11.8, PCDHGC4, PNPLA7, SPACA6P, RPS17L, RP11-48B3.4, AC005076.5, AC008174.3, PCDHB6, CCDC81, SH2D4B, CASP16, SRD5A2, RP11-254B13.1, RP11-1105G2.3, CTB-152G17.6, SAMD15, PRKG2, NUGGC, NOXO1, EPS8L1, LINC00086, RP11-1391J7.1, TTC18, MYLK2, ODF3L2, SOCS2-AS1, ASIC3, AC117395.1, ABCA9, ACOT12, ST6GALNAC1, FAM65B, CPNE7, RGS16, RP4-798A10.2, LINC00894, AC012442.6, PRKG1-AS1, CTAGE8, CTD-2015H6.3, CCDC71L, C9orf163, TBC1D3F, CTD-2083E4.4, LINC00176, USP3-AS1, and NRG3, even more preferably it is for upregulation of all of these genes. This use is preferably for treatment of liver cancer, such as for treatment of PTEN-deficient liver cancer, wherein the liver cancer is preferably associated with lowered or insufficient expression of said gene. These genes were found to be upregulated by miRNA-193a in HUH7 cells (Example 1.2.1).

The invention provides a miRNA-193a molecule, isomiR, mimic, or source thereof as described herein, or a miRNA-193a for use in treating a condition associated with PTEN-deficiency such as for use as a PTEN agonist, wherein the miRNA-193a molecule, isomiR, mimic, or source thereof is for downregulation of a gene selected from the group consisting of RPS17L, GPR137C, EEF1A1P19,

NEFH, KRT14, RP5-973M2.2, OVOL2, RP11-873E20.1, RP5-968P14.2, MYB, AC000068.5, NOTUM, RP11-209D14.2, RP11-326K13.4, RP11-339B21.10, IRF8, HIST1H4C, DPF3, RP11-276H7.3, RP4-694A7.4, RP11-17M16.2, KB-226F1.2, SHBG, LAT2, SNORA33, SNORD12, AC005592.2, RP11-796E2.4, RP11-280G9.1, NOG, LINC00035, 7SK, GJB2, MYH11, BHLHE41, RP11-211N8.2, IL12A, EPB41L3, ROR2, UNC5CL, NINJ2, SUCNR1, CTD-2369P2.2, MYLK4, SLC35D2, SHMT2, ERMP1, TEX15, COL20A1, SORL1, PHLDA2, C10orf91, TWISTNB, HPD, PLAU, IL17RD, RNF182, KRAS, LL22NC03-N14H11.1, AC004158.2, ANKRD44, STMN1, CSPG5, PARD6A, FOXRED2, TMPPE, TNFRSF21, DNASE1L2, HHAT, TOX3, STARD7, MPP2, B3GNT3, ZDHHC18, RP11-173M1.8, PITPNB, RP11-340I6.6, ETV1, ATP5SL, EPHB3, AIMP2, PI3, DHCR24, DAZAP2, C9orf47, ZNF365, RP11-204C16.4, SLC30A7, KIAA1875, NYAP1, CCND1, CHD5, SHOX2, ST3GAL4, SEPN1, KLRG2, VAMP8, AP2M1, FAM60A, SULF2, ZSWIM5, MED21, RP11-24B19.3, Z83851.4, DUSP7, C1QBP, NCEH1, TBX20, UBP1, RP11-421N8.1, LY6K, GPR146, ST3GAL5, ATP5F1, OSMR, CBL, CCDC28A, YWHAZP2, YWHAZ, DPY19L1, EXTL2, NAP1L5, CTC-428G20.3, ETS1, UBE2L6, GREB1, FAM168B, CLDN4, YWHAZP3, ALX1, CRKL, RPS17, HFE, TRIM62, MSANTD3, ZMAT3, ENDOD1, KIAA1644, MOSPD2, FIBCD1, ATP8B2, PRNP, DLEU2, SLC2A12, WSB2, VGF, SERINC2, DCTN5, XK, NUP50, SMPD1, CNOT6, RP11-395A13.2, GABPA, CLSTN1, POLE3, BOD1, LRRC8A, SLC35G1, TP53INP1, AGPAT1, HPRT1, RUSC1, SLC23A2, PDE3A, EBF1, FANCE, WDYHV1, MAX, WDFY2, MCL1, MORN4, FAM72A, CDCA7L, TPP1, AREL1, COPRS, NT5E, TMEM121, 43346, SLC30A1, PRRG4, RBBP5, LAMC2, SLC35D1, C18orf54, GLYCTK, DPM3, HACE1, CDK6, GPATCH11, IDH2, PTPLB, EMILIN2, CCNA2, FAM60CP, TK2, FAM20B, GNPDA1, TIMP4, NR2F6, TMEM180, TRAF1, DERA, ATP8B3, XYLT1, SLC39A10, KLHL2, PIK3AP1, IDS, CADM1, TBL1XR1, KCNMA1, FAM101B, PPTC7, SLC29A3, AP5M1, PEX11B, MEX3C, ARF3, PLD6, INO80C, SNX10, NUDT15, CCDC149, SLC26A2, GNAI3, DCAF7, APOL6, ADCY9, NUDT21, PRR5L, HYOU1, BCYRN1, CCNDBP1, DSEL, PAFAH2, FAF2, SLC25A15, NEIL2, USP39, GCH1, FCHSD2, TXLNA, TMEM135, RN7SL2, RAB11FIP5, NAGA, ACOT8, WDR82, PCDHAC2, VAV3, SRP54, RN7SL1, FAM72D, SEC31A, TYW3, ZNF512B, HCG11, ARHGAP29, SAPCD2, PALM3, MIR17HG, DGKH, CASP9, LINC00657, TMEM30A, SLC30A4, CHEK1, RTKN2, IGSF3, NBL1, TGFBR3, RP11-67L2.2, STRADB, APPL1, ARPC5, NIPA1, ZNF710, CA12, NET1, CTD-2196E14.9, ABI2, R3HDM1, SFXN1, MESDC1, MTA2, DOCK10, PHACTR2, KBTBD11, ELK3, PSRC1, MSANTD2, RASGRF2, ATP6V1B2, ALDH9A1, LARS2, CDKL5, RNF216P1, LRRC40, LUZP1, MORC4, MYLK, PLAUR, CCSER2, RP11-73M18.7, ERBB2IP, ACSS2, NOL9, DLEU1, C17orf58, PITHD1, SEC61A1, ARHGAP19, CDC42EP2, HNRNPUL2, BCAT2, RP11-329A14.1, ST5, NUDT3, TNFSF9, PADI2, EMC6, IRF1, PLXNA2, COPS3, CCP110, ABCA12, MPST, CYTH1, PLEKHB2, MED19, GALNT14, MLKL, TOR4A, SYNRG, AFAP1L1, TRAK2, SGMS1, MARCKSL1, IL6R, PIP4K2C, JADE3, CBX1, HELZ, NSF, IFI27L2, TMEM216, SDE2, RTN4RL2, SSRP1, TRPA1, GDF11, SPECC1L, RUFY2, DNAJC3, KIAA1191, AC007560.1, HSBP1, IL11, UNG, HEG1, MAP4K5, PPM1F, GLO1, ANKRD13A, KIF1B, KIAA1147, TRAFD1, PAK4, FAM114A2, DIO2, POPDC3, PLEK2, DNAJC16, NT5DC3, RAB27B, TWF1, CLN6, KDM7A, R3HDM4, ZNF618, LRP4, ITPKB, PDPK1, ALKBH5, C11orf24, DSTYK, AAED1, CEP41, MAP3K3, KLHL15, PTPLA, AFMID, LMNB2, MLLT11, DESI1, WDR5, B4GALT6, CCNJ, SENP1, ZBTB14, SIPA1L2, PHF19, TP53BP2, ASF1B, USP43, SS18, CHCHD5, BCL2L2, CAPN15, ADNP2, RCAN3, RNF2, TAP2, SOS2, HDAC3, AP1S2, GFPT1, ABR, FOCAD, ERRFI1, RC3H2, EML4, PTPN9, AFF4, CD97, RABEPK, SQSTM1, PRR14L, HP1BP3, GPRC5B, CBFB, ARPC2, GPC6, TCF7L2, GALNT2, TRIP6, PIK3R1, DDAH1, RHOU, UBE2Z,

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SFT2D2, PDE4D, WHSC1, UPP1, FAM115C, EPDR1, RASA3, XPNPEP1, CDC45, MYADM, HN1L, BCOR, PRKAA2, RAPH1, CCSER2, CHEK1, NAB1, SLCO4A1, ADRBK1, PXN, B4GALNT1, TSPAN14, RIN1, TCOF1, SMG5, HP1BP3, RP11-1055B8.7, HSBP1, SKA2, OGFRL1, CDT1, SGMS1, MCM10, APPL1, ATP6V1B2, TROVE2, CD97, TRIP13, SS18, PHLDA1, TRIM25, FOSL1, ID3, PPP1R26, PPP3R1, RFC3, MRPS18B, GPC1, SET, IDS, MED14, IER2, TFPI2, UBFD1, CDCA4, OGFR, CNBP, PAPOLA, MRPL19, TNFAIP2, AKR1C3, TOMM34, FGFRL1, MCM2, KIAA0141, ADNP, LPCAT1, CDC6, MLEC, KIDINS220, AGFG1, HMGB1, LIF, IDH3A, UHMK1, TRIP6, RBM8A, FARSA, URB1, PITPNA, GNB1, WWTR1, SETP14, RPS21, CAPRIN1, TGOLN2, STC2, OSGIN1, NOTCH3, IDH1, BAZ1B, DDB1, TNPO1, LASP1, PCBP1, FASN, TUBB, ACTB,RP11-313P13.5, CTB-31N19.3, LINC00607, LRRC15, RGS17P1, NPAS3, CTD-3203P2.2, CSTF3-AS1, CTD-2342J14.6, CTD-2537I9.5, MYEOV, ANKRD31, CIDEC, MYO1G, SRRM3, LINC01132, ENDOD1, TSGA10IP, ADH1A, IL11, RP11-572C15.6, CD207, RP11-274H2.5, TFF3, UXT-AS1, RPS19P3, RP11-305K5.1, CTD-2192J16.20, LL0XNC01-250H12.3, ZSCAN23, LINC01096, RPSAP52, CDC42EP3, AK4P3, GALNT16, ETS1, SEC14L2, CHST6, RP11-255H23.2, LINC01057, ULK2, FAM162B, RP11-1017G21.5, CTD-2161E19.1, MFSD4, ASAP3, AC026150.5, AC005077.12, LINC00312, TRIM62, CCDC28A, ROM1, TRPV3, RP11-73M18.9, HHAT, B3GNT3, TMEM30B, CRYAA, TFAP2A-AS1, TMEM151A, DACT3, SLC35D2, CCDC17, TGFBR3, TIMP4, MPP2, MYCN, TWISTNB, C19orf77, CCND1, NT5E, PTX3, RP11-116D2.1, SOCS3, SHMT2, PRR15L, DOK7, NAPA-AS1, SPP1, ERMP1, UBE2L6, NACAD, SLC6A12, KCNG3, CHCHD2P6, ERBB4, ANGPTL2, FAM150A, LOX, ANKLE1, ACOT8, ST3GAL5, AMPD3, SLC15A1, IL17RD, MYADML2, C8A, FOXRED2, GRIN2D, STMN1, DCAF7, TRIM17, HR, C1QBP, LINC00657, HFE, RP11-469M7.1, ATP5SL, FAM60CP, RP11-421N8.1, MPZ, SLC29A3, PNRC2, ARHGAP19, CDC42EP4, FAM168B, GTF2H2B, SORL1, PPARGC1A, P2RY1, KRAS, PHLDA2, DPY19L1, CCDC149, CCNJ, TNFRSF21, RUSC1, UBP1, IDS, DCTN5, SYNE3, LAMC2, KDM7A, LEF1, GABPA, PCBD1, PCYOX1L, TNFSF9, PDGFRB, MAT1A, VAMP8, ARID3B, CXXC4, MYB, ATP5F1, RP11-204C16.4, RP11-973N13.2, FAM101B, ENPP4, KRT80, HYOU1, PITPNB, WSB2, CRKL, UPK1A-AS1, AP2M1, FAM60A, PSRC1, DUSP7, DDAH1, ANKRD1, FAM203A, CNOT6, CER1, RP11-613M10.6, ATP8B2, IL6R, AAED1, ESRRG, INO80C, HSPB8, SLC23A2, SOX5, PDE3A, HFE2, NPTX1, ADCY9, MAX, NPPB, SLC30A7, RAB11FIP5, ZCCHC10, PAG1, MAPK8, FOXC1, UNC5CL, STARD7, LRRC8A, HRK, MISP, AIMP2, PIK3R1, PLAG1, POLE3, ACPL2, NCEH1, SCNN1A, AP5M1, CLSTN1, AC005077.14, HEG1, SLC39A5, MCL1, MED21, INPPL1, DAZAP2, ELFN1, CDK6, ST3GAL4, TGFB2, PRICKLE2, CYTH1, PLEKHA8, TAF4B, RP11-340I6.6, EFNB1, RP11-91J19.4, CTD-2196E14.9, B4GALT4, RASA3, GREB1, ZDHHC18, KRT17, ELMO2, MSANTD3, AGPAT1, YWHAZP3, CGNL1, CUX2, SH3BP5, ZMAT3, SCP2, PEX11B, PPM1K, KIAA1191, GFPT1, GALNT13, C18orf54, CXCR4, ETV1, RNF146, RGL1, HPRT1, EIF4B, CDC42EP2, CTD-2369P2.2, ABI2, BFSP1, SLC6A15, PELI2, TRAK2, DERA, TPP1, EFEMP1, FCHSD2, RSF1, TP53INP1, TK2, PPTC7, HACE1, BOD1, DLX1, YWHAZ, FAM114A2, EFNB2, SMPD1, UBE2F, GPR176, GRB7, ZBTB5, ATOH8, TWSG1, PRNP, OLFML2A, ARPC5, RP11-342K6.1, GCH1, NOTUM, LUZP1, SPECC1L, NUDT21, APPL1, SFXN1, FAT4, UNC119B, ZMIZ1, SCLT1, CD97, AREL1, NYNRIN, ADAMTS1, SEC61A1, SIX4, PNMA3, FAF2, INPP5B, CTGF, OSTF1, TYW3, RAB5B, CBX1, TBC1D12, USP39, ACSS3, CYR61, PCDH17, LMCD1, KIAA1147, EEF1A1P13, KIF3A, EDN1, RP11-53O19.3, SMARCA2, EFNA4, GPR133, RBBP5, NCF2, NUP50, OGFRL1, WDFY2, DHCR24, SOS2, YWHAZP2, KLHL2, IGSF3, CCDC80, THSD7A, ZNF618, ACSS2, PDPK1, BCAT2, PHACTR2, GLIS2, MARCKSL1, C11orf24, CBL,

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SEPN1, ARID3B, CHAF1A, CDKN2C, PIF1, FAM72B, HACE1, BRCA1, CCNE2, STEAP2, RAD17, AGPAT1, PAQR4, CLSPN, TIMP4, PRPS2, KIF14, CADM1, USP39, CCNJ, GALNT13, MCL1, CCP110, RTN4RL2, FAM64A, UBP1, FAM60A, HYOU1, CXorf57, ARHGAP11A, MOSPD2, PKMYT1, KIAA0101, CKAP2L, PP13439, IL22RA1, CDK2, PLAUR, CNOT6, MND1, BAAT, DUSP7, SFXN2, AL390877.1, MED21, EFNA4, GPATCH11, FAM111A, MOCOS, DHFRP1, SAMD9, BHMT, RP11-253E3.3, NUDT21, CNKSR2, ACSS3, SREK1IP1, CTD-2196E14.9, LRMP, BRIP1, CRKL, RP11-340I6.6, MGAT4A, PCYOX1L, MYCN, ZMAT3, LPAR3, NUDT15, CDK1, MCM6, TRAK2, NSF, ROR1, MYBL2, R3HDM1, RGS10, RILPL2, KANK2, PRIM1, PHF19, CA12, CLN6, MKI67, SFXN1, SLC45A3, RMI2, HELLS, GAS2, KIF2C, IL17RD, STAMBPL1, NUP50, SPATA5, KLHL2, RGL1, HNRNPUL2, B4GALNT2, CENPM, COPS3, CCNF, CCDC149, RNF168, ORAI1, DERA, APOL6, AUNIP, PPIL3, GBA2, RP11-613M10.6, MAP3K3, ZBTB5, CDC6, POLA2, PCBD1, GNPDA1, SKA3, ORC1, ACOT11, PHACTR2, KIF18B, NCAPG, PLD6, FCHSD2, ACPL2, ERBB2IP, CXCR4, MELK, PTGDR2, CDK6, PIGA, RP1-249H1.4, TK1, IL6R, KIAA1147, C17orf58, CHST14, CEP41, UBR7, MASTL, ARPC5, TONSL, RP11-67L2.2, SAPCD2, UTP18, OSMR, AURKB, IQCC, ITPRIPL1, MSANTD3, SLC26A2, C14orf80, RAD51, LMNB1, UBE2T, SLC25A15, FANCE, PAK4, ZNF512B, DHFR, WDFY2, ZNF618, INCENP, IGF2BP1, ESPL1, PODXL, SS18L1, NR2F6, CHRNA5, MAPK8, KIFC1, MMS22L, BCAT2, OAS3, CDCA4, NAGA, TMPPE, CAPN15, RGS2, RNF146, AP5M1, SYNRG, SCP2, RP1-60O19.1, LRRC8A, SGK2, DGKG, NUSAP1, IDH3A, KIF4A, MRPS18B, MBL2, GRB7, FAM20B, CDC25A, PDE4D, TIPIN, TMEM216, RAD51AP1, RP11-21L23.2, BLM, SAAL1, YWHAZP3, TXLNA, KIAA1191, ETS1, KIF15, FANCG, MAX, AREL1, KANK4, CDCA3, NIPA1, FARSA, RFWD3, CGNL1, ATP8B2, MAB21L2, EFHD1, FOCAD, ARMCX4, H2AFX, DEK, WDR62, PPTC7, KIRREL, PRR14L, SSRP1, UBALD2, LINC00657, HJURP, FGF19, GREB1, KNTC1, MCM4, SLC35G1, MARCKSL1, HEG1, MGME1, TAPT1, TPP1, FAF2, RP5-1024G6.8, ATAD5, LARS2, PLK1, ANKRD13A, ARHGEF34P, ATAD2, PAFAH2, TUFM, SLFN13, SKA2, UNC119B, SEC61A1, FEN1, ARF3, SPECC1L, CABLES2, MCM3, SMIM13, BRCA2, GINS1, HMGB1, TMEM30A, ALDH9A1, E2F1, PAG1, LMNB2, CECR2, SYTL5, TMEM194B, WHSC1, IWS1, JADE3, EIF4B, MYLK, SMPD1, PLEKHB2, CENPE, RP11-121L10.3, MPC1, CENPF, TUBA1B, PTPN9, ZWINT, ENTPD5, DSN1, DEPDC1B, SLC43A3, FOXM1, IDS, MORC4, BUB1B, MDM2, GALNT1, NR0B2, KIF11, HELZ, C16orf59, MTHFD1, CDC20P1, TP53INP1, XRCC2, RCAN3, ITPKA, PLEKHA8, NDC80, TOP2A, DOLPP1, CASP2, GNL3L, ZCCHC10, GINS3, ABCB10, RAB11FIP5, TRIP13, SLC39A5, FAM83D, WDR82, TBL1XR1, DUT, ZNF395, RECQL4, TCF4, CHAF1B, TFAP4, USP1, ASPM, REXO4, LRRC40, SLC7A5, LIG1, SPP1, PIP4K2C, PDPK1, DNA2, ESCO2, LSM14B, GTSE1, HP1BP3, C10orf12, MCM7, PDE3A, ARHGEF39, CTDSP2, TWF1P1, RFC3, SP4, ACD, PLSCR1, MAD2L1, DKK1, CBX1, AKR1C2, TUBB4B, ZNF346, PLEKHA6, KIF18A, GXYLT1, SLC30A1, MAP7D3, ZNF710, YWHAZP2, RAD54L, WDR5, ARPC2, CBFB, EZH2, CASP8AP2, TFDP1, GLYCTK, SOS2, MXD3, TPRN, GLO1, RRP7A, EML4, MTA2, STIL, PLXNC1, MAGI3, QDPR, PARP14, CDC20, SIPA1L2, MSH2, RRM1, ELMO2, IQGAP3, KIAA0430, TACC3, PTPLB, NOL9, SEC22C, PBX1, UBE2C, POLQ, HK2, RFC2, TUBA4A, EXOSC3, SS18, WDHD1, CTDSPL2, HSBP1, YWHAZ, NCAPH, RBM8A, XPNPEP1, IGSF3, POLE, C11orf82, RP11-475C16.1, SLC19A2, ADRBK2, PPAT, TWF1, FST, SGMS1, KIF22, SLC20A2, MRPL19, MKL2, TRAFD1, ALKBH5, NUCKS1, DNMT1, ACSS2, INPPL1, PRR11, RAB5B, EIF4BP7, PRTG, ARHGEF5, DESI1, TMEM135, TUBG1, EIF4BP6, LIMD1, MBNL3, PLK4, CMTM4, SLC30A9, POLR1E, BRI3BP, PITPNA, HMGB2, BOD1, NASP, SLC35D1, ELOVL2, SCAMP4, SMG6, ARHGEF12, POLR2D, FANCD2, LPHN2, SMC4, WDR48, POLA1, KIF20A, DLGAP5, RSF1,

SRP54, PIP4K2A, NET1, CDCA8, SYNM, MPST, PNP, SLC18B1, IDH2, OSGIN1, NUP210, RBM10, MDC1, C11orf24, RPL27A, CDCA2, KIF1B, DYNLL2, PTPN3, TCOF1, LBR, RPS21, KIDINS220, LGR4, KIF23, TOMM20, LAMC1, GLYR1, RPS6KB2, RCC1, TMPO, PTK2, TPX2, SPAG5, CAPRIN1, GTF3C5, SLBP, HMGB1P5, CCNB1, AFF4, ANLN, SEC31A, GSR, H2AFZ, PTTG1IP, and SQSTM1. More preferably it is for downregulating all of these genes. This use is preferably for treatment of cancer, such as for treatment of PTEN-deficient cancer, wherein the cancer is preferably associated with increased or exacerbating expression of said gene. These genes were found to be downregulated by miRNA-193a in Example 1.2.1.

In more preferred embodiments, it is for downregulation of a gene selected from the group consisting of RPS17L, GPR137C, EEF1A1P19, NEFH, KRT14, RP5-973M2.2, OVOL2, RP11-873E20.1, RP5-968P14.2, MYB, AC000068.5, NOTUM, RP11-209D14.2, RP11-326K13.4, RP11-339B21.10, IRF8, HIST1H4C, DPF3, RP11-276H7.3, RP4-694A7.4, RP11-17M16.2, KB-226F1.2, SHBG, LAT2, SNORA33, SNORD12, AC005592.2, RP11-796E2.4, RP11-280G9.1, NOG, LINC00035, 7SK, GJB2, MYH11, BHLHE41, RP11-211N8.2, IL12A, EPB41L3, ROR2, UNC5CL, NINJ2, SUCNR1, CTD-2369P2.2, MYLK4, SLC35D2, SHMT2, ERMP1, TEX15, COL20A1, SORL1, PHLDA2, C10orf91, TWISTNB, HPD, PLAU, IL17RD, RNF182, KRAS, LL22NC03-N14H11.1, AC004158.2, ANKRD44, STMN1, CSPG5, PARD6A, FOXRED2, TMPPE, TNFRSF21, DNASE1L2, HHAT, TOX3, STARD7, MPP2, B3GNT3, ZDHHC18, RP11-173M1.8, PITPNB, RP11-340I6.6, ETV1, ATP5SL, EPHB3, AIMP2, PI3, DHCR24, DAZAP2, C9orf47, ZNF365, RP11-204C16.4, SLC30A7, KIAA1875, NYAP1, CCND1, CHD5, SHOX2, ST3GAL4, SEPN1, KLRG2, VAMP8, AP2M1, FAM60A, SULF2, ZSWIM5, MED21, RP11-24B19.3, Z83851.4, DUSP7, C1QBP, NCEH1, TBX20, UBP1, RP11-421N8.1, LY6K, GPR146, ST3GAL5, ATP5F1, OSMR, CBL, CCDC28A, YWHAZP2, YWHAZ, DPY19L1, EXTL2, NAP1L5, CTC-428G20.3, ETS1, UBE2L6, GREB1, FAM168B, CLDN4, YWHAZP3, ALX1, CRKL, RPS17, HFE, TRIM62, MSANTD3, ZMAT3, ENDOD1, KIAA1644, MOSPD2, FIBCD1, ATP8B2, PRNP, DLEU2, SLC2A12, WSB2, VGF, SERINC2, DCTN5, XK, NUP50, SMPD1, CNOT6, RP11-395A13.2, GABPA, CLSTN1, POLE3, BOD1, LRRC8A, SLC35G1, TP53INP1, AGPAT1, HPRT1, RUSC1, SLC23A2, PDE3A, EBF1, FANCE, WDYHV1, MAX, WDFY2, MCL1, MORN4, FAM72A, CDCA7L, TPP1, AREL1, COPRS, NT5E, TMEM121, 43346, SLC30A1, PRRG4, RBBP5, LAMC2, SLC35D1, C18orf54, GLYCTK, DPM3, HACE1, CDK6, GPATCH11, IDH2, PTPLB, EMILIN2, CCNA2, FAM60CP, TK2, FAM20B, GNPDA1, TIMP4, NR2F6, TMEM180, TRAF1, DERA, ATP8B3, XYLT1, SLC39A10, KLHL2, PIK3AP1, IDS, CADM1, TBL1XR1, KCNMA1, FAM101B, PPTC7, SLC29A3, AP5M1, PEX11B, MEX3C, ARF3, PLD6, INO80C, SNX10, NUDT15, CCDC149, SLC26A2, GNAI3, DCAF7, APOL6, ADCY9, NUDT21, PRR5L, HYOU1, BCYRN1, CCNDBP1, DSEL, PAFAH2, FAF2, SLC25A15, NEIL2, USP39, GCH1, FCHSD2, TXLNA, TMEM135, RN7SL2, RAB11FIP5, NAGA, ACOT8, WDR82, PCDHAC2, VAV3, SRP54, RN7SL1, FAM72D, SEC31A, TYW3, ZNF512B, HCG11, ARHGAP29, SAPCD2, PALM3, MIR17HG, DGKH, CASP9, LINC00657, TMEM30A, SLC30A4, CHEK1, RTKN2, IGSF3, NBL1, TGFBR3, RP11-67L2.2, STRADB, APPL1, ARPC5, NIPA1, ZNF710, CA12, NET1, CTD-2196E14.9, ABI2, R3HDM1, SFXN1, MESDC1, MTA2, DOCK10, PHACTR2, KBTBD11, ELK3, PSRC1, MSANTD2, RASGRF2, ATP6V1B2, ALDH9A1, LARS2, CDKL5, RNF216P1, LRRC40, LUZP1, MORC4, MYLK, PLAUR, CCSER2, RP11-73M18.7, ERBB2IP, ACSS2, NOL9, DLEU1, C17orf58, PITHD1, SEC61A1, ARHGAP19, CDC42EP2, HNRNPUL2, BCAT2, RP11-329A14.1, ST5, NUDT3, TNFSF9, PADI2, EMC6, IRF1, PLXNA2, COPS3, CCP110, ABCA12, MPST, CYTH1, PLEKHB2, MED19, GALNT14, MLKL,

TOR4A, SYNRG, AFAP1L1, TRAK2, SGMS1, MARCKSL1, IL6R, PIP4K2C, JADE3, CBX1, HELZ, NSF, IFI27L2, TMEM216, SDE2, RTN4RL2, SSRP1, TRPA1, GDF11, SPECC1L, RUFY2, DNAJC3, KIAA1191, AC007560.1, HSBP1, IL11, UNG, HEG1, MAP4K5, PPM1F, GLO1, ANKRD13A, KIF1B, KIAA1147, TRAFD1, PAK4, FAM114A2, DIO2, POPDC3, PLEK2, DNAJC16, NT5DC3, RAB27B, TWF1, CLN6, KDM7A, R3HDM4, ZNF618, LRP4, ITPKB, PDPK1, ALKBH5, C11orf24, DSTYK, AAED1, CEP41, MAP3K3, KLHL15, PTPLA, AFMID, LMNB2, MLLT11, DESI1, WDR5, B4GALT6, CCNJ, SENP1, ZBTB14, SIPA1L2, PHF19, TP53BP2, ASF1B, USP43, SS18, CHCHD5, BCL2L2, CAPN15, ADNP2, RCAN3, RNF2, TAP2, SOS2, HDAC3, AP1S2, GFPT1, ABR, FOCAD, ERRFI1, RC3H2, EML4, PTPN9, AFF4, CD97, RABEPK, SQSTM1, PRR14L, HP1BP3, GPRC5B, CBFB, ARPC2, GPC6, TCF7L2, GALNT2, TRIP6, PIK3R1, DDAH1, RHOU, UBE2Z, DYNC2H1, ENOX2, IER3IP1, ZC3H7B, ZNF324, SPOPL, FBXW2, ORAI1, MUC5AC, C4orf46, KIDINS220, MYADM, SLC3A2, PM20D2, PSEN1, RPS6KB2, TPCN2, GALNT1, RFWD3, GALNT13, FOXN2, TWF1P1, FKBP9, CCL2, RNF168, GINS3, MRPL42, LYRM2, PTTG1IP, NRIP1, SSX2IP, DEF8, WDR48, TLR6, EXOSC3, SCP2, FILIP1, INPPL1, TTLL4, TCEB3, SEC22C, IWS1, GBE1, GNL3L, GOSR2, LGR4, SAAL1, UHRF1BP1, SLC29A1, WDR6, VPS37B, HSPA13, TOMM20, PCBD1, CHML, SLC7A5, TP53RK, RUSC2, UTP18, STARD3, C2orf49, BRPF3, PODXL, TUBA1B, PDE8A, DYNLL2, CAPN10, HMGB1, IL4R, SYT1, TUFM, PCBP1, TMBIM1, KCTD5, POM121C, WHSC1, CTDSP2, AGAP2-AS1, KDM5C, PTK2, CPNE3, KIAA0430, CAMKK1, TPCN1, KLHL9, TRIM25, CAPRIN1, UBFD1, MED14, TMEM164, ELMO2, KANK2, ABCB10, CNBP, ITPRIPL2, SOGA1, QDPR, B4GALNT1, FBXW5, TROVE2, FGD6, SUDS3, MTHFD1, KIF14, MAP3K2, AKAP12, OSER1, ACTR3, KIAA0141, ABCE1, HELLS, MRPL19, EIF2AK1, EPHB2, XPNPEP1, YAP1, RBFOX2, CDCA5, ENTPD4, ATP2B4, RBM10, LPCAT1, TPD52, CDK2, AGFG1, WWC3, LBR, PPP2R4, EIF4B, EXTL3, BTBD11, POM121, RIPK2, SFN, MCM2, TMEM230, CMTM4, GSR, TUBA4A, EDEM1, KIRREL, GOLPH3, NF1, TGFB2, PPP3R1, AKR1C3, NOTCH2, CCDC88A, KIAA1522, CTCF, BCAR1, SREBF2, GBF1, WWTR1, PDE4D, CDK4, PGRMC1, AKR1C2, MAP7D1, SET, NCOA3, SERINC3, ARHGAP11A, DEK, PRKCA, MLEC, SYNM, GNB1, PLS3, DDB1, F2RL1, GPC1, and SERPINE1, even more preferably it is for downregulation of all of these genes. This use is preferably for treatment of lung cancer, such as for treatment of PTEN-deficient lung cancer, wherein the cancer is preferably associated with increased or exacerbating expression of said gene. These genes were found to be downregulated by miRNA-193a in A549 cells (Example 1.2.1).

In other more preferred embodiments, it is for downregulation of a gene selected from the group consisting of KRT79, HMGCLL1, LINC00920, BTBD11, RP11-390F4.8, NEURL3, RP11-423P10.2, PAX5, KCNIP1, CD93, PLCB2, RP11-290F20.2, PDGFRB, MEDAG, CRISPLD1, RP5-1086K13.1, DLL1, AL139099.1, AC007383.3, AC046143.3, DNM3, AC111200.7, C11orf35, RP5-1157M23.2, PDE5A, CSF2, CMAHP, C6orf58, ITPKA, SLC22A14, SLC29A3, FOXRED2, ACTG2, SULF2, FAM211A, AC011043.1, CYS1, CTD-2313J17.5, AKNAD1, RP11-456K23.1, APOBEC3F, ZMYND15, RP11-588K22.2, CYP2D7P, ERMP1, ADAM22, ABCA9, GRB7, LL22NC03-86G7.1, HSPB7, FAM196B, SOX9-AS1, FAM227B, BEST3, TRAM1L1, SGIP1, ADCY7, PCED1B, SEPN1, APOBEC3G, CCDC28A, NGFR, MPP2, IL17RD, PLAU, TMEM173, IFT27, CTD-2292P10.4, ZNRF2P2, NT5E, DGKB, TWISTNB, STMN1, RTN4RL2, SLC25A34, HFE, S100A16, RP11-807H7.1, KRT15, ITGB3, CIB2, SHMT2, GAB2, CMTM8, GALNT13, CCDC149, GALNT14, SLC35D2, CCND1, SYNPO2, ATP5SL, ETV1, TMEM216, TNFRSF1B, USP18, BCAT2, ACOT8, HYOU1, AP2M1, HTR7, PALM3, RP4-760C5.5, OTUB2, PLEKHA5, MIR621, TMPPE, RGS2, TNFRSF21, ERAP2, DCAF7, SFXN2, KRAS, DAZAP2, CLSTN1,

ARHGDIB, FAM114A2, TP53INP1, TCEAL8, ST6GALNAC3, CERS1, PTPRE, PDE3A, CTSO, SLC30A4, ENDOD1, SLC23A2, C1QBP, UBE2L6, CNRIP1, ST3GAL5, ENPP4, PARD3B, PLD6, DPY19L1, ABCA8, MORN4, MYB, SLC26A2, NSF, FAT4, TPP1, SLC30A7, ZNF512B, ACPL2, RP11-27I1.4, EDNRA, A4GALT, ZNF836, RNF146, PLCD1, STARD7, PEX11B, UPRT, CEP41, PTPRZ1, AGPAT1, ARHGAP19, XAF1, DHCR24, OSMR, AGAP2, MAST4, ACSS2, FBXL16, RHOU, RP11-18I14.10, GBP3, POU2F2, AC009948.5, FAT3, PLCD3, LRRC8C, PGPEP1, SEC31A, SLC18B1, ISLR2, LINC00669, ZMAT3, IL1B, AIMP2, CCNJ, MOSPD2, GLYCTK, ST3GAL4, LRRC8A, TNIP3, MSANTD3, ANKRD13A, PCBD1, DERA, ARHGAP27, GLDCP1, GABPA, DGKA, ATP8B2, RUSC1, ZNF362, PRPF40B, SAMD9L, STS, RAB5B, CCL20, PCYOX1L, NFE2L3, USP27X, KDM7A, CDC42EP2, MMP1, FAM72B, GPR146, WNK4, MEF2BNB, MYOZ3, PADI2, CDKL5, HTR7P1, PTCH1, OAS2, ZNF365, OBSCN, PDE4D, WSB2, CYTH1, NCEH1, KIF5C, PRNP, MTSS1, FAM60A, LINC00657, GPD1L, FOCAD, DCTN5, PIK3R1, UBP1, RP11-340I6.6, ZDHHC18, LOX, PIGA, CA12, APOLD1, PGM5, AKAP12, MCL1, PHLDA2, ZNF608, HACE1, BMF, IGSF3, PITPNB, ZSWIM3, ERBB2IP, NUDT18, PTPN9, ZCCHC10, ITGA2, PIP4K2C, TRAK2, LGR4, AP5M1, EBF1, DOCK4, AL390877.1, MED21, ELMO3, AC108676.1, GPRASP2, NAGA, CNOT6, ATP5F1, ZNF710, EPM2A, OSBPL5, COPRS, FCHSD2, TRIB2, TK2, TBX20, RUFY2, SREK1IP1, GNAI3, RP11-421N8.1, IL8, FAM132B, YWHAZ, TAF9B, WDFY2, YWHAZP3, MARCKSL1, ETS1, TRIM62, HK2P1, ALDH9A1, OSBP2, TMEM180, GNPDA1, SAMD9, BTN3A2, YWHAZP2, PTK2, PNRC2, RAD17, IQCD, DNAJB9, ARHGEF9, POLE3, ARMCX2, DPM3, KANK2, DOK3, PLAUR, INPPL1, NT5DC3, DNMBP, LRRC40, ARHGEF40, SYNRG, GPATCH11, IWS1, RGL1, SEC61A1, PHACTR2, CDC14B, ZNF181, KLHL2, CBX7, IDS, PAK4, FAM72A, MPST, WBP5, ARF3, ACSL5, UBE2Q2P6, DDAH1, ASAP3, TRO, GAS1, PTPLB, ST5, SCP2, DOCK10, PXK, ARHGAP29, CXCL2, HECW1, LAMC2, R3HDM4, MAP3K3, MLLT11, GBE1, HYAL2, RAB11FIP5, GRAMD4, C11orf95, ADAMTS18, APBB2, CCSER2, WDR48, FAF2, STC1, IDH1, NUDT3, PARP14, NET1, AKR1C3, CHCHD5, HEMK1, TUFM, ELK3, DGKQ, CDK6, LPAR1, GDF15, CTDSP2, GULP1, MMP14, SIX4, LARS2, CD38, LRP5, CRKL, SMPD1, DUSP16, JAK2, B3GNT1, KIAA1147, FAM214B, PARD6A, SLC12A9, SS18L1, DGKH, PSEN1, ENOX2, PAX6, UFL1, FAM210B, TPCN1, SMG6, MAGI3, PALMD, NEIL2, PDK4, APAF1, AGFG1, SLC35D1, SLC25A15, RNF215, GALNT1, HEG1, TRAF1, SRP54, PDGFD, HNRNPUL2, MDM2, TMEM30A, RSPO2, GPC6, PLEKHA2, CACNG4, CASZ1, PAG1, EXTL2, IFIT3, KANK1, RNF2, TNIK, PTPN21, ENTPD4, QDPR, PTPN3, SYNJ2, TMEM164, KITLG, FBXL15, PGAP1, DENND4C, GSDMD, TRAPPC9, ALKBH5, TRAFD1, DAB2, JADE3, PDPK1, COPS3, ABL1, EVA1C, EML4, SFXN1, LRP3, DDX60, EIF4BP3, DNAJC3, TGFBR3, DAK, CTTNBP2NL, GNAI1, STARD3, TGM2, SLC9A3, IRF1, HK2, PLEKHB2, MAGEF1, PPTC7, RPS6KB2, ADAMTS15, EIF4BP7, SCAMP4, ADAMTSL1, NDFIP2, EIF4B, GPR176, MORC4, ERBB2, FAM20B, AREL1, GNL3L, USP39, SLC39A10, BOD1, ATP6V1B2, ARHGAP18, KIAA0430, GFPT1, EIF4BP6, SREBF2, FBXL17, MAX, CBFB, NECAP2, GEM, CDC42EP3, KIAA1522, KLHL9, CBL, KIAA1644, RCAN1, SUSD5, JADE2, GRHL3, SMARCA1, USP40, SQSTM1, KIF1B, LUZP1, SMIM14, MEX3C, ARHGEF1, NUP50, HELZ, CCDC90B, PPM1H, BCAR1, RAB27B, PSMB8, ANTXR1, SENP1, F2RL1, ARPC5, SIPA1L2, LNPEP, UBALD2, ZC3H7B, NUDT21, YAP1, FAM65A, LRBA, BMPR2, FRMD6, APPL1, AMIGO2, SCAMP1, AES, LPHN2, ZNF395, WDR82, HPRT1, PRKCA, TDO2, TCF4, TRIM8, SFT2D2, SLC20A2, ADAMTS1, SEC23B, RSF1, CPNE3, MAMLD1, DYRK2, LLGL1, NR2F2, TRIP6, SOS2, ARPC2, ERRFI1, IDO1, PLSCR1, RNF182, BNC2, STAM, MX1, TCTN3, CHML, ELMO2, PITPNA, GALNT2, KLF3, RIPK2, PPM1F, LPCAT1, TBX18,

MRPS18B, KIRREL, HSPA13, MAP4K5, LRRC8D, MAGED2, NCOA3, BACH1, IL7R, CCNA2, KDM5C, SLC30A1, CCNY, PIP4K2A, DDB1, RND3, DAPK1, GOLPH3, SSRP1, INTS3, FAM168B, TMCC3, CDK4, ZMIZ1, TM4SF1, NSD1, MTA2, SNHG5, GIT1, PPP2R4, KIAA1191, TXLNA, RC3H2, TMBIM1, TNFAIP8, HELZ2, UHMK1, CREBBP, WIPI2, FRMD8, PLIN2, NOTCH2, LIF, ANGPTL4, DUSP4, SLC7A5, LAMC1, PLS3, and SNX9, even more preferably it is for downregulation of all of these genes. This use is preferably for treatment of breast cancer, more preferably of triple negative breast cancer, wherein the cancer is preferably associated with increased or exacerbating expression of said gene. These genes were found to be downregulated by miRNA-193a in BT549 cells (Example 1.2.1).

In other more preferred embodiments, it is for downregulation of a gene selected from the group consisting of GPRC5B, RP11-30P6.6, LEF1, RGS17P1, CTC-428G20.6, CAMKV, RP11-440D17.3, RASA4, OXCT2, GRAP, CTA-217C2.2, ADAMTS16, AC119673.1, MPP2, CAMK2B, FGFR2, MIR103A2, LINC00460, RP11-540B6.3, AC005789.11, RP11-196O16.1, TCERG1L, TNFRSF1B, ARMCX4, STON2, PARD6A, FAM156A, AGAP1-IT1, AC010525.6, MYRF, FBXL16, MAPK13, RLTPR, EXOC3L4, CCDC28A, HMX3, NDN, TP73, CTA-445C9.15, EXPH5, PHLDA2, RASSF5, ST3GAL5, 03-Sep, STMN1, INSRR, SHMT2, N4BP3, TWISTNB, CACNG6, PLAU, ERMP1, FOXRED2, SEPN1, KALRN, LRP4, IL1RL1, AC009061.1, PDE9A, TGM2, IGSF9B, PTGER2, DAZAP2, PITPNB, FAM132B, FKBP9L, ATP5SL, STARD7, HOXD13, RHOV, WDFY2, GNA15, HYOU1, DDAH1, INO80C, UBE2L6, ATP8B2, PRKCH, AP2M1, DHCR24, TOR4A, TMEM121, SRRM3, ARHGAP19, SLC39A10, RP11-82L18.2, AGPAT1, DND1, NT5E, GJB2, SLC30A7, F2RL1, FAM105A, ELK3, GCH1, GRTP1, NID1, SLC30A1, IRF1, PTK7, SERINC2, TMEM173, MARCKSL1, CCND1, FIBCD1, KIAA1644, COPRS, P2RX5, ZNF365, HHAT, TNFRSF21, VAMP8, SLC35D2, RP11-340I6.6, KRAS, ZDHHC18, WNT9A, IGSF3, DPM3, ALDH1A3, PRDM8, SLC26A2, ROR1, ACSS2, C11orf95, GALNT14, STC1, IL8, NPIPB4, UBP1, NR2F6, PRNP, USP39, DUSP7, FAM101B, FAM60A, ST3GAL4, OSMR, SH2B2, FAM168B, STRADB, ZNF703, TRIM62, SOX18, YWHAZ, CDK6, GNAI3, RP11-204C16.4, FOXL1, ACPL2, GNPDA1, LRRC8A, GREB1, SLC30A4, SORL1, TBC1D5, RP3-425P12.4, ALX4, NCEH1, CHST14, MCL1, VASH2, SLC45A3, AIMP2, RUSC1, RASL11A, ICAM1, RP11-329A14.1, HEG1, PIK3R1, ETS1, KIAA1147, ANKLE1, CXCL3, PTX3, EFNB2, FAM20B, DGKH, YWHAZP2, DPY19L1, YWHAZP3, DCAF7, BCAT2, SCAMP4, DCTN5, RAB11FIP5, BOD1, ZMAT3, C12orf39, CCNJ, WSB2, GPR161, POLE3, NEFH, GPR3, RBM24, SUCNR1, B4GALNT3, IDH2, TEX15, TERT, RP11-101E13.5, SFXN1, C16orf59, C1QBP, TGFBR3, ZCCHC10, KLHL2, IL6R, AP5M1, GALNT13, PSRC1, PDGFRB, LMNB2, COL5A3, MYEOV, TMEM164, SERPINE1, CXCL2, STAMBPL1, GFPT1, DERA, WDYHV1, PDPK1, SIPA1L2, CCNDBP1, MAX, KANK2, PITHD1, IL4R, NT5DC3, ATP5F1, FAM60CP, PFDN1, CA12, PMAIP1, NPTX1, CLSTN1, MOSPD2, NUDT21, SLC35D1, GABPA, TRAFD1, RP11-22P6.3, UBE2Q2P6, NUDT15, SLC7A5, MESDC1, ADCY1, TMEM216, PDE3A, ENDOD1, CRKL, LOXL1, NHS, NES, TBX2, DMTN, EGR1, GPATCH11, CNOT6, TEAD3, UNG, AREL1, PLSCR1, HPRT1, RNF138, TAF4B, RFWD3, MAMLD1, ARHGAP26, AKAP12, PAK4, TXLNA, MPST, TNFAIP8, RAB5B, SMPD1, PM20D2, MSANTD3, CXCL1, SOX7, PAPPA2, CMTM3, CAPN15, RP11-421N8.1, DOCK10, SEC61A1, KCNK5, NAGA, LINC00941, CXCL5, TBL1XR1, FAM72D, ZG16B, TMOD1, PNRC2, GDF11, SEC31A, PLCD3, PTPLB, PLEKHB2, FOSB, NRIP3, HSD11B2, GPR27, WDR5, ARF3, RNF216P1, ZNF35, CASP9, SLC29A3, ST8SIA4, SCP2, FCHSD2, ABR, ARHGEF40, KLHL15, PPM1F, KCTD12, APLN, DTL, CCNA2, SRP54, SLC16A6, LRRC40, MED21, EML4, TNFRSF8, IL1RAP, HFE, FOXN2, ALKBH5, CCDC85C, SLC23A2, ARPC4, GLO1, SYNRG, ORAI1, ZNF678, NOTCH2, ST5, LUZP1, KIF1B,

KCTD5, DLX1, RGS2, TANGO2, FAM72B, CASP2, UBE2Z, SSH3, FAF2, ADCY9, C18orf54, MAFF, MAP3K3, RBBP5, KLHL23, JADE3, ZNF618, BAI2, CBX1, PLXNA2, CDK2, CBFB, CBL, NUP50, GLI2, MMP1, CMTM4, BMP6, PSEN1, JAG2, LINC00657, ARHGAP29, ACSS3, ARPC5, TUBG1, FOCAD, TUFM, ZC3H7B, KIF26A, TP73-AS1, PAG1, RC3H2, SENP1, MTA2, CDCA7, SLC29A1, TRAK2, RNF2, POM121C, RNF146, TONSL, TEAD4, ELMO2, ENTPD4, BRPF3, PGRMC1, CLN6, OSBPL10, ERRFI1, PODXL, AMIGO2, LRRC8C, ANKRD13A, GALNT1, ASAP3, NUDT4, OSBPL8, CDC42EP2, SLC19A2, IL18R1, SMOX, EFNB1, TMEM30A, POM121, SLC16A9, UNC119B, ARPC2, INPPL1, KIRREL, CNKSR2, BCL2L2, TOMM20, SPRY4, SDC1, AFF4, FOS, SH2B3, KIAA1191, RNF215, SLC18B1, CTDSP2, PXK, TCEB3, SREBF2, C12orf49, KLHL8, APOL6, UBALD2, HK2, NET1, RUFY2, C17orf58, C11orf24, CDCA7L, SAMD8, MAPK8, NOTCH1, PEX11B, HSPA13, PPTC7, DMRTA2, NEIL2, COPS3, TPD52, HNRNPUL2, FKBP9, EXOSC3, CCP110, PLAUR, GATA2, ABI2, SSRP1, SYNJ2, CBX6, CHCHD5, WDR82, PPP2R4, HSF1, ERBB2IP, PCBD1, SREK1IP1, MAP4K5, FRMD8, CRLF3, DDA1, EIF4B, FERMT3, CSRNP1, IWS1, LARS2, ID1, R3HDM1, ENOX2, WNT5A, FBXW2, PTK2, MTFR1, WNK2, SCAMP1, QDPR, PPAT, HELZ2, TK2, LPHN2, FZD8, TMBIM1, ALDH9A1, ELF4, BHLHE40, NUDT3, ASF1B, STS, WDR6, JAG1, PSMB8, PIP4K2C, CYP51A1P2, RNH1, THRA, MAP7D1, MFN2, PHF19, RNF168, ETS2, ANTXR2, SLC35G1, MEX3C, UTP18, PPP4R1, MDC1, HELLS, ATP6V0A2, DYNLL2, GOLPH3, SQSTM1, PATZ1, DESI1, GALNT2, HIP1, LINC00152, SAPCD2, FAM210B, PLXNA1, R3HDM4, REXO4, TYW3, CCDC14, SPECC1L, STARD4, ABCB10, NSF, ALG2, MAGEA1, KRT80, ZBED4, DEF8, SH3PXD2B, LSM14B, DUSP5, PAQR4, HSPB8, TRIB3, FBXW5, RBM10, SFT2D2, PDE4D, WHSC1, UPP1, FAM115C, EPDR1, RASA3, XPNPEP1, CDC45, MYADM, HN1L, BCOR, PRKAA2, RAPH1, CCSER2, CHEK1, NAB1, SLCO4A1, ADRBK1, PXN, B4GALNT1, TSPAN14, RIN1, TCOF1, SMG5, HP1BP3, RP11-1055B8.7, HSBP1, SKA2, OGFRL1, CDT1, SGMS1, MCM10, APPL1, ATP6V1B2, TROVE2, CD97, TRIP13, SS18, PHLDA1, TRIM25, FOSL1, ID3, PPP1R26, PPP3R1, RFC3, MRPS18B, GPC1, SET, IDS, MED14, IER2, TFPI2, UBFD1, CDCA4, OGFR, CNBP, PAPOLA, MRPL19, TNFAIP2, AKR1C3, TOMM34, FGFRL1, MCM2, KIAA0141, ADNP, LPCAT1, CDC6, MLEC, KIDINS220, AGFG1, HMGB1, LIF, IDH3A, UHMK1, TRIP6, RBM8A, FARSA, URB1, PITPNA, GNB1, WWTR1, SETP14, RPS21, CAPRIN1, TGOLN2, STC2, OSGIN1, NOTCH3, IDH1, BAZ1B, DDB1, TNPO1, LASP1, PCBP1, FASN, and TUBB, ACTB, even more preferably it is for downregulation of all of these genes. This use is preferably for treatment of lung cancer, such as for treatment of PTEN-deficient lung cancer, wherein the cancer is preferably associated with increased or exacerbating expression of said gene. These genes were found to be downregulated by miRNA-193a in H460 cells (Example 1.2.1).

In other more preferred embodiments, it is for downregulation of a gene selected from the group consisting of RP11-313P13.5, CTB-31N19.3, LINC00607, LRRC15, RGS17P1, NPAS3, CTD-3203P2.2, CSTF3-AS1, CTD-2342J14.6, CTD-2537I9.5, MYEOV, ANKRD31, CIDEC, MYO1G, SRRM3, LINC01132, ENDOD1, TSGA10IP, ADH1A, IL11, RP11-572C15.6, CD207, RP11-274H2.5, TFF3, UXT-AS1, RPS19P3, RP11-305K5.1, CTD-2192J16.20, LL0XNC01-250H12.3, ZSCAN23, LINC01096, RPSAP52, CDC42EP3, AK4P3, GALNT16, ETS1, SEC14L2, CHST6, RP11-255H23.2, LINC01057, ULK2, FAM162B, RP11-1017G21.5, CTD-2161E19.1, MFSD4, ASAP3, AC026150.5, AC005077.12, LINC00312, TRIM62, CCDC28A, ROM1, TRPV3, RP11-73M18.9, HHAT, B3GNT3, TMEM30B, CRYAA, TFAP2A-AS1, TMEM151A, DACT3, SLC35D2, CCDC17, TGFBR3, TIMP4, MPP2, MYCN, TWISTNB, C19orf77, CCND1, NT5E, PTX3, RP11-116D2.1, SOCS3, SHMT2, PRR15L, DOK7, NAPA-AS1, SPP1,

ERMP1, UBE2L6, NACAD, SLC6A12, KCNG3, CHCHD2P6, ERBB4, ANGPTL2, FAM150A, LOX, ANKLE1, ACOT8, ST3GAL5, AMPD3, SLC15A1, IL17RD, MYADML2, C8A, FOXRED2, GRIN2D, STMN1, DCAF7, TRIM17, HR, C1QBP, LINC00657, HFE, RP11-469M7.1, ATP5SL, FAM60CP, RP11-421N8.1, MPZ, SLC29A3, PNRC2, ARHGAP19, CDC42EP4, FAM168B, GTF2H2B, SORL1, PPARGC1A, P2RY1, KRAS, PHLDA2, DPY19L1, CCDC149, CCNJ, TNFRSF21, RUSC1, UBP1, IDS, DCTN5, SYNE3, LAMC2, KDM7A, LEF1, GABPA, PCBD1, PCYOX1L, TNFSF9, PDGFRB, MAT1A, VAMP8, ARID3B, CXXC4, MYB, ATP5F1, RP11-204C16.4, RP11-973N13.2, FAM101B, ENPP4, KRT80, HYOU1, PITPNB, WSB2, CRKL, UPK1A-AS1, AP2M1, FAM60A, PSRC1, DUSP7, DDAH1, ANKRD1, FAM203A, CNOT6, CER1, RP11-613M10.6, ATP8B2, IL6R, AAED1, ESRRG, INO80C, HSPB8, SLC23A2, SOX5, PDE3A, HFE2, NPTX1, ADCY9, MAX, NPPB, SLC30A7, RAB11FIP5, ZCCHC10, PAG1, MAPK8, FOXC1, UNC5CL, STARD7, LRRC8A, HRK, MISP, AIMP2, PIK3R1, PLAG1, POLE3, ACPL2, NCEH1, SCNN1A, AP5M1, CLSTN1, AC005077.14, HEG1, SLC39A5, MCL1, MED21, INPPL1, DAZAP2, ELFN1, CDK6, ST3GAL4, TGFB2, PRICKLE2, CYTH1, PLEKHA8, TAF4B, RP11-340I6.6, EFNB1, RP11-91J19.4, CTD-2196E14.9, B4GALT4, RASA3, GREB1, ZDHHC18, KRT17, ELMO2, MSANTD3, AGPAT1, YWHAZP3, CGNL1, CUX2, SH3BP5, ZMAT3, SCP2, PEX11B, PPM1K, KIAA1191, GFPT1, GALNT13, C18orf54, CXCR4, ETV1, RNF146, RGL1, HPRT1, EIF4B, CDC42EP2, CTD-2369P2.2, ABI2, BFSP1, SLC6A15, PELI2, TRAK2, DERA, TPP1, EFEMP1, FCHSD2, RSF1, TP53INP1, TK2, PPTC7, HACE1, BOD1, DLX1, YWHAZ, FAM114A2, EFNB2, SMPD1, UBE2F, GPR176, GRB7, ZBTB5, ATOH8, TWSG1, PRNP, OLFML2A, ARPC5, RP11-342K6.1, GCH1, NOTUM, LUZP1, SPECC1L, NUDT21, APPL1, SFXN1, FAT4, UNC119B, ZMIZ1, SCLT1, CD97, AREL1, NYNRIN, ADAMTS1, SEC61A1, SIX4, PNMA3, FAF2, INPP5B, CTGF, OSTF1, TYW3, RAB5B, CBX1, TBC1D12, USP39, ACSS3, CYR61, PCDH17, LMCD1, KIAA1147, EEF1A1P13, KIF3A, EDN1, RP11-53O19.3, SMARCA2, EFNA4, GPR133, RBBP5, NCF2, NUP50, OGFRL1, WDFY2, DHCR24, SOS2, YWHAZP2, KLHL2, IGSF3, CCDC80, THSD7A, ZNF618, ACSS2, PDPK1, BCAT2, PHACTR2, GLIS2, MARCKSL1, C11orf24, CBL, CCNDBP1, NDUFC1, ERBB2IP, IRF1, EIF4BP6, PAFAH2, ALDH9A1, SIPA1L2, HSBP1, HNRNPUL2, NRP2, NUDT4P1, SDE2, SGMS1, SLC30A1, FOCAD, SERINC2, DESI1, TBL1XR1, TMEM30A, PLEKHB2, DYNLL2, HELZ, TSPAN14, PHGDH, RP1-203P18.1, C17orf103, TRAFD1, DUSP16, NUDT4, FLNC, RGS2, EIF4BP3, DUSP1, TMEM59L, GADD45B, WWC3, RP11-329A14.1, MRPL42, ELOVL7, BACH2, MAP4K5, GNPDA1, NET1, PBX1, BCL2L2, ATP6V1B2, RNF2, SYNRG, SMIM13, COPS3, ARPC2, MDM2, VGLL3, MIR22HG, TRIM10, HSPA13, PTK2, PCDH9, ZC3H7B, LARS2, PITHD1, C1orf106, MAGI3, TNIK, CHSY1, KANK2, TXLNA, TUFM, GMEB1, IWS1, ZNF710, TSC22D3, MVB12A, TMEM216, TAF8, SREK1IP1, IDH2, KIF1B, SLC39A10, STRADB, SLC7A5, PAK4, PTPN9, TGM2, R3HDM1, UGT2B7, CHCHD5, TMEM164, RUSC2, MESDC1, COPRS, EIF4BP7, NOTCH1, USP53, MTA2, NUDT15, DGKH, PLCD3, LPHN2, SLC6A19, KIRREL, IRGQ, RPS6KB2, PSEN1, ANKRD13A, MOCOS, SLC34A2, AMZ1, GBA2, EML4, LINC00511, TEAD4, CA12, KDM5C, CABLES1, NINJ1, WDR82, MAST4, IGFBP4, LPCAT1, CBX6, ZNF512B, ARF3, TMEM135, PDE4D, LSM14B, AFF4, DYRK2, SS18, PTTG1IP, GLYR1, LUM, NEDD9, JADE3, SEPN1, GGCX, MEX3C, ARHGAP29, MECP2, AMOTL2, PPP1R26, MAGEF1, GABARAPL1, GLIS3, IDH1, SEC22C, NR2F6, PHF10, KATNB1, R3HDM4, AES, WDR48, GNAI3, MYLK, DDA1, HK2, CAPRIN1, CADM4, UNG, SENP5, ARFIP1, KIF14, SLC35D1, NSF, FBXW2, RND3, PLS3, TLE4, CBFB, ALKBH5, CDC14B, GRAMD4, SLC19A2, ELF4, EPHA2, SCAMP4, ARHGEF12, PITPNM1, GGA3, FAM20B, GLO1, MTMR12, DLC1, TAPT1, MPST, UBE2J1, ID3, PRKAA2, PDXK, PIP4K2C, TRIP6,

CASP2, NECAP2, TUBB4A, MRPL19, GALNT1, CD2AP, RBFOX2, GOLPH3, PITPNA, TMEM230, KIAA0430, RP11-427H3.3, PPP2R4, AJUBA, KLHL9, EEF1A2, MYADM, RBM8A, PRR14L, AKAP12, NUS1, YAP1, CTDSP2, CHML, PTPLB, DNAJA1, CLN6, DLG1, C12orf49, ZBED6CL, CAB39, ZNF629, FILIP1L, ETNK1, LRRFIP1, NUFIP2, SFT2D2, RAB21, SMAD3, NF1, RPL27A, LARP4B, FKBP9, EP300, TOMM20, CREBBP, SSRP1, SEC31A, BRPF3, SERPINE1, SERINC3, S100A14, CDCA7L, PIP5K1A, GSR, SQSTM1, BAZ2A, SLC20A2, SON, TMBIM1, LAMC1, LGR4, APOH, IGF2BP1, ARFGAP2, BCAR1, FZD5, GDF15, RP11-475C16.1, WDR6, and ACTB, even more preferably it is for downregulation of all of these genes. This use is preferably for treatment of liver cancer, such as for treatment of PTEN-deficient liver cancer, wherein the cancer is preferably associated with increased or exacerbating expression of said gene. These genes were found to be downregulated by miRNA-193a in HEP3B cells (Example 1.2.1).

In other more preferred embodiments, it is for downregulation of a gene selected from the group consisting of NRG4, RAC2, HMGA1P3, SAMD5, RP11-168L7.1, TMEFF2, CTA-14H9.5, AP001059.5, TMEM130, B3GNT4, NPHP3-AS1, HIST1H1E, SLC25A21, RP11-3P17.4, RP11-820L6.1, CTD-2555O16.2, RN7SL381P, RP11-274H2.3, KCNQ4, AC007292.3, RP3-330M21.5, FSIP1, HIST1H2BF, BRSK2, ARHGAP22, CREG2, KCNH2, CENPCP1, CCDC13, CTC-428G20.6, TMEM52B, NEFH, RP11-401P9.4, MYB, RP11-35G9.3, PRL, SYNPO2L, RASL10A, GOLGA7B, RP11-10O17.1, SMTNL2, LINC00337, CTD-3092A11.1, CTD-2589H19.6, PLAU, TRPA1, RP11-326K13.4, MPP2, FAM101B, C1QBP, ZNF33B, LEF1, SHMT2, CDC45, CSPG4, PSMB8, UBE2L6, STMN1, RP11-424C20.2, ARHGAP19, UHRF1, FOXRED2, FAM111B, TWISTNB, VAMP8, TMEM30B, SORL1, RP11-296O14.3, SLC35D2, E2F8, SLC30A2, KRT23, CCDC28A, ERMP1, RRM2, FCRLB, FAM72A, EVA1A, EXO1, PSRC1, DCAF7, MCM10, FAM72D, PNRC2, DPY19L1, GPR137C, CDT1, ST3GAL4, TGFBR3, ST3GAL5, FAM168B, SPC24, ZDHHC18, C8orf37, PDGFRB, IFIT3, PAX6, ABI2, FBXO5, KDM4D, ATP5F1, LPPR1, NT5E, RP11-386G11.10, RBL1, RP11-421N8.1, CDCA7, C12orf39, ATP5SL, TCF19, E2F2, SULF2, NRGN, ACOT8, POLE3, VASH1, GABPA, HIST4H4, STARD7, CHEK1, CASP9, COLGALT2, ETV1, DDAH1, INO80C, RP11-411B10.4, PCNA, WDR76, COPRS, TPBG, SLC15A1, CCNA2, PHLDA2, SLC23A2, TYMS, HPRT1, SLC29A3, TRPM6, TNFRSF21, NCEH1, DTL, DHCR24, PITPNB, WSB2, DCTN5, ADCY9, GINS2, CDCA5, THSD7A, ASF1B, E2F7, SPC25, CCND1, RUSC1, DAZAP2, TICRR, CLSTN1, RP5-837I24.1, CDCA7L, FAM60CP, LRRC34, PPP2R2B, CRISPLD1, DSCC1, RP5-1033H22.2, SLC30A7, ENPP4, UNG, MCM5, KRAS, MCM2, TRHDE, AIMP2, AP2M1, SEPN1, ARID3B, CHAF1A, CDKN2C, PIF1, FAM72B, HACE1, BRCA1, CCNE2, STEAP2, RAD17, AGPAT1, PAQR4, CLSPN, TIMP4, PRPS2, KIF14, CADM1, USP39, CCNJ, GALNT13, MCL1, CCP110, RTN4RL2, FAM64A, UBP1, FAM60A, HYOU1, CXorf57, ARHGAP11A, MOSPD2, PKMYT1, KIAA0101, CKAP2L, PP13439, IL22RA1, CDK2, PLAUR, CNOT6, MND1, BAAT, DUSP7, SFXN2, AL390877.1, MED21, EFNA4, GPATCH11, FAM111A, MOCOS, DHFRP1, SAMD9, BHMT, RP11-253E3.3, NUDT21, CNKSR2, ACSS3, SREK1IP1, CTD-2196E14.9, LRMP, BRIP1, CRKL, RP11-340I6.6, MGAT4A, PCYOX1L, MYCN, ZMAT3, LPAR3, NUDT15, CDK1, MCM6, TRAK2, NSF, ROR1, MYBL2, R3HDM1, RGS10, RILPL2, KANK2, PRIM1, PHF19, CA12, CLN6, MKI67, SFXN1, SLC45A3, RMI2, HELLS, GAS2, KIF2C, IL17RD, STAMBPL1, NUP50, SPATA5, KLHL2, RGL1, HNRNPUL2, B4GALNT2, CENPM, COPS3, CCNF, CCDC149, RNF168, ORAI1, DERA, APOL6, AUNIP, PPIL3, GBA2, RP11-613M10.6, MAP3K3, ZBTB5, CDC6, POLA2, PCBD1, GNPDA1, SKA3, ORC1, ACOT11, PHACTR2, KIF18B, NCAPG, PLD6, FCHSD2, ACPL2, ERBB2IP, CXCR4, MELK, PTGDR2, CDK6, PIGA, RP1-

249H1.4, TK1, IL6R, KIAA1147, C17orf58, CHST14, CEP41, UBR7, MASTL, ARPC5, TONSL, RP11-67L2.2, SAPCD2, UTP18, OSMR, AURKB, IQCC, ITPRIPL1, MSANTD3, SLC26A2, C14orf80, RAD51, LMNB1, UBE2T, SLC25A15, FANCE, PAK4, ZNF512B, DHFR, WDFY2, ZNF618, INCENP, IGF2BP1, ESPL1, PODXL, SS18L1, NR2F6, CHRNA5, MAPK8, KIFC1, MMS22L, BCAT2, OAS3, CDCA4, NAGA, TMPPE, CAPN15, RGS2, RNF146, AP5M1, SYNRG, SCP2, RP1-60O19.1, LRRC8A, SGK2, DGKG, NUSAP1, IDH3A, KIF4A, MRPS18B, MBL2, GRB7, FAM20B, CDC25A, PDE4D, TIPIN, TMEM216, RAD51AP1, RP11-21L23.2, BLM, SAAL1, YWHAZP3, TXLNA, KIAA1191, ETS1, KIF15, FANCG, MAX, AREL1, KANK4, CDCA3, NIPA1, FARSA, RFWD3, CGNL1, ATP8B2, MAB21L2, EFHD1, FOCAD, ARMCX4, H2AFX, DEK, WDR62, PPTC7, KIRREL, PRR14L, SSRP1, UBALD2, LINC00657, HJURP, FGF19, GREB1, KNTC1, MCM4, SLC35G1, MARCKSL1, HEG1, MGME1, TAPT1, TPP1, FAF2, RP5-1024G6.8, ATAD5, LARS2, PLK1, ANKRD13A, ARHGEF34P, ATAD2, PAFAH2, TUFM, SLFN13, SKA2, UNC119B, SEC61A1, FEN1, ARF3, SPECC1L, CABLES2, MCM3, SMIM13, BRCA2, GINS1, HMGB1, TMEM30A, ALDH9A1, E2F1, PAG1, LMNB2, CECR2, SYTL5, TMEM194B, WHSC1, IWS1, JADE3, EIF4B, MYLK, SMPD1, PLEKHB2, CENPE, RP11-121L10.3, MPC1, CENPF, TUBA1B, PTPN9, ZWINT, ENTPD5, DSN1, DEPDC1B, SLC43A3, FOXM1, IDS, MORC4, BUB1B, MDM2, GALNT1, NR0B2, KIF11, HELZ, C16orf59, MTHFD1, CDC20P1, TP53INP1, XRCC2, RCAN3, ITPKA, PLEKHA8, NDC80, TOP2A, DOLPP1, CASP2, GNL3L, ZCCHC10, GINS3, ABCB10, RAB11FIP5, TRIP13, SLC39A5, FAM83D, WDR82, TBL1XR1, DUT, ZNF395, RECQL4, TCF4, CHAF1B, TFAP4, USP1, ASPM, REXO4, LRRC40, SLC7A5, LIG1, SPP1, PIP4K2C, PDPK1, DNA2, ESCO2, LSM14B, GTSE1, HP1BP3, C10orf12, MCM7, PDE3A, ARHGEF39, CTDSP2, TWF1P1, RFC3, SP4, ACD, PLSCR1, MAD2L1, DKK1, CBX1, AKR1C2, TUBB4B, ZNF346, PLEKHA6, KIF18A, GXYLT1, SLC30A1, MAP7D3, ZNF710, YWHAZP2, RAD54L, WDR5, ARPC2, CBFB, EZH2, CASP8AP2, TFDP1, GLYCTK, SOS2, MXD3, TPRN, GLO1, RRP7A, EML4, MTA2, STIL, PLXNC1, MAGI3, QDPR, PARP14, CDC20, SIPA1L2, MSH2, RRM1, ELMO2, IQGAP3, KIAA0430, TACC3, PTPLB, NOL9, SEC22C, PBX1, UBE2C, POLQ, HK2, RFC2, TUBA4A, EXOSC3, SS18, WDHD1, CTDSPL2, HSBP1, YWHAZ, NCAPH, RBM8A, XPNPEP1, IGSF3, POLE, C11orf82, RP11-475C16.1, SLC19A2, ADRBK2, PPAT, TWF1, FST, SGMS1, KIF22, SLC20A2, MRPL19, MKL2, TRAFD1, ALKBH5, NUCKS1, DNMT1, ACSS2, INPPL1, PRR11, RAB5B, EIF4BP7, PRTG, ARHGEF5, DESI1, TMEM135, TUBG1, EIF4BP6, LIMD1, MBNL3, PLK4, CMTM4, SLC30A9, POLR1E, BRI3BP, PITPNA, HMGB2, BOD1, NASP, SLC35D1, ELOVL2, SCAMP4, SMG6, ARHGEF12, POLR2D, FANCD2, LPHN2, SMC4, WDR48, POLA1, KIF20A, DLGAP5, RSF1, SRP54, PIP4K2A, NET1, CDCA8, SYNM, MPST, PNP, SLC18B1, IDH2, OSGIN1, NUP210, RBM10, MDC1, C11orf24, RPL27A, CDCA2, KIF1B, DYNLL2, PTPN3, TCOF1, LBR, RPS21, KIDINS220, LGR4, KIF23, TOMM20, LAMC1, GLYR1, RPS6KB2, RCC1, TMPO, PTK2, TPX2, SPAG5, CAPRIN1, GTF3C5, SLBP, HMGB1P5, CCNB1, AFF4, ANLN, SEC31A, GSR, H2AFZ, PTTG1IP, and SQSTM1, even more preferably it is for downregulation of all of these genes. This use is preferably for treatment of liver cancer, such as for treatment of PTEN-deficient liver cancer, wherein the cancer is preferably associated with increased or exacerbating expression of said gene. These genes were found to be downregulated by miRNA-193a in HUH7 cells (Example 1.2.1).

In preferred embodiments the miRNA-193a is for use in treating a cancer associated with at least one active pathway selected from the group of active pathways as listed in tables 6, 9, 12, 15, and 18, preferably with increased activity of said pathway, more preferably with increased activity of all

pathways listed in tables 6, 9, 12, 15, and 18. In preferred embodiments the miRNA-193a is for use in treating a cancer associated with at least one aberrantly expressed gene associated with a pathway selected from the group of associated genes as listed in tables 6, 9, 12, 15, and 18. Increased or active expression of a pathway or gene is preferably assessed by comparison to expression in a healthy cell or tissue sample or untreated cell or tissue sample. This use is preferably for decreasing expression of said pathway. This use is preferably for modulating expression of at least one gene associated with the pathway, wherein the associated gene is preferably selected from the group of associated genes shown in tables 6, 9, 12, 15, and 18, more preferably it is for modulating all said genes. More preferably it is for treating a lung cancer with at least one active pathway selected from the group of active pathways as listed in table 6 or 12. More preferably it is for treating a breast cancer with at least one active pathway selected from the group of active pathways as listed in table 9. More preferably it is for treating a liver cancer with at least one active pathway selected from the group of active pathways as listed in table 15 or 18.

In preferred embodiments the miRNA-193a is for use in treating a cancer associated with at least one aberrant pathway selected from the group of aberrant pathways as listed in tables 7, 10, 13, 16, and 19, more preferably with aberrant activity of all pathways listed in tables 7, 10, 13, 16, and 19. In preferred embodiments the miRNA-193a is for use in treating a cancer associated with at least one aberrantly expressed gene associated with a pathway selected from the group of associated genes as listed in tables 7, 10, 13, 16, and 19. Aberrant expression of a pathway or gene is preferably assessed by comparison to expression in a healthy cell or tissue sample or untreated cell or tissue sample. Aberrant expression is preferably an increased activity. In other preferred embodiments, aberrant expression is a decreased activity. This use is preferably for modulating expression of said pathway. This use is preferably for modulating expression of at least one gene associated with the pathway, wherein the associated gene is preferably selected from the group of associated genes shown in tables 7, 10, 13, 16, and 19, more preferably it is for modulating all said genes. More preferably it is for treating a lung cancer with at least one aberrant pathway selected from the group of aberrant pathways as listed in table 7 or 13. More preferably it is for treating a breast cancer with at least one aberrant pathway selected from the group of aberrant pathways as listed in table 10. More preferably it is for treating a liver cancer with at least one aberrant pathway selected from the group of aberrant pathways as listed in table 16 or 19.

In preferred embodiments the miRNA-193a is for use in treating a cancer associated with at least one aberrant pathway, preferably downregulated pathway, selected from the group of aberrant pathways as listed in tables 8, 11, 14, 17, and 20, preferably with decreased activity of said pathway, more preferably with decreased activity of all pathways listed in tables 8, 11, 14, 17, and 20. In preferred embodiments the miRNA-193a is for use in treating a cancer associated with at least one aberrantly expressed gene associated with a pathway selected from the group of associated genes as listed in tables 8, 11, 14, 17, and 20. Decreased or aberrant expression of a pathway or gene is preferably assessed by comparison to expression in a healthy cell or tissue sample or untreated cell or tissue sample. This use is preferably for increasing expression of said pathway. This use is preferably for modulating expression of at least one gene associated with the pathway, wherein the associated gene is preferably selected from the group of associated genes shown in tables 8, 11, 14, 17, and 20, more preferably it is for modulating all said genes. More preferably it is for treating a lung cancer with at least

one aberrant pathway selected from the group of aberrant pathways as listed in table 8 or 14. More preferably it is for treating a breast cancer with at least one aberrant pathway selected from the group of aberrant pathways as listed in table 11. More preferably it is for treating a liver cancer with at least one aberrant pathway selected from the group of aberrant pathways as listed in table 17 or 20.

Compositions for use according to the invention and miRNA for use according to the invention promote cell cycle arrest in tumour cells. In preferred embodiments, the miRNA for use according to the invention or the composition for use according to the invention are for use in the treatment of cancer, wherein the use is for inducing cell cycle arrest. Cell cycle arrest profiles can be measured for example by performing either nuclei imaging or flow cytometry, preferably as demonstrated in the examples. In this context, cell cycle arrest is preferably the induction of a G2/M or a SubG1 cell cycle arrest profile. Preferably, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70% or 75%, or more tumour cells undergo cell cycle arrest. Preferably, when the miRNA for use according to the invention is for treating PTEN-deficient melanoma, liver cancer, carcinoma, lung cancer, or pancreas cancer, the miRNA for use according to the invention is for increasing cell cycle arrest profiles.

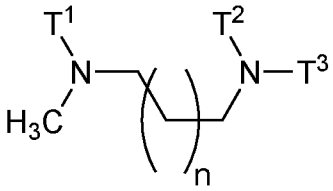
Composition

The invention also relates to compositions comprising the miRNA for use according to the invention, wherein the composition is for that same use. Such a composition comprises a miRNA-193a or a source thereof as for use according to the invention. It is referred to hereinafter as a composition for use according to the invention. Preferably such compositions are pharmaceutical compositions. Such compositions further preferably comprise a pharmaceutically acceptable solvent, or a pharmaceutically acceptable excipient, or a pharmaceutically acceptable diluent, or a pharmaceutically acceptable carrier.

Preferred compositions for use according to the invention comprise a miRNA-193a or a source thereof, preferably wherein the miRNA-193a is a miRNA193a molecule, an isomiR, or a mimic thereof. More preferably, compositions for use according to the invention comprise a miRNA-193a or a source thereof, wherein the miRNA-193a is a miRNA-193a molecule, an isomiR, or a mimic thereof, and is an oligonucleotide with a seed sequence comprising at least 6 of the 7 nucleotides of the seed sequence represented by SEQ ID NO: 22. Highly preferred compositions comprise nanoparticles as later defined herein.

In preferred embodiments, this aspect provides the composition for use according to the invention, further comprising a further miRNA or precursor thereof, wherein the further miRNA is selected from the group consisting of miRNA-323, miRNA-342, miRNA-520f, miRNA-520f-i3, miRNA-3157, and miRNA-7, or an isomiR thereof, or a mimic thereof

The inventors have surprisingly found that a nanoparticle formulation comprising a diamino lipid provides excellent results when used as compositions for use according to the invention. Accordingly, in preferred embodiments the composition for use according to the invention is a nanoparticle composition, the nanoparticle comprising a diamino lipid and a miRNA-193a or a source thereof as defined above, wherein the diamino lipid is of general formula (I)



(I)

wherein

n is 0, 1, or 2, and

T¹, **T²**, and **T³** are each independently a C_{10}-C_{18} chain with optional unsaturations and with zero, one, two, three, or four substitutions, wherein the substitutions are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy.

Such a composition is referred to hereinafter as a nanoparticle composition for use according to the invention. In the context of this application, a nanoparticle is a particle with dimensions in the nanometer range, or in some cases in the micrometer range. Preferably, a nanoparticle is as least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200 or more nanometer in diameter, where a diameter is preferably an average diameter of a population of nanoparticles. Preferably, a nanoparticle is at most 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 2000, 5000, or 10000 nanometer in diameter. More preferably, nanoparticles have an average diameter of 40-300 nm, even more preferably of 50-200 nm, even more preferably of 50-150 nm, most preferably of 65-85 nm, such as about 70 nm.

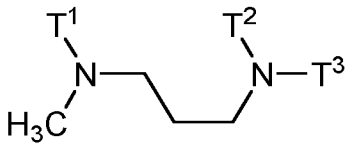
Nanoparticle compositions for use according to the invention comprise lipid nanoparticles that further comprise an oligonucleotide. The oligonucleotide can be seen as the cargo or the payload of the nanoparticle. Accordingly, the nanoparticles can for example be micelles, liposomes, lipoplexes, unilamellar vesicles, multilamellar vesicles, or cross-linked variants thereof. It is preferred that the nanoparticles are micelles, liposomes, or lipoplexes. When reference is made to the composition of the nanoparticles, reference to the diamino lipid and optional further excipients is intended, and no reference to any cargo substances is intended. As a non-limiting example, when the nanoparticle is said to comprise 50 mol% of the diamino lipid and 50 mol% of other excipients, the molar percentages only relate to the diamino lipid and those other excipients; the oligonucleotide molar fraction or the molar fraction of solvents is not taken into account.

When the invention relates to a composition comprising more than one miRNA molecule, isomiR, mimic, or source thereof it is encompassed that each miRNA molecule, isomiR, mimic, or source thereof may be present each in a separate composition. Each composition can be sequentially or simultaneously administered to a subject, or mixed prior to use into a single composition. Alternatively, it is also encompassed that more than one miRNA molecules, isomiRs, mimics, or sources thereof is present in a single composition as defined herein.

The nanoparticle compositions for use according to the invention comprises a diamino lipid of general formula (I), but it may also comprise further lipids. In preferred embodiments, the diamino lipid is the most prevalent lipid in the nanoparticle by molar percent. As used herein, the term lipid refers to substances that are soluble in nonpolar solvents such as CH_2Cl_2. The diamino lipids used in the invention

have three tails linked to a spacer and thus resemble naturally occurring triglyceride lipids. Several such lipids are known (US8691750).

The diamino lipid of general formula (I) comprises two tertiary amines that are separated by an aliphatic spacer of varying length. The spacer helps determine the headgroup size of the lipid. n can be 0, 1, or 2, so the spacer is in effect an 1,2-ethylene, *n*-1,3-propylene, or *n*-1,4-butylene spacer. In particular preferred embodiments, n is 0. In particular preferred embodiments, n is 1. In particular preferred embodiments, n is 2. It is most preferred that n is 1. Accordingly, in preferred embodiments the invention provides a nanoparticle composition for use according to the invention, wherein the diamino lipid is of general formula (I) wherein **n** is 1. Accordingly, in preferred embodiments the invention provides a nanoparticle composition for use according to the invention, wherein the diamino lipid is of general formula (I-1)



(I-1)

Wherein **T¹**, **T²**, and **T³** are each independently a C_{10}-C_{18} chain with optional unsaturations and with zero, one, two, three, or four substitutions, wherein the substitutions are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy.

T^1, T^2, and T^3 can be seen as the tails of the lipid, and are aliphatic C_{10}-C_{18} with optional unsaturations and up to four optional substitutions. T^1, T^2, and T^3 can be independently selected, or the same choice can be made for two or three of T^1, T^2, and T^3. In preferred embodiments, this aspect provides the nanoparticle composition for use according to the invention, wherein the diamino lipid is of general formula (I) wherein **T¹**, **T²**, and **T³** are identical. Identical should not be so narrowly construed as to imply that the natural abundance of isotopes should be contemplated – identical should preferably only refer to the molecular structure as would be represented in a drawn structural formula.

Longer chains will generally lead to more rigid lipid membranes. In this application the number in C_{10}-C_{18} refers to the longest continuous chain that can be determined, and not to the total C content. As a non-limiting example, an n-dodecyl chain with an *n*-propyl substitution at a 6-position comprises 15 C atoms but is a C_{12} chain because the longest continuous chain has a length of 12 C atoms. Unsaturations can lead to less rigid membranes if the unsaturation is *cis* in the chain, bending it. A preferred unsaturation is *cis*. In preferred embodiments, T^1, T^2, and T^3 contain zero, one, two, three, or four unsaturations. In more preferred embodiments, T^1, T^2, and T^3 contain one, two, three, or four unsaturations. In even more preferred embodiments, T^1, T^2, and T^3 contain one, two, or three unsaturations, preferably three unsaturations.

The optional substitutions are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy A preferred optional substitution is a C_1-C_4 alkyl, more preferably a C_1-C_2 alkyl, most preferably methyl (-CH_3). There are zero, one, two, three, or four of such substitutions, which means that substitutions can be absent. As such the substitutions are optional. Preferably, there are zero, one, two, or three such substitutions.

In preferred embodiments, T^1, T^2, and T^3 are each independently a C_{10}-C_{16} chain with optional unsaturations and with zero, one, two, three, or four substitutions, wherein the substitutions are selected

from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy. In more preferred embodiments, T^1, T^2, and T^3 are each independently a C_{10}-C_{14} chain with optional unsaturations and with zero, one, two, three, or four substitutions, wherein the substitutions are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy. Most preferably, T^1, T^2, and T^3 are each independently a C_{12} chain with optional unsaturations and with zero, one, two, three, or four substitutions, wherein the substitutions are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy.

In preferred embodiments, T^1, T^2, and T^3 are each independently a C_{10}-C_{18} chain with one, two, three, or four unsaturations and with zero, one, two, three, or four substitutions, wherein the substitutions are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy.

In preferred embodiments, T^1, T^2, and T^3 are each independently a C_{10}-C_{18} chain with one, two, or three unsaturations and with one, two, three, or four substitutions, wherein the substitutions are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy.

In preferred embodiments, T^1, T^2, and T^3 are each independently a C_{10}-C_{18} chain with one, two, or three unsaturations and with one, two, three, or four substitutions, wherein the substitutions are selected from the group consisting of C_1-C_4 alkyl.

In preferred embodiments, T^1, T^2, and T^3 are each independently a C_{10}-C_{14} chain with one, two, or three unsaturations and with one, two, or three substitutions, wherein the substitutions are selected from the group consisting of C_1-C_2 alkyl.

Preferred embodiments for T^1, T^2, and T^3 are (with a name in systematic C_n numbering, wherein a number after a colon (as in $C1_{2:3}$) indicates the degree of unsaturation) (2*E*, 6*E*)-farnesyl ($C_{12:3}$), lauryl (C_{12}), tridecyl (C_{13}), myristryl (C_{14}), pentadecyl (C_{15}), cetyl (C_{16}), margaryl (C_{17}), stearyl (C_{18}), α-linolenyl ($C_{18:3}$), γ-linolenyl ($C_{18:3}$), linoleyl ($C_{18:2}$), stearidyl ($C_{18:4}$), vaccenyl ($C_{18:1}$), oleyl ($C_{18:1}$), elaidyl ($C_{18:1}$), palmitoleyl ($C_{16:1}$), (2*E*, 6*Z*)-farnesyl, (2*Z*, 6*E*)-farnesyl, (2*Z*, 6*Z*)-farnesyl, and 3,7,11-trimethyldodecyl.

Accordingly, in preferred embodiments this aspect provides the nanoparticle composition for use according to the invention, wherein the diamino lipid is of general formula (I) wherein **T^1**, **T^2**, and **T^3** are each independently selected from the group consisting of farnesyl, lauryl, tridecyl, myristryl, pentadecyl, cetyl, margaryl, stearyl, α-linolenyl, γ-linolenyl, linoleyl, stearidyl, vaccenyl, oleyl, elaidyl, palmitoleyl, and 3,7,11-trimethyldodecyl. Preferably, **T^1**, **T^2**, and **T^3** are each independently selected from the group consisting of farnesyl, lauryl, tridecyl, myristryl, pentadecyl, cetyl, α-linolenyl, γ-linolenyl, linoleyl, stearidyl, oleyl, palmitoleyl, and 3,7,11-trimethyldodecyl. More preferably, **T^1**, **T^2**, and **T^3** are each independently selected from the group consisting of farnesyl, lauryl, tridecyl, myristryl, stearidyl, palmitoleyl, and 3,7,11-trimethyldodecyl. Even more preferably, **T^1**, **T^2**, and **T^3** are each independently selected from the group consisting of farnesyl, lauryl, tridecyl, myristryl, and 3,7,11-trimethyldodecyl. Even more preferably, **T^1**, **T^2**, and **T^3** are each independently selected from the group consisting of farnesyl, lauryl, and 3,7,11-trimethyldodecyl. Most preferably, **T^1**, **T^2**, and **T^3** are each independently farnesyl, such as (2*E*,6*E*) farnesyl, (2*E*,6*Z*) farnesyl, (2*Z*,6*E*) farnesyl, or (2*Z*,6*Z*) farnesyl; preferably they are each (2*E*,6*E*) farnesyl.

Farnesyl is also known as 3,7,11-trimethyldodeca-2,6,10-trienyl and is an unsaturated linear C_{12} chain; it can be (2*E*,6*E*), (2*E*,6*Z*), (2*Z*,6*E*), or (2*Z*,6*Z*); preferably it is (2*E*,6*E*). Lauryl is also known as dodecyl and is a saturated linear C_{12} chain. Tridecyl is a saturated linear C_{13} chain. Myristryl is also known as tetradecyl and is a saturated linear C_{14} chain. Pentadecyl is a saturated linear C_{15} chain. Cetyl

is also known as palmityl and is a saturated linear C_{16} chain. Margaryl is also known as heptadecyl and is a saturated linear C_{17} chain. Stearyl is also known as octadecyl and is a saturated linear C_{18} chain. α-linolenyl is also known as (9*Z*,12*Z*,15*Z*)-9,12,15-octadecatrienyl and is an unsaturated linear C_{18} chain. γ-linolenyl is also known as (6*Z*, 9*Z*, 12*Z*)-6,9,12-octadecatrienyl and is an unsaturated linear C_{18} chain. Linoleyl is also known as (9*Z*,12*Z*)-9,12-octadecadienyl and is an unsaturated linear C_{18} chain. Stearidyl is also known as (6*Z*,9*Z*,12*Z*,15*Z*)-6,9,12,15-octadecatetraenyl and is an unsaturated linear C_{18} chain. Vaccenyl is also known as (*E*)-octadec-11-enyl and is an unsaturated linear C_{18} chain. Oleyl is also known as (9*Z*)-octadec-9-enyl and is an unsaturated linear C_{18} chain. Elaidyl is also known as (9*E*)-octadec-9-enyl and is an unsaturated linear C_{18} chain. Palmitoleyl is also known as (9*Z*)-hexadec-9-enyl and is an unsaturated linear C_{16} chain. 3,7,11-trimethyldodecyl is saturated farnesyl and is a saturated linear C_{12} chain.

The composition can further comprise solvents and/or excipients, preferably pharmaceutically acceptable excipients. Preferred solvents are aqueous solutions such as pharmaceutically acceptable buffers, for example PBS or citrate buffer. A preferred citrate buffer comprises 50 mM citrate at pH 2.5-3.5 such as pH 3, preferably set using NaOH. A preferred PBS is at pH 7-8 such as pH 7.4. PBS preferably does not comprise bivalent cations such as Ca^{2+} and Mg^{2+}. Another preferred pharmaceutically acceptable excipient is ethanol. Most preferably, the composition comprises a physiological buffer such as PBS or a Good's buffer or Hepes-buffered saline or Hank's balanced salt solution or Ringer's balanced salt solution or a Tris buffer. Preferred compositions are pharmaceutical compositions. The composition can comprise further excipients. These further excipients can be comprised in the nanoparticles.

In preferred embodiments, this aspect provides the nanoparticle composition for use according to the invention, further comprising a sterol, preferably selected from the group consisting of adosterol, brassicasterol, campesterol, cholecalciferol, cholestenedione, cholestenol, cholesterol, delta-7-stigmasterol, delta-7-avenasterol, dihydrotachysterol, dimethylcolesterol, ergocalciferol, ergosterol, ergostenol, ergostatrienol, ergostadienol, ethylcholestenol, fusidic acid, lanosterol, norcholestadienol, β-sitosterol, spinasterol, stigmastanol, stigmastenol, stigmastadienol, stigmastadienone, stigmasterol, and stigmastenone, more preferably cholesterol. More particularly, in preferred embodiments, this aspect provides the nanoparticle composition for use according to the invention, wherein the nanoparticles further comprise a sterol, preferably selected from the group consisting of adosterol, brassicasterol, campesterol, cholecalciferol, cholestenedione, cholestenol, cholesterol, delta-7-stigmasterol, delta-7-avenasterol, dihydrotachysterol, dimethylcolesterol, ergocalciferol, ergosterol, ergostenol, ergostatrienol, ergostadienol, ethylcholestenol, fusidic acid, lanosterol, norcholestadienol, β-sitosterol, spinasterol, stigmastanol, stigmastenol, stigmastadienol, stigmastadienone, stigmasterol, and stigmastenone, more preferably cholesterol.

Preferably, such a further comprised sterol is not conjugated to any moiety. Conjugated sterols can also be comprised, as will be explained later herein. As such, both conjugated and unconjugated sterols can be comprised. Unless explicitly indicated otherwise, reference to a sterol is intended as reference to an unconjugated sterol.

When a sterol is comprised in the composition, it is preferably comprised in the nanoparticle, and preferably at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, or 70 mol% of sterol is comprised;

preferably at most 80, 75, 70, 65, 60, 65, 50, 45, 40, 35, or 30 mol% of sterol is comprised. As explained above, this molar percentage only pertains to the substances making up the lipid nanoparticle, and not to solvents or cargo such as oligonucleotides. When a sterol is comprised in the composition, preferably 5 to 70 mol%, 15 to 60 mol%, 25 to 60 mol%, 35 to 60 mol%, 40 to 60 mol%, or 45 to 55 mol% is comprised; more preferably 40 to 60 mol% or 45 to 55 mol% is comprised, most preferably 45 to 55 mol% is comprised, such as 48 mol% or 54 mol%.

In preferred embodiments, this aspect provides the nanoparticle composition for use according to the invention, further comprising a phospholipid, preferably selected from the group consisting of distearoyl phosphatidylcholine (DSPC), dipalmitoyl phosphatidylcholine (DPPC), dimyristoyl phosphatidylcholine (DMPC), dilauroyl phosphatidylcholine (DLPC), dioleyl phosphatidylcholine (DOPC), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), egg phosphatidylcholine (EggPC), soy phosphatidylcholine (SoyPC), more preferably distearoyl phosphatidylcholine (DSPC). More particularly, in preferred embodiments, this aspect provides the nanoparticle composition for use according to the invention, wherein the nanoparticles further comprise a phospholipid, preferably selected from the group consisting of distearoyl phosphatidylcholine (DSPC), dipalmitoyl phosphatidylcholine (DPPC), dimyristoyl phosphatidylcholine (DMPC), dilauroyl phosphatidylcholine (DLPC), dioleyl phosphatidylcholine (DOPC), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), egg phosphatidylcholine (EggPC), soy phosphatidylcholine (SoyPC), more preferably distearoyl phosphatidylcholine (DSPC).

Preferably, such a further comprised phospholipid is not conjugated to any moiety. Conjugated phospholipids can also be comprised, as will be explained later herein. As such, both conjugated and unconjugated phospholipids can be comprised.

When a phospholipid is comprised in the composition, it is preferably comprised in the nanoparticle, and preferably at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, or 60 mol% of phospholipid is comprised; preferably at most 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, or 5 mol% of phospholipid is comprised. As explained above, this molar percentage only pertains to the substances making up the lipid nanoparticle, and not to solvents or cargo such as oligonucleotides. When a phospholipid is comprised in the composition, preferably 0 to 40 mol%, 0 to 35 mol%, 0 to 30 mol%, 5 to 30 mol%, 5 to 25 mol%, or 5 to 20 mol% is comprised; more preferably 5 to 20 mol% or 5 to 15 mol% is comprised, most preferably 5 to 15 mol% is comprised, such as 10 mol% or 11 mol%.

In preferred embodiments, this aspect provides the nanoparticle composition for use according to the invention, further comprising a conjugate of a water soluble polymer and a lipophilic anchor, wherein:

i) the water soluble polymer is selected from the group consisting of poly(ethylene glycol) (PEG), poly(hydroxyethyl-l-asparagine) (PHEA), poly-(hydroxyethyl-L-glutamine) (PHEG), poly(glutamic acid) (PGA), polyglycerol (PG), poly(acrylamide) (PAAm), poly(vinylpyrrolidone) (PVP), poly(N-(2-hydroxypropyl)methacrylamide) (PHPMA), and poly(2-oxazoline) (POx) such as poly(2-methyl-2-oxazoline) (PMeOx) and poly(2-ethyl-2-oxazoline) (PEtOx), or copolymers thereof

and wherein

ii) the lipophilic anchor is selected from the group consisting of a sterol, a lipid, and a vitamin E derivative. Preferably, the lipophilic anchor is a lipid, more preferably a diglyceride.

More particularly, in preferred embodiments, this aspect provides the nanoparticle composition for use according to the invention, wherein the nanoparticles further comprise a conjugate of a water soluble polymer and a lipophilic anchor as described above. The water soluble polymer generally increases the colloidal stability of the nanoparticles, to which is it linked via the lipophilic anchor. In general, the lipophilic anchor embeds in the lipid bilayer or in the micelle, and thus links the water soluble polymer to the surface of the nanoparticle. The use of such water soluble polymers for this purpose is known in the art (Knop et al., 2010, doi: 10.1002/anie.200902672). A preferred water soluble polymer is poly(ethylene glycol). Preferably, the water soluble polymer has a molecular weight ranging from about 750 Da to about 15000 Da, more preferably from about 1000 Da to about 6000 Da, even more preferably from about 1000 Da to about 3000 Da, most preferably from about 1500 Da to about 3000 Da, such as about 2000 Da. Accordingly, PEG-2000 is a preferred water soluble polymer for use in a conjugate as described above. The water soluble polymer is preferably a linear polymer, and is preferably conjugated at one of its two termini. The other terminus is preferably uncharged at physiological conditions, such as a hydroxyl group or a methyl or ethyl ether. Preferably, the non-conjugated terminus is a methyl ether or a hydroxyl group, most preferably a methyl ether.

The lipophilic anchor to which the water soluble polymer is conjugated generally serves to ensure a connection between the water soluble polymer and the nanoparticle. The particular conjugation between the polymer and the anchor is not important, a skilled person can select any suitable chemical bond such as an ester bond, an amide bond, an ether linkage, a triazole, or any other moiety resulting from conjugating a water soluble polymer to a lipophilic anchor. The use of small linkers is also envisaged, such as succinic acid or glutaric acid. The lipophilic anchor is selected from the group consisting of a sterol, a lipid, and a vitamin E derivative. Preferred sterols are described above. Preferred vitamin E derivatives are tocopherols and tocotrienols such as alpha-tocopherol, beta-tocopherol, gamma-tocopherol, delta-tocopherol, and corresponding tocotrienols. Preferably, the lipophilic anchor is a lipid, more preferably a diglyceride or a phospholipid. Examples of preferred lipids are described above, examples of preferred diglycerides are distearoylglycerol, preferably 1,2-distearoyl-sn-glycerol, dipalmitoylglycerol, preferably 1,2-dipalmitoyl-sn-glycerol, dioleoylglycerol, preferably 1,2-dioleoyl-sn-glycerol, and diarachidoylglycerol, preferably 1,2-diarachidoyl-sn-glycerol. A most preferred diglyceride is distearoylglycerol, preferably 1,2-distearoyl-sn-glycerol.

Suitable examples of conjugates as described above are (1,2-distearoyl-sn-glycerol)-[methoxy(polyethylene glycol-2000)] ether, (1,2-distearoyl-sn-glycerol)-[methoxy(polyethylene glycol-1500)] ether, (1,2-distearoyl-sn-glycerol)-[methoxy(polyethylene glycol-3000)]ether, (1,2-distearoyl-sn-glycerol)-[hydroxy(polyethylene glycol-2000)]ether, (1,2-distearoyl-sn-glycerol)-[hydroxy(polyethylene glycol-1500)]ether, (1,2-distearoyl-sn-glycerol)-[hydroxy(polyethylene glycol-3000)]ether, (1,2-distearoyl-sn-glyceryl)-[methoxy(polyethylene glycol-2000)carboxylate], (1,2-distearoyl-sn-glyceryl)-[methoxy(polyethylene glycol-1500) carboxylate], (1,2-distearoyl-sn-glyceryl)-[methoxy(polyethylene glycol-3000) carboxylate], (1,2-distearoyl-sn-glyceryl)-[hydroxy(polyethylene glycol-2000) carboxylate], (1,2-distearoyl-sn-glyceryl)-[hydroxy(polyethylene glycol-1500) carboxylate], (1,2-distearoyl-sn-

glyceryl)-[hydroxy(polyethylene glycol-3000) carboxylate], (1,2-distearoyl-sn-glyceryl)-[methoxy(polyethylene glycol-2000) carbamate], (1,2-distearoyl-sn-glyceryl)-[methoxy(polyethylene glycol-1500) carbamate], (1,2-distearoyl-sn-glyceryl)-[methoxy(polyethylene glycol-3000) carbamate], (1,2-distearoyl-sn-glyceryl)-[hydroxy(polyethylene glycol-2000) carbamate], (1,2-distearoyl-sn-glyceryl)-[hydroxy(polyethylene glycol-1500) carbamate], and (1,2-distearoyl-sn-glyceryl)-[hydroxy(polyethylene glycol-3000) carbamate], wherein the stearoyl moieties can optionally be replaced by other fatty acids, preferably by other C_{10}-C_{20} fatty acids. For carbamates and esters as described above, the parent amines and parent alcohols and parent carboxylic acids can also be switched around, for example a PEG-alcohol can be reacted with a carboxylic acid analogue of a diglyceride. Most preferred examples of conjugates are (1,2-distearoyl-sn-glycerol)-[methoxy(polyethylene glycol-2000)] ether, which is also known as DSG-PEG (CAS#: 308805-39-2), and its ester analogue (1,2-distearoyl-sn-glyceryl)-[methoxy(polyethylene glycol-2000)carboxylate], and its carbamate analogue (1,2-distearoyl-sn-glyceryl)-[methoxy(polyethylene glycol-2000) carbamate] or 1,2-distearoyloxy propylamine 3-N-methoxy(polyethylene glycol)-2000 carbamoyl which is also known as DSA-PEG, and its amide analogue.

When a conjugate as described above is comprised in the composition, it is preferably comprised in the nanoparticle, and preferably at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 mol% of conjugate is comprised; preferably at most 6.5, 6.0, 5.5, 5.0, 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1.0, 0.9, 0.8, 0.7, 0.6, or 0.5 mol% of conjugate is comprised. As explained above, this molar percentage t only pertains to the substances making up the lipid nanoparticle, and not to solvents or cargo such as oligonucleotides. When a conjugate is comprised in the composition, preferably 0 to 4 mol%, 0 to 3 mol%, 0.3 to 3 mol%, 0.5 to 3 mol%, 0.5 to 2.5 mol%, or 1 to 2.5 mol% is comprised; more preferably 0.5 to 2.5 mol% or 0.7 to 2.5 mol% is comprised, most preferably 0.8 to 2.4 mol% is comprised, such as 1 mol% or 2 mol%.

Preferred nanoparticles comprise a diamino lipid and a sterol. Further preferred nanoparticles comprise a diamino lipid and a phospholipid. Further preferred nanoparticles comprise a diamino lipid and a conjugate of a water soluble polymer and a lipophilic anchor. Preferred nanoparticles comprise a diamino lipid and a sterol and a phospholipid. Preferred nanoparticles comprise a diamino lipid and a sterol and a conjugate of a water soluble polymer and a lipophilic anchor. Preferred nanoparticles comprise a diamino lipid and a phospholipid and a conjugate of a water soluble polymer and a lipophilic anchor. Most preferred nanoparticles comprise a diamino lipid and a sterol and a phospholipid and a conjugate of a water soluble polymer and a lipophilic anchor.

In preferred embodiments, this aspect provides the nanoparticle composition for use according to the invention, wherein the nanoparticles comprise:

i) 20-60 mol% of diamino lipid, and
ii) 0-40 mol% of phospholipid, and
iii) 30-70 mol% of a sterol, preferably cholesterol, and
iv) 0-10 mol% of a conjugate of a water soluble polymer and a lipophilic anchor as defined above.

In further preferred embodiments the nanoparticles comprise

i) 25-55 mol% of diamino lipid, and

ii) 1-30 mol% of phospholipid, and

iii) 35-65 mol% of a sterol, preferably cholesterol, and

iv) 0.1-4 mol% of a conjugate of a water soluble polymer and a lipophilic anchor.

In further preferred embodiments the nanoparticles comprise

i) 30-50 mol% of diamino lipid, and

ii) 5-15 mol% of phospholipid, and

iii) 40-60 mol% of a sterol, preferably cholesterol, and

iv) 0.5-2.5 mol% of a conjugate of a water soluble polymer and a lipophilic anchor.

In further preferred embodiments the nanoparticles comprise

i) about 38-42 mol% of diamino lipid, and

ii) about 8-12 mol% of phospholipid, and

iii) about 46-50 mol% of a sterol, preferably cholesterol, and

iv) about 1.8-2.2 mol% of a conjugate of a water soluble polymer and a lipophilic anchor.

The composition for use according to the invention can advantageously comprise additional therapeutically active agents. In preferred embodiments is provided the composition for use according to the invention, further comprising an additional pharmaceutically active compound, preferably selected from the group consisting of a PP2A methylating agent, an inhibitor of hepatocyte growth factor (HGF), an antibody, a PI3K inhibitor, an Akt inhibitor, an mTOR inhibitor, a binder of a T cell co-stimulatory molecule such as a binder of OX40, and a chemotherapeutic agent. Chemotherapeutic agents are defined later herein.

A PP2A methylating agent can activate PP2A, which in turn activates tumour suppressors such as p53 (see US2007280918). A particularly preferred PP2A methylating agent is betaine (betaine hydrate or also trimethylammonio-2 acetate) or one of its pharmaceutically acceptable salts, in particular betaine citrate. An HGF inhibitor can inhibit HGF, which is coexpressed, often over-expressed, on various human solid tumors including tumors derived from lung, colon, rectum, stomach, kidney, ovary, skin, multiple myeloma and thyroid tissue (see WO2009126842). Preferred HGF inhibitors are truncated HGF proteins such as NKI (N terminal domain plus kringle domain 1; Lokker et al., J. Biol. Chem. 268:17145, 1993); NK2 (N terminal domain plus kringle domains 1 and 2; Chan et al, Science 254:1382, 1991); and NK4 (N-terminal domain plus four kringle domains), which was shown to partially inhibit the primary growth and metastasis of murine lung tumor LLC in a nude mouse model (Kuba et al, Cancer Res. 60:6737, 2000), anti-HGF mAbs such as L2G7 (Kim et al, Clin Cancer Res 12:1292, 2006 and US Patent No. 7,220,410), HuL2G7 (WO 07115049 A2), the human mAbs described in WO 2005/017107 A2, and the HGF binding proteins described in WO 07143090 A2 or WO 07143098 A2. PI3K inhibitors are widely known. Preferred PI3K inhibitors are GSK2636771B, GSK2636771, idelalisib, copanlisib, duvelisib, and alpelisib. Akt inhibitors are widely known. Preferred Akt inhibitors are VQD-002, perifosine, miltefosine, MK-2206, AZD5363, and ipatasertib. mTOR inhibitors are widely known. Preferred mTOR inhibitors are sirolimus, everolimus, ridaforolimus, temsirolimus, umirolimus, and zotarolimus. Binder of a T cell co-stimulatory molecule are described in WO2019106605. A preferred such binder is a binder of OX40 such as an antibody against OX40.

Method for agonizing PTEN

The invention also provided a method for agonising PTEN, the method comprising the step of contacting a cell with a miRNA-193a as defined for use above, or with a composition as defined for use above. Accordingly, the cell is contacted with a miRNA-193a molecule, isomiR, mimic, or source thereof. The method van be an in vivo, in vitro, or ex vivo method, and preferably it is an in vitro or ex vivo method. Agonising PTEN is as defined elsewhere herein, and is preferably increasing expression of PTEN or increasing PTEN protein activity or increasing PTEN protein levels, more preferably it is increasing PTEN protein activity. PTEN activity of levels are preferably increased by at least 5%, more preferably by at least 25%. Ways for contacting a cell are widely known in the art; preferably the miRNA is added to the cell culture medium without further excipients, or it is transfected such as by using transfection reagents.

General Definitions

In this document and in its claims, the verb "to comprise" and its conjugations is used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. In addition, reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present, unless the context clearly requires that there be one and only one of the elements. The indefinite article "a" or "an" thus usually means "at least one".

The word “about” or “approximately” when used in association with a numerical value (e.g. about 10) preferably means that the value may be the given value more or less 1% of the value. When moieties or substructures of molecules are said to be identical, the natural abundance distribution of isotopes is not accounted for. The identical nature refers to a structural formula as it would be drawn.

As used herein, mol% refers to molar percentage, which is also known as a mole fraction or a molar fraction or a mole percent or an amount fraction. It relates to the amount in moles of a constituent, divided by the total amount of all constituents in a mixture, also expressed in moles.

In the context of this invention, a decrease or increase of a parameter to be assessed means a change of at least 5% of the value corresponding to that parameter. More preferably, a decrease or increase of the value means a change of at least 10%, even more preferably at least 20%, at least 30%, at least 40%, at least 50%, at least 70%, at least 90%, or 100%. In this latter case, it can be the case that there is no longer a detectable value associated with the parameter.

The use of a substance as a medicament as described in this document can also be interpreted as the use of said substance in the manufacture of a medicament. Similarly, whenever a substance is used for treatment or as a medicament, it can also be used for the manufacture of a medicament for treatment. Products for use are suitable for use in methods of treatment, for example in a method for treating a condition associated with PTEN-deficiency, preferably a PTEN-deficient cancer, the method comprising the step of administering to a subject a miRNA-193a for use according to the invention, or a composition for use according to the invention.

The present invention has been described above with reference to a number of exemplary embodiments. Modifications and alternative implementations of some parts or elements are possible, and are included in the scope of protection as defined in the appended claims. All citations of literature and patent documents are hereby incorporated by reference.

"Modulate" as used herein, for example with regard to expression of a gene, means to change any natural or existing level of function, for example it means affecting expression by increasing or

reducing it. Modulation includes upregulating or agonizing, e.g., signaling, as well as downregulating, antagonizing, or blocking signaling or interactions with a ligand or compound or molecule that happen in the unchanged or unmodulated state. Thus, modulators may be agonists or antagonists. Agonist or antagonist activity can be measured in vitro by various assays know in the art such as, but not limited to, measurement of cell signalling, cell proliferation, immune cell activation markers, and cytokine production, optionally including comparison to unmodulated reference samples. Agonist or antagonist activity can also be measured in vivo by various assays that measure surrogate end points such as, but not limited to the measurement of T cell proliferation or cytokine production.

General technologies referred to herein

MicroRNA molecules ("miRNAs") are generally 21 to 22 nucleotides in length, though lengths of 17 and up to 25 nucleotides have been reported. Any length of 17, 18, 19, 20, 21, 22, 23, 24, 25 is therefore encompassed within the present invention. The miRNAs are each processed from a longer precursor RNA molecule ("precursor miRNA"). Precursor miRNAs are transcribed from non-protein-encoding genes. A precursor may have a length of at least 50, 70, 75, 80, 85, 100, 150, 200 nucleotides or more. The precursor miRNAs have two regions of complementarity that enables them to form a stem-loop- or fold-back-like structure, which is cleaved by enzymes called Dicer and Drosha in animals. Dicer and Drosha are ribonuclease III-like nucleases. The processed miRNA is typically a portion of the stem.

The processed miRNA (also referred to as "mature miRNA") becomes part of a large complex, known as the RNA-Induced Silencing Complex (RISC) complex, to (down or up)-regulate a particular target gene. Examples of animal miRNAs include those that perfectly or imperfectly basepair with the mRNA target, resulting in either mRNA degradation or inhibition of translation respectively (Olsen et al, 1999; Seggerson et al, 2002). SiRNA molecules also are processed by Dicer, but from a long, double-stranded RNA molecule. SiRNAs are not naturally found in animal cells, but they can function in such cells in a RNA-induced silencing complex (RISC) to direct the sequence-specific cleavage of an mRNA target (Denli et al, 2003).

The study of endogenous miRNA molecules is described in U.S. Patent Application 60/575,743. A miRNA is apparently active in the cell when the mature, single-stranded RNA is bound by a protein complex that regulates the translation of mRNAs that hybridize to the miRNA. Introducing exogenous RNA molecules that affect cells in the same way as endogenously expressed miRNAs requires that a single-stranded RNA molecule of the same sequence as the endogenous mature miRNA be taken up by the protein complex that facilitates translational control. A variety of RNA molecule designs have been evaluated. Three general designs that maximize uptake of the desired single-stranded miRNA by the miRNA pathway have been identified. An RNA molecule with a miRNA sequence having at least one of the three designs may be referred to as a synthetic miRNA.

miRNA molecules of the invention can replace or supplement the gene silencing activity of an endogenous miRNA. An example of such molecules, preferred characteristics and modifications of such molecules and compositions comprising such molecules is described in WO2009/091982.

miRNA molecules of the invention or isomiRs or mimics or sources thereof comprise, in some embodiments, two RNA molecules wherein one RNA is identical to a naturally occurring, mature miRNA. The RNA molecule that is identical to a mature miRNA is referred to as the active strand or the antisense strand. The second RNA molecule, referred to as the complementary strand or the sense strand, is at

least partially complementary to the active strand. The active and complementary strands are hybridized to create a double-stranded RNA, that is similar to the naturally occurring miRNA precursor that is bound by the protein complex immediately prior to miRNA activation in the cell. Maximizing activity of said miRNA requires maximizing uptake of the active strand and minimizing uptake of the complementary strand by the miRNA protein complex that regulates gene expression at the level of translation. The molecular designs that provide optimal miRNA activity involve modifications of the complementary strand. Two designs incorporate chemical modifications of the complementary strand. The first modification involves creating a complementary RNA with a group other than a phosphate or hydroxyl at its 5' terminus. The presence of the 5' modification apparently eliminates uptake of the complementary strand and subsequently favors uptake of the active strand by the miRNA protein complex. The 5' modification can be any of a variety of molecules including NH_2, $NHCOCH_3$, biotin, and others. The second chemical modification strategy that significantly reduces uptake of the complementary strand by the miRNA pathway is incorporating nucleotides with sugar modifications in the first 2-6 nucleotides of the complementary strand. It should be noted that the sugar modifications consistent with the second design strategy can be coupled with 5' terminal modifications consistent with the first design strategy to further enhance miRNA activities. The third miRNA design involves incorporating nucleotides in the 3' end of the complementary strand that are not complementary to the active strand. Hybrids of the resulting active and complementary RNAs are very stable at the 3' end of the active strand but relatively unstable at the 5' end of the active strand. Studies with siRNAs indicate that 5' hybrid stability is a key indicator of RNA uptake by the protein complex that supports RNA interference, which is at least related to the miRNA pathway in cells. The inventors have found that the judicious use of mismatches in the complementary RNA strand significantly enhances the activity of said miRNA.

Further definitions for nucleic acids, nucleobases, nucleosides, nucleotides, nucleic acid analogues, modified nucleotides, preparation of nucleic acids, design of miRNAs, 5' blocking agents, host cells and target cells, delivery methods, and nanoparticle functionalisation are preferably as described in WO2013/095132.

Therapeutic Applications

miRNAs that affect phenotypic traits provide intervention points for therapeutic applications as well as diagnostic applications (by screening for the presence or absence of a particular miRNA, or altered concentration of a particular miRNA). It is specifically contemplated that RNA molecules of the present invention can be used to treat any of the diseases or conditions discussed in the previous section. Moreover, any of the methods described above can also be employed with respect to therapeutic and diagnostic aspects of the invention. For example, methods with respect to detecting miRNAs or screening for them can also be employed in a diagnostic context. In therapeutic applications, an effective amount of the miRNAs of the present invention is administered to a cell, which may or may not be in an animal. In some embodiments, a therapeutically effective amount of the miRNAs of the present invention is administered to an individual for the treatment of disease or condition. The term "effective amount" as used herein is defined as the amount of the molecules of the present invention that are necessary to result in the desired physiological change in the cell or tissue to which it is administered. The term "therapeutically effective amount" as used herein is defined as the amount of the molecules of the present

invention that achieves a desired effect with respect to a disease or condition associated with a disease or condition as earlier defined herein. A skilled artisan readily recognizes that in many cases the molecules may not provide a cure but may provide a partial benefit, such as alleviation or improvement of at least one symptom. In some embodiments, a physiological change having some benefit is also considered therapeutically beneficial. Thus, in some embodiments, an amount of molecules that provides a physiological change is considered an "effective amount" or a "therapeutically effective amount."

In certain embodiments, pharmaceutical compositions may comprise, for example, at least about 0.1% of an active compound. In other embodiments, an active compound may comprise 2% to 75% of the weight of the unit, or 25% to 60%, for example, and any range derivable therein. In other non-limiting examples, a dose may also comprise less than 1 microgram/kg/body weight, or 1 microgram/kg/body weight, from 5 microgram/kg/body weight, 10 microgram/kg/body weight, 50 microgram/kg/body weight, 100 microgram/kg/body weight, 200 microgram/kg/body weight, 350 microgram/kg/body weight, 500 microgram/kg/body weight, 1 milligram/kg/body weight, 5 milligram/kg/body weight, 10 milligram/kg/body weight, 50 milligram/kg/body weight, 100 milligram/kg/body weight, 200 milligram/kg/body weight, 350 milligram/kg/body weight, or 500 milligram/kg/body weight, to 1000 mg/kg/body weight or more per administration, and any range derivable therein. In non-limiting examples of a derivable range from the numbers listed herein, a range of 5 mg/kg/body weight to 100 mg/kg/body weight, 5 microgram/kg/body weight to 500 milligram/kg/body weight, etc., can be administered, based on the numbers described above.

In any case, the composition may comprise various antioxidants to retard oxidation of one or more component. Additionally, the prevention of the action of microorganisms can be brought about by preservatives such as various antibacterial and antifungal agents, including but not limited to parabens, chlorobutanol, phenol, sorbic acid, thimerosal or combinations thereof.

The molecules may be formulated into a composition in a free base, neutral or salt form. Pharmaceutically acceptable salts, include the acid addition salts, e.g., those formed with the free amino groups of a proteinaceous composition, or which are formed with inorganic acids such as for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric or mandelic acid. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as for example, sodium, potassium, ammonium, calcium or ferric hydroxides; or such organic bases as isopropylamine, trimethylamine, histidine or procaine.

The composition is generally a suspension of nanoparticles in an aqueous medium. However, it can be lyophilized and provided as a powder, wherein the powder comprises the nanoparticles and optionally buffer salts or other excipients.

Effective Dosages

The molecules of the invention will generally be used in an amount effective to achieve the intended purpose. For use to treat or prevent a disease condition, the molecules of the invention, or pharmaceutical compositions thereof, are administered or applied in a therapeutically effective amount. A therapeutically effective amount is an amount effective to ameliorate or prevent the symptoms, or prolong the survival of the patient being treated. Determination of a therapeutically effective amount is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure provided herein. For systemic administration, a therapeutically effective dose can be estimated initially from in

vitro assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the EC50 as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from in vivo data, e.g., animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data. Dosage amount and interval may be adjusted individually to provide plasma levels of the molecules which are sufficient to maintain therapeutic effect. Usual patient dosages for administration by injection range from 0.01 to 0.1 mg/kg/day, or from 0.1 to 5 mg/kg/day, preferably from 0.5 to 1 mg/kg/day or more. Therapeutically effective serum levels may be achieved by administering multiple doses each day.

In cases of local administration or selective uptake, the effective local concentration of the proteins may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation. The amount of molecules administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. The therapy may be repeated intermittently while symptoms detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs or treatment (including surgery).

Sequence identity

"Sequence identity" is herein defined as a relationship between two or more nucleic acid (nucleotide, polynucleotide, RNA, DNA) sequences, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between nucleic acid sequences, as the case may be, as determined by the match between strings of such sequences. "Identity" and "similarity" can be readily calculated by known methods, including but not limited to those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heine, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; and Carillo, H., and Lipman, D., SIAM J. Applied Math., 48:1073 (1988). In an embodiment, identity is assessed on a whole length of a given SEQ ID NO.

Preferred methods to determine identity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in publicly available computer programs. Preferred computer program methods to determine identity and similarity between two sequences include e.g. the GCG program package (Devereux, J., et al., Nucleic Acids Research 12 (1): 387 (1984)), BestFit, BLASTP, BLASTN, and FASTA (Altschul, S. F. et al., J. Mol. Biol. 215:403-410 (1990). The BLAST X program is publicly available from NCBI and other sources (BLAST Manual, Altschul, S., et al., NCBI NLM NIH Bethesda, MD 20894; Altschul, S., et al., J. Mol. Biol. 215:403-410 (1990). The well-known Smith Waterman algorithm may also be used to determine identity.

Preferred parameters for nucleic acid comparison include the following: Algorithm: Needleman and Wunsch, J. Mol. Biol. 48:443-453 (1970); Comparison matrix: matches=+10, mismatch=0; Gap Penalty: 50; Gap Length Penalty: 3. Available as the Gap program from Genetics Computer Group, located in Madison, Wis. Given above are the default parameters for nucleic acid comparisons.

Chemotherapeutic agents

Examples of chemotherapeutic agents for use in combinations according to the invention include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC- 1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CBI-TMI); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gamma and calicheamicin omega); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authrarnycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L- norleucine, doxorubicin (including morpholmo-doxorubicm, cyanomorpholino- doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalarnycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK polysaccharide complex; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-II); topoisomerase inhibitor RFS 2000;

difluorometlhylornithine (DMFO); retinoids such as retinoic acid; capecitabine; gefitinib and pharmaceutically acceptable salts, acids or derivatives of any of the above.

Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumours such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LYI 17018, onapristone, and toremifene; aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestanie, fadrozole, vorozole, letrozole, and anastrozole; and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-α, Raf and H-Ras; ribozymes such as a VEGF expression inhibitor and a HER2 expression inhibitor; vaccines such as gene therapy vaccines and pharmaceutically acceptable salts, acids or derivatives of any of the above. A list of U.S. FDA approved oncology drags with their approved indications can be found on the World Wide Web at accessdata.fda.gov/scripts/cder/onctools/druglist.cfm. A suitable RNR inhibitor is selected from the group consisting of gemcitabine, hydroxyurea, clolar, clofarabine, and triapine. A suitable AURKB inhibitor is selected from the group consisting of: AZD1152, VX-680, MLN8054, MLN8237, PHA680632, PH739358, Hesperidin, ZM447439, JNJ770621, SU6668, CCT129202, AT9283, MP529, SNS314, R763, ENMD2076, XL228, TTP687, PF03814735 and CYC116. Another suitable anticancer drug is gefitinib.

Figure legends

Figure 1 - Canonical pathway analysis. (A) Top 25 canonical pathways regulated by miR-193a in at least three cell lines at 24h ranked based on P value. Dotted line indicates $P < 0.01$. White bar: activated, black bar: inhibited, grey bar: direction not determined. (B) Treemap of genes that were identified in at least 4 significant pathways. Box size corresponds to the number of pathways in which the gene was differentially expressed.

Figure 2 - Genes downregulated by miR-193a in the PTEN pathway. Genes that were significantly downregulated by miR-193a (average relative expression compared to mock < 1, $P < 0.05$) at 24h in at least three cell lines are shown without hatching. PTEN is highlighted in black. Pointy arrows indicate stimulation whereas bar-headed arrows indicate inhibition.

Figure 3 - Biological functions affected by miRNA-193a. Biological functions relevant to (tumour) cells with z-scores <-2 and >2. All *P* values are smaller than 0.00001.

Figure 4 - Western blotting of miR-193a-3p targets in the PTEN pathway. Human tumor cell lines were transfected with 10 nM scrambled control or 10 nM miRNA-193a and lysed after 72h. Clarified whole cell lysates were immunoblotted for FAK, P70S6K, PIK3R1 and TGFBRIII. Vinculin and tubulin are loading controls. Boxes indicate protein downregulation.

Figure 5 - Western blotting of phosphoproteins in the PTEN pathway. Human tumor cell lines were transfected with 10 nM scrambled control or 10 nM miRNA-193a and lysed after 72h. Clarified whole cell lysates were immunoblotted for pSer473 AKT, AKT, pThr202/Tyr204 ERK1/2, ERK1/2, pSer259 c-RAF and c-RAF. Vinculin and tubulin are loading controls. Full boxes indicate protein downregulation and dashed boxes indicate protein upregulation.

Figure 6 - Transfection with miRNA-193a induces surface expression of CRT in A2058 and HEP3B cells. ***A***-***B***) graphs show percentages of live ($DAPI^-$) and dying ($DAPI^{low}$), but not dead ($DAPI^+$) cells, expressing CRT on their surface, for A2058 (***A***) and HEP3B (***B***) cells transfected with 0.1, 1, 3 and 10 nM of miRNA-193a, or a mock transfection control. ***C***-***D***) Panels show the cytofluorometric plots of A2058 (***C***) and HEP3B (***D***) cells, analyzed 72 hours post transfection.

Figure 7 - Co-culture with miRNA-193a transfected A2058 tumor cells enhances the proliferation of T cells. PBMCs were labeled with CFSE and kept in culture alone, or in co-culture with mock transfected or miRNA-193a transfected A2058 cells. Cytofluorometric plots show the level of CFSE of $CD3^+$ T cells, after 2 days or 6 days of co-culture.

Figure 8 - Effect of human Peripheral Blood Mononuclear Cells (PBMCs) on human melanoma A2058 and NSCLC A549 tumor cells. Human melanoma A2058 (A) and NSCLC A549 (B) tumor cells were co-cultured with the indicated ratio of human PBMCs to tumor cells for 72 h either in the absence or the presence of human anti CD3/CD28 antibodies (T cell activator). Then surviving cells were fixed and stained with crystal violet. The relative percentage of surviving cells (as compared to similar experimental conditions in the absence of PBMCs) was quantified by colorimetry of the stained cells (Feoktistova et al., 2016). Error bars represent SD to the mean of 3 independent replicates.

Figure 9 - Effect of human Peripheral Blood Mononuclear Cells (PBMCs) on human melanoma A2058 (A) and NSCLC A549 (B) tumor cells upon tumor cell transfection with miRNA-193a. Human melanoma A2058 and NSCLC A549 tumor cells were transfected (RNAiMAX) with the indicated concentrations of either negative miRNA control (3A1) or miR-193a-3p, after which cells were co-cultured with the indicated ratio of human PBMCs to tumor cells for the indicated times. Then surviving cells were fixed and stained with crystal violet. The relative percentage of surviving cells (as compared to mock transfected condition)) was quantified by colorimetry of the stained cells (Feoktistova et al., 2016). N.S.: not significant, *: $p<0.05$ and **: $p<0.01$ as determined by the Student t tests (asymptotic significance [2-tailed]). Error bars represent SD to the mean of 3 independent replicates.

Examples

Example 1 - RNA-sequencing, differential gene expression, and pathway analysis after treatment of different cancer cell lines with miRNA-193a

Implementation of high-throughput RNA-sequencing (RNA-seq) has become a powerful tool for comprehensive characterization of the whole transcriptome at gene and exon levels and with a unique ability to identify differentially expressed genes, novel genes and transcripts at high resolution and efficiency. However, till date, very few miRNAs have been characterized for their specific role in cancer development. Hence, we have used the high-throughput RNA-seq after overexpressing a miRNA-193a (viz. a miRNA-193a-3p mimic) in 5 different cancer cell lines including A540 and H460 (both lung cancer), Huh7 and Hep3B (both liver cancer), and BT549 (breast cancer) at 24h post-transfection with miR-193a at 10nM. The gene expression was compared to mock as control and differentially expressed genes and

their cellular pathways were subsequently identified.

1.1 Materials & Methods

1.1.1 Cell preparation for RNA-seq

Human cancer cell lines were cultured in appropriate media (Table 1) and seeded into 6-well plates 24h before transfection with 10 nM miRNA-193a-3p mimic or mock using Lipofectamine RNAiMAX (Thermofisher). The mimic was a double stranded mimic wherein the antisense strand consisted of an RNA oligonucleotide having SEQ ID NO: 56 (the canonical miRNA-193a-3p), and wherein the sense strand consisted of an oligonucleotide represented by SEQ ID NO: 218.

Reagents were aspirated 16h after transfection and cells were passaged into new 6-well plates. Media was aspirated 24h after transfection and plates were stored at -80 °C. Three independent replicates were performed for each cell line.

Table 1: Cell line details.

Cell line	Cancer type	Medium
A549	Lung (NSCLC)	F-12K + 10% FBS + P/S
BT549	Breast (TNBC)	RPMI-1640 + 10% FBS + P/S + 0.023 IU/mL insulin
H460	Lung (NSCLC)	RPMI-1640 + 10% FBS + P/S
HEP3B	Liver (HCC)	EMEM + 10% FBS + P/S
HUH7	Liver (HCC)	DMEM low glucose+ 10% FBS + P/S + L-glutamine

FBS: fetal bovine serum, P/S: penicillin streptomycin

1.1.2 RNA isolation for RNA-seq

RNA was isolated using the miRNeasy Mini kit (Qiagen). The procedure included on-column DNase treatment. RNA concentration was measured on NanodropOne. 150 ng of each independent replicate was pooled and 450 ng samples (having sample IDs A549 Mock_24, A549 miRNA-193a-3p_24, BT549 Mock_24, BT549 miRNA-193a-3p_24, H460 Mock_24, H460 miRNA-193a-3p_24, HEP3B Mock_24, HEP3B miRNA-193a-3p_24, HUH7 Mock_24, and HUH7 miRNA-193a-3p_24) were submitted to GenomeScan BV (Leiden, The Netherlands).

1.1.3 RNA-seq procedure

PolyA enrichment was performed followed by next generation RNA-Seq using Illumina NovaSeq 6000 at GenomeScan BV. The data processing workflow included raw data quality control, adapter trimming, and alignment of short reads. The reference GRCh37.75.dna.primary_assembly was used for alignment of the reads for each sample. Based on the mapped locations in the alignment file the frequency of how often a read was mapped on a transcript was determined (feature counting). The counts were saved to count files, which serve as input for downstream RNA-Seq differential expression analysis.

1.1.4 Data analysis for RNA-seq

Differential expression analysis was performed on the short read data set by GenomeScan BV. The read counts were loaded into the DESeq package v1.30.0, a statistical package within the R platform v3.4.4. DESeq was specifically developed to find differentially expressed genes between two conditions (mock

versus miRNA-193a-3p) for RNA-seq data with small sample size and over-dispersion. The differential expression comparison grouping is provided in Table .

Table 2: Expression comparison setup.

Comparison	Condition A	Condition B
1	A549_Mock_24	A549_miRNA-193a-3p_24
2	BT549_Mock_24	BT549_miRNA-193a-3p_24
3	H460_Mock_24	H460_miRNA-193a-3p_24
4	HEP3B_Mock_24	HEP3B_miRNA-193a-3p_24
5	HUH7_Mock_24	HUH7_miRNA-193a-3p_24

5

1.1.5 Pathway analysis

Lists of genes that were significantly ($P < 0.05$) differentially expressed in our RNA-seq dataset were uploaded and analyzed using Ingenuity Pathway Analysis (IPA) software (www.ingenuity.com).

10 1.2 Results

1.2.1 Genes regulated by miR-193a-3p mimic in solid tumor cell lines

Lists of significantly ($P < 0.05$) differentially expressed genes (relative expression miRNA-193a / relative expression mock) at 24h after transfection were created for all cell lines (see description of invention). Most genes were downregulated as compared to mock (relative expression miRNA-193a / relative 15 expression mock < 1) (see Table 3).

Table 3: Number of genes down- and upregulated by 193a-3p mimic per cell line.

	24h	
	Down	Up
A549	615	220
BT549	620	168
H460	656	215
HEP3B	599	166
HUH7	683	200

Fout! Verwijzingsbron niet gevonden.4 shows genes with known roles in cancer that were 20 downregulated by miRNA-193a in each cell line. Genes that were downregulated in all cell lines include: CCND1, CDK6, KRAS, MCL1, NT5E, STMN1, TGFBR3 and YWHAZ.

Table 4: Genes of interest downregulated by miR-193a per cell line.

Cel lines	Downregulated genes
A549	CAPRIN1, CCNA2, CCND1, CDK4, CDK6, CHEK1, DCAF7, DDB1, ETS1, HDAC3, HMGB1, IL17RD, KRAS, MCL, MPP2, NOTCH2, NT5E, PLAU, PSEN1, PTK2, RAB27B, SEPN1, SLC7A5, SOS2, ST3GAL4, STAT3, STMN1, TGFB2, TGFBR2, TGFBR3, TNFRSF21, YAP1, YWHAZ

BT549	CCNA2, CCND1, CDC25A, CDK4, CDK6, CSF2, DCAF7, DDB1, ETS1, GRB7, HIC2, IDO1, IL17RD, KRAS, MCL1, MDM2, MPP2, NOTCH2, NT5E, PLAU, PSEN1, PTK2, RAB27B, SEPN1, SLC7A5, SOS2, ST3GAL4, STMN1, TGFBR3, TNFRSF1B, TNFRSF21, YAP1, YWHAZ
H460	CAPRIN1, CCNA2, CCND1, CDK6, CDKN1A, CHEK1, CXCL1, CXCL5, DCAF7, DDB1, ETS1, HMGB1, IL17RD, KRAS, MAPK8, MCL1, MPP2, NOTCH1, NOTCH2, NOTCH3, NT5E, PLAU, PSEN1, PTK2, SEPN1, SLC7A5, ST3GAL4, STMN1, TGFBR3, TNFRSF1B, TNFRSF21
HEP3B	AJUBA, CAPRIN1, CCND1, CDK6, CRYAA, DCAF7, ERBB4, ETS1, GRB7, IL17RD, KRAS, MAPK8, MCL1, MDM2, MPP2, NOTCH1, NT5E, PSEN1, PTK2, SEPN1, SLC7A5, SOS2, ST3GAL4, STMN1, TGFBR2, TGFBR3, TNFRSF1B, TNFRSF21, YAP1, YWHAZ
HUH7	BRCA1, CCNA2, CCND1, CDC25A, CDK1, CDK6, CHEK1, DCAF7, E2F1, ETS1, EZH2, FEN1, FOXM1, GRB7, HMGB1, IL17RD, KRAS, MAPK8, MCL1, MDM2, MELK, MPP2, NT5E, PLAU, PLK1, RAD51, SEPN1, SLC7A5, ST3GAL4, STMN1, TGFBR3, TNFRSF21, YWHAZ

1.2.2 Cellular pathways regulated by miR-193a in solid tumor cell lines

IPA was performed to identify canonical pathways that are affected in miRNA-193a treated cells compared to mock, based on the differential expression data. Tables 6 - 20 show all the significantly regulated pathways in each cell line. Because the objective was to develop new treatment options by more closely defining the mode of action of miR-193a across cancer types, we next analyzed the pathways that were regulated by genes differentially expressed in at least three cell lines. This analysis showed that the majority of pathways was affected or inhibited (Figure 1A), including many growth factor signalling pathways which induce cellular proliferation and tumour progression. The most enriched canonical pathway, the tumour suppressive PTEN pathway, was indicated to be activated (z-score of 2.309). Differentially expressed genes in this pathway include RPS6KB2, KRAS, PDGFRB, SOS2, TGFBR3, CASP9, INPPL1, PIK3R1, PTK2, CBL, PDPK1, CCND1, BCAR1, and MAGI3 (Figure 2).

Other identified pathways were significantly inhibited, including Neuregulin signalling (z-score of -2.333) and HGF signalling (z-score of -3.162). Genes from our differential expression dataset that participate in these pathways are shown in Figure 1b and include PI3KR1, KRAS, SOS2 and PTK2. Many are important components of growth factor signalling and mitogen-activated protein kinase (MAPK) pathways, inducing nuclear signals for cellular proliferation and tumour progression.

Subsequently, IPA software was used to predict downstream effects of the observed gene expression changes on biological functions and disease processes. Out of the 100 most significant biological functions that were changed by 193a at 24h, those that were inhibited (z-score < -2) were related to cell survival, proliferation, migration, or cancer, and those that were activated (z-score > 2) were related to (tumour) cell death (Figure 3). Furthermore, the majority of the affected biological functions (55% at 24h) belonged to the category Cancer (Table 5, which shows categories of top 100 biological functions ranked based on the number of miRNA-193a-regulated functions (all P <0.00001) at 24h).

Table 5: Biological function categories.

24h	
Category	**# functions**
Cancer	55
Cell movement	10
Cell death and survival	9
Cell growth and development	7
Organismal development and survival	6
Nervous system function	5
Cardiovascular	3
Cell maintenance	3
DNA replication	1
Hematological disease	1

Table 6 – A549 lung cancer upregulated pathways and associated genes

Pathway Name	**Gene**
PTEN Signaling	BCAR1, CASP9, CBL, CCND1, INPPL1, KRAS, PDPK1, PIK3R1, PTK2, RPS6KB2, SOS2, TGFBR2, TGFBR3
Cell Cycle: G1/S Checkpoint Regulation	CCND1, CDK2, CDK4, CDK6, HDAC3, MAX, TGFB2
RhoGDI Signaling	ACTR3, ARPC2, ARPC5, CDH1, CDH16, CDH8, GNAI3, GNAZ, GNB1, PAK4, PIP4K2C, PRKCA, RHOU
VDR/RXR Activation	HOXA10, IL12A, NCOA3, PRKCA, TGFB2, THBD
Pyrimidine Ribonucleotides Interconversion	AK7, ENTPD7, NUDT15, SLC25A42
Endocannabinoid Cancer Inhibition Pathway	ADCY9, CASP9, CCND1, CDH1, GNAI3, PIK3R1, PTK2, SMPD1, TCF7L2
Sumoylation Pathway	CDH1, ETS1, FOS, MYB, RHOU, SENP1, TDG
Pyrimidine Ribonucleotides De Novo Biosynthesis	AK7, ENTPD7, NUDT15, SLC25A42
HIPPO signaling	LATS2, SFN, TP53BP2, WWTR1, YAP1, YWHAZ
PD-1, PD-L1 cancer immunotherapy pathway	CDK2, IL12A, LATS2, PDCD4, PIK3R1, TGFB2, YAP1
PPARα/RXRα Activation	ADCY9, CHD5, KRAS, NCOA3, NOTUM, PRKCA, SOS2, TGFB2, TGFBR2, TGFBR3
GPCR-Mediated Integration of Enteroendocrine Signaling Exemplified by an L Cell	ADCY9, ADRB1, GNAI3, NOTUM
Apoptosis Signaling	CAPN10, CASP9, KRAS, MCL1, PRKCA
AMPK Signaling	ADRB1, AK7, CCNA2, CCND1, PDPK1, PHLPP2, PIK3R1, PPM1F

Table 7 - A549 lung cancer aberrant pathways and associated genes

Pathway Name	**Gene**
TR/RXR Activation	ADRB1, AKR1C1/AKR1C2, AKR1C3, ATP2A1, COL6A3, DIO2, HDAC3, KLF9, NCOA3, PIK3R1, SREBF2, TBL1XR1

Molecular Mechanisms of Cancer	ADCY9, APH1B, CASP9, CBL, CCND1, CDH1, CDK2, CDK4, CDK6, CHEK1, FOS, GNAI3, GNAZ, HHAT, KRAS, MAX, NF1, PAK4, PIK3R1, PRKCA, PSEN1, PTK2, RASGRF2, RHOU, SOS2, TGFB2, TGFBR2
Epithelial Adherens Junction Signaling	ACTR3, ARPC2, ARPC5, CDH1, KRAS, MYH11, NOTCH2, SSX2IP, TCF7L2, TGFB2, TGFBR2, TGFBR3, TUBA1B, TUBA4A
Coagulation System	F3, PLAU, PLAUR, SERPINA5, SERPINE1, THBD
Germ Cell-Sertoli Cell Junction Signaling	BCAR1, CDH1, KRAS, MAP3K2, MAP3K3, PAK4, PDPK1, PIK3R1, PTK2, RHOU, TGFB2, TGFBR2, TUBA1B, TUBA4A
Chronic Myeloid Leukemia Signaling	CCND1, CDK4, CDK6, CRKL, HDAC3, KRAS, PIK3R1, SOS2, TGFB2, TGFBR2
Pancreatic Adenocarcinoma Signaling	CASP9, CCND1, CDK2, CDK4, KRAS, PIK3R1, PLD6, STAT3, TGFB2, TGFBR2
Tight Junction Signaling	CDK4, CLDN2, CLDN4, FOS, GOSR2, MYH11, MYLK, NSF, NUDT21, PARD6A, TGFB2, TGFBR2, TJP3
p53 Signaling	CCND1, CCNG1, CDK2, CDK4, CHEK1, PIK3R1, SFN, TP53BP2, TP53INP1
Phenylalanine Degradation I (Aerobic)	PCBD1, QDPR
Gap Junction Signaling	ADCY9, ADRB1, GJB2, GNAI3, KRAS, MAP3K2, NOTUM, NPR1, PIK3R1, PPP3R1, PRKCA, SOS2, TUBA1B, TUBA4A
HER-2 Signaling in Breast Cancer	CASP9, CCND1, CDK6, KRAS, PARD6A, PIK3R1, PRKCA, SOS2
Bile Acid Biosynthesis, Neutral Pathway	AKR1C1/AKR1C2, AKR1C3, SCP2
Antiproliferative Role of TOB in T Cell Signaling	CCNA2, CDK2, TGFB2, TGFBR2
Folate Polyglutamylation	MTHFD1, SHMT2
Protein Citrullination	PADI1, PADI2
Regulation of the Epithelial-Mesenchymal Transition Pathway	APH1B, CDH1, ETS1, KRAS, NOTCH2, PARD6A, PIK3R1, PSEN1, SOS2, STAT3, TCF7L2, TGFB2, TGFBR2
Th1 and Th2 Activation Pathway	APH1B, BHLHE41, IL12A, IL4R, IL6R, IRF1, NOTCH2, PIK3R1, PSEN1, STAT3, TGFBR2, TGFBR3
Serotonin Receptor Signaling	ADCY9, GCH1, MAOB, PCBD1, QDPR
Erythropoietin Signaling	CBL, FOS, KRAS, PDPK1, PIK3R1, PRKCA, SOS2
FAK Signaling	BCAR1, CAPN10, KRAS, PAK4, PDPK1, PIK3R1, PTK2, SOS2
Myc Mediated Apoptosis Signaling	CASP9, KRAS, PIK3R1, SFN, SOS2, YWHAZ
GADD45 Signaling	CCND1, CDK2, CDK4
DNA Methylation and Transcriptional Repression Signaling	DNMT3B, HIST1H4C, MTA2, SUDS3
Thyroid Cancer Signaling	BDNF, CCND1, CDH1, KRAS, TCF7L2
Sphingomyelin Metabolism	SGMS1, SMPD1
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	FOS, KRAS, PPP3R1, SOS2, TGFB2, TGFBR2, VAV3
Lipoate Salvage and Modification	LIPT1
Prostate Cancer Signaling	CASP9, CCND1, CDK2, KRAS, PDPK1, PIK3R1, SOS2
Folate Transformations I	MTHFD1, SHMT2
Factors Promoting Cardiogenesis in Vertebrates	CDK2, NOG, PRKCA, TCF7L2, TGFB2, TGFBR2, TGFBR3

Estrogen Receptor Signaling	HDAC3, KRAS, MED14, MED21, NCOA3, NRIP1, RBFOX2, SOS2, TAF7L
Calcium Transport I	ATP2A1, ATP2B4
Hereditary Breast Cancer Signaling	CCND1, CDK4, CDK6, CHEK1, FANCE, HDAC3, KRAS, PIK3R1, SFN
Sertoli Cell-Sertoli Cell Junction Signaling	BCAR1, CDH1, CLDN2, CLDN4, KRAS, MAP3K2, MAP3K3, TGFBR3, TJP3, TUBA1B, TUBA4A
Role of JAK family kinases in IL-6-type Cytokine Signaling	IL6R, OSMR, STAT3
Axonal Guidance Signaling	ACTR3, ARPC2, ARPC5, BCAR1, BDNF, CRKL, EPHB2, EPHB3, GNAI3, GNAZ, GNB1, KRAS, NOTUM, PAK4, PIK3R1, PLXNA2, PPP3R1, PRKCA, PTK2, SEMA4G, SOS2, TUBA1B, TUBA4A
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	CCL2, CCND1, CEBPD, F2RL1, FOS, IL6R, KRAS, NOTUM, PIK3R1, PPP3R1, PRKCA, ROR2, STAT3, TCF7L2, TLR6, TRAF1
Glucocorticoid Receptor Signaling	CCL2, FOS, HMGB1, KRAS, KRT14, MED14, NCOA3, NRIP1, PIK3R1, PLAU, PPP3R1, SERPINE1, SOS2, STAT3, TAF7L, TGFB2, TGFBR2
T Cell Receptor Signaling	CBL, FOS, KRAS, PIK3R1, PPP3R1, SOS2, VAV3
Glycine Biosynthesis I	SHMT2
Guanine and Guanosine Salvage I	HPRT1
L-cysteine Degradation III	MPST
Lipoate Biosynthesis and Incorporation II	LIPT1
FAT10 Cancer Signaling Pathway	STAT3, TGFB2, TGFBR2, TGFBR3
IL-4 Signaling	IL4R, INPPL1, KRAS, PIK3R1, RPS6KB2, SOS2
Cholesterol Biosynthesis I	DHCR24, LBR
Cholesterol Biosynthesis II (via 24, 25-dihydrolanosterol)	DHCR24, LBR
Cholesterol Biosynthesis III (via Desmosterol)	DHCR24, LBR
Breast Cancer Regulation by Stathmin1	ADCY9, CDK2, GNAI3, GNB1, KRAS, PIK3R1, PRKCA, SOS2, STMN1, TUBA1B, TUBA4A
Ephrin A Signaling	BCAR1, PIK3R1, PTK2, VAV3
Phenylalanine Degradation IV (Mammalian, via Side Chain)	HPD, MAOB
Ethanol Degradation II	ACSS2, ALDH9A1, DHRS9
T Helper Cell Differentiation	IL12A, IL4R, IL6R, STAT3, TGFBR2
Extrinsic Prothrombin Activation Pathway	F3, THBD
Granzyme B Signaling	CASP9, LMNB2
Vitamin-C Transport	SLC23A2, SLC2A3
L-carnitine Biosynthesis	ALDH9A1
Methylglyoxal Degradation I	GLO1
N-acetylglucosamine Degradation I	GNPDA1
Tetrahydrobiopterin Biosynthesis I	GCH1
Tetrahydrobiopterin Biosynthesis II	GCH1
Thiosulfate Disproportionation III (Rhodanese)	MPST
Thyroid Hormone Metabolism I (via Deiodination)	DIO2
Thyronamine and Iodothyronamine Metabolism	DIO2
Tyrosine Biosynthesis IV	PCBD1

Circadian Rhythm Signaling	BHLHE41, PER1, PER2
CD27 Signaling in Lymphocytes	CASP9, FOS, MAP3K2, MAP3K3
Leptin Signaling in Obesity	ADCY9, NOTUM, PDE3A, PIK3R1, STAT3
Natural Killer Cell Signaling	INPPL1, KRAS, PAK4, PIK3R1, PRKCA, SOS2, VAV3
Angiopoietin Signaling	CASP9, KRAS, PAK4, PIK3R1, PTK2
IL-15 Production	DSTYK, EPHB2, EPHB3, IRF1, PTK2, ROR2, TWF1
Dermatan Sulfate Degradation (Metazoa)	CEMIP2, IDS
IL-17A Signaling in Fibroblasts	CCL2, CEBPD, FOS
Noradrenaline and Adrenaline Degradation	ALDH9A1, DHRS9, MAOB
RAR Activation	ADCY9, AKR1C3, DHRS9, FOS, NR2F6, NRIP1, PDPK1, PIK3R1, PRKCA, TGFB2
Dopamine Receptor Signaling	ADCY9, GCH1, MAOB, PCBD1, QDPR
Cell Cycle Control of Chromosomal Replication	CDK2, CDK4, CDK6, MCM2
Unfolded protein response	CEBPD, DNAJC3, EDEM1, SREBF2
1D-myo-inositol Hexakisphosphate Biosynthesis II (Mammalian)	INPPL1, ITPKB
D-myo-inositol (1, 3, 4)-trisphosphate Biosynthesis	INPPL1, ITPKB
Differential Regulation of Cytokine Production in Macrophages and T Helper Cells by IL-17A and IL-17F	CCL2, IL12A
FAT10 Signaling Pathway	SQSTM1, UBE2Z
Methylglyoxal Degradation III	AKR1C1/AKR1C2, AKR1C3
G-Protein Coupled Receptor Signaling	ADCY9, ADRB1, GNAI3, KRAS, PDE3A, PDE4D, PDE8A, PDPK1, PIK3R1, PLD6, PRKCA, SOS2, STAT3
Cell Cycle Regulation by BTG Family Proteins	CCND1, CDK2, CDK4
Acetate Conversion to Acetyl-CoA	ACSS2
Glutathione Redox Reactions II	GSR
Heme Biosynthesis from Uroporphyrinogen-III I	CPOX
Melatonin Degradation II	MAOB
N-acetylglucosamine Degradation II	GNPDA1
DNA damage-induced 14-3-3σ Signaling	CDK2, SFN
Oxidative Ethanol Degradation III	ACSS2, ALDH9A1
Notch Signaling	APH1B, NOTCH2, PSEN1
Nur77 Signaling in T Lymphocytes	CASP9, MAP3K2, MAP3K3, PPP3R1
Docosahexaenoic Acid (DHA) Signaling	CASP9, PDPK1, PIK3R1
The Visual Cycle	AKR1C3, DHRS9
Endoplasmic Reticulum Stress Pathway	CASP9, DNAJC3
Putrescine Degradation III	ALDH9A1, MAOB
IL-12 Signaling and Production in Macrophages	FOS, IL12A, IRF1, IRF8, PIK3R1, PRKCA, TGFB2
Tetrahydrofolate Salvage from 5, 10-methenyltetrahydrofolate	MTHFD1
Tyrosine Degradation I	HPD
dTMP De Novo Biosynthesis	SHMT2
Polyamine Regulation in Colon Cancer	KRAS, MAX
Human Embryonic Stem Cell Pluripotency	BDNF, NOG, PDPK1, PIK3R1, TCF7L2, TGFB2, TGFBR2
Hepatic Fibrosis / Hepatic Stellate Cell Activation	CCL2, COL20A1, COL6A3, IL4R, IL6R, MYH11, SERPINE1, TGFB2, TGFBR2

Role of PI3K/AKT Signaling in the Pathogenesis of Influenza	CASP9, CRKL, GNAI3, PIK3R1
CD40 Signaling	FOS, PIK3R1, STAT3, TRAF1
Calcium-induced T Lymphocyte Apoptosis	ATP2A1, ORAI1, PPP3R1, PRKCA
Apelin Cardiac Fibroblast Signaling Pathway	SERPINE1, TGFB2
Differential Regulation of Cytokine Production in Intestinal Epithelial Cells by IL-17A and IL-17F	CCL2, IL12A
Ethanol Degradation IV	ACSS2, ALDH9A1
Superpathway of D-myo-inositol (1, 4, 5)-trisphosphate Metabolism	INPPL1, ITPKB
Adenine and Adenosine Salvage III	HPRT1
Glycogen Biosynthesis II (from UDP-D-Glucose)	GBE1
UDP-N-acetyl-D-glucosamine Biosynthesis II	GFPT1
Urea Cycle	CPS1
Zymosterol Biosynthesis	LBR
IL-1 Signaling	ADCY9, FOS, GNAI3, GNAZ, GNB1
Clathrin-mediated Endocytosis Signaling	ACTR3, AP1S2, AP2M1, ARPC2, ARPC5, CBL, EPHB2, PIK3R1, PPP3R1
Tryptophan Degradation X (Mammalian, via Tryptamine)	ALDH9A1, MAOB
Role of JAK1 and JAK3 in γc Cytokine Signaling	IL4R, KRAS, PIK3R1, STAT3
nNOS Signaling in Neurons	CAPN10, PPP3R1, PRKCA
Corticotropin Releasing Hormone Signaling	ADCY9, ARPC5, BDNF, FOS, GNAI3, NPR1, PRKCA
α-Adrenergic Signaling	ADCY9, GNAI3, GNB1, KRAS, PRKCA
Glycoaminoglycan-protein Linkage Region Biosynthesis	XYLT1
Superpathway of Serine and Glycine Biosynthesis I	SHMT2
Tryptophan Degradation to 2-amino-3-carboxymuconate Semialdehyde	AFMID
Role of Tissue Factor in Cancer	F2RL1, F3, KRAS, PIK3R1, PLAUR, PRKCA
IL-15 Signaling	KRAS, PIK3R1, PTK2, STAT3
ATM Signaling	CBX1, CDK2, CHEK1, HP1BP3, RNF168
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	CHEK1, SFN, YWHAZ
T Cell Exhaustion Signaling Pathway	FOS, IL12A, IL6R, KRAS, PIK3R1, STAT3, TGFBR2, TGFBR3
Phagosome Maturation	ATP6V1B2, DYNC2H1, GOSR2, NSF, TUBA1B, TUBA4A, VPS37B
Primary Immunodeficiency Signaling	RFX5, TAP2, UNG
TNFR1 Signaling	CASP9, FOS, PAK4
Histidine Degradation III	MTHFD1
Salvage Pathways of Pyrimidine Deoxyribonucleotides	TK2
Superpathway of Cholesterol Biosynthesis	DHCR24, LBR
Amyloid Processing	APH1B, CAPN10, PSEN1
Phagosome Formation	NOTUM, PIK3R1, PRKCA, RHOU, TLR6, VTN
Toll-like Receptor Signaling	FOS, IL12A, TLR6, TRAF1
UVB-Induced MAPK Signaling	FOS, PIK3R1, PRKCA
Antiproliferative Role of Somatostatin Receptor 2	GNB1, KRAS, NPR1, PIK3R1
Dopamine Degradation	ALDH9A1, MAOB
TNFR2 Signaling	FOS, TRAF1

Heme Biosynthesis II	CPOX
Leucine Degradation I	BCAT2
UDP-N-acetyl-D-galactosamine Biosynthesis II	GNPDA1
Transcriptional Regulatory Network in Embryonic Stem Cells	HIST1H4C, SET, STAT3
Cellular Effects of Sildenafil (Viagra)	ADCY9, MYH11, MYLK, NOTUM, PDE3A, PDE4D
Acetone Degradation I (to Methylglyoxal)	CYP1A1
Role of p14/p19ARF in Tumor Suppression	PIK3R1
Sonic Hedgehog Signaling	DYRK1B
4-1BB Signaling in T Lymphocytes	TNFSF9, TRAF1
Dolichyl-diphosphooligosaccharide Biosynthesis	DPM3
Glycine Betaine Degradation	SHMT2
Virus Entry via Endocytic Pathways	AP1S2, AP2M1, KRAS, PIK3R1, PRKCA
Retinoic acid Mediated Apoptosis Signaling	CASP9, IRF1
SPINK1 Pancreatic Cancer Pathway	F2RL1, TGFBR2
Androgen Signaling	CCND1, GNAI3, GNAZ, GNB1, PRKCA, SHBG
Dermatan Sulfate Biosynthesis	DSEL, XYLT1
Iron homeostasis signaling pathway	ABCB10, ATP6V1B2, HFE, IL6R, PCBP1, STAT3
Lipid Antigen Presentation by CD1	AP2M1
NAD Salvage Pathway II	NT5E
Cancer Drug Resistance By Drug Efflux	KRAS, PIK3R1
CTLA4 Signaling in Cytotoxic T Lymphocytes	AP1S2, AP2M1, PIK3R1
MSP-RON Signaling Pathway	CCL2, IL12A, PIK3R1
IL-9 Signaling	PIK3R1, STAT3
Retinoate Biosynthesis I	AKR1C3, DHRS9
Bupropion Degradation	CYP1A1
D-myo-inositol (1, 4, 5)-Trisphosphate Biosynthesis	PIP4K2C
IL-17A Signaling in Gastric Cells	FOS
Role of CHK Proteins in Cell Cycle Checkpoint Control	CDK2, CHEK1
Semaphorin Signaling in Neurons	PAK4, PTK2, RHOU
Glutathione Redox Reactions I	GSR
IL-22 Signaling	STAT3
Role of JAK1, JAK2 and TYK2 in Interferon Signaling	STAT3
Tumoricidal Function of Hepatic Natural Killer Cells	CASP9
TWEAK Signaling	CASP9, TRAF1
p38 MAPK Signaling	MAX, RPS6KB2, TGFB2, TGFBR2
Role of IL-17A in Arthritis	CCL2, PIK3R1
Cleavage and Polyadenylation of Pre-mRNA	NUDT21
Guanosine Nucleotides Degradation III	NT5E
Interferon Signaling	IRF1, MED14
Ceramide Signaling	FOS, KRAS, PIK3R1, SMPD1
Phototransduction Pathway	GNB1, RGS9BP
Phosphatidylglycerol Biosynthesis II (Non-plastidic)	AGPAT1
Pyrimidine Deoxyribonucleotides De Novo Biosynthesis I	AK7
Tryptophan Degradation III (Eukaryotic)	AFMID

NF-κB Activation by Viruses	KRAS, PIK3R1, PRKCA
Acyl-CoA Hydrolysis	ACOT8
Urate Biosynthesis/Inosine 5'-phosphate Degradation	NT5E
IL-17 Signaling	CCL2, KRAS, PIK3R1
Mitochondrial Dysfunction	APH1B, ATP5PB, CASP9, GSR, MAOB, PSEN1
IL-17A Signaling in Airway Cells	MUC5AC, PIK3R1, STAT3
April Mediated Signaling	FOS, TRAF1
Inhibition of Matrix Metalloproteases	RECK, TIMP4
CDP-diacylglycerol Biosynthesis I	AGPAT1
Fatty Acid α-oxidation	ALDH9A1
Granzyme A Signaling	SET
Androgen Biosynthesis	AKR1C3
Isoleucine Degradation I	BCAT2
NAD biosynthesis II (from tryptophan)	AFMID
Hematopoiesis from Pluripotent Stem Cells	IL11, IL12A
CCR5 Signaling in Macrophages	FOS, GNAI3, GNB1, PRKCA
Role of MAPK Signaling in the Pathogenesis of Influenza	CCL2, KRAS, PRKCA
Serotonin Degradation	ALDH9A1, DHRS9, MAOB
GABA Receptor Signaling	ADCY9, ALDH9A1, AP2M1, NSF
Antioxidant Action of Vitamin C	NOTUM, PLD6, SLC23A2, SLC2A3
Macropinocytosis Signaling	KRAS, PIK3R1, PRKCA
Gustation Pathway	ADCY9, GNB1, PDE3A, PDE4D, PDE8A, PLD6
B Cell Activating Factor Signaling	FOS, TRAF1
Estrogen Biosynthesis	AKR1C3, CYP1A1
Mechanisms of Viral Exit from Host Cells	LMNB2, PRKCA
Role of PKR in Interferon Induction and Antiviral Response	CASP9, IRF1
Adenosine Nucleotides Degradation II	NT5E
Choline Biosynthesis III	PLD6
Superpathway of Citrulline Metabolism	CPS1
FcγRIIB Signaling in B Lymphocytes	KRAS, PDPK1, PIK3R1
Heparan Sulfate Biosynthesis (Late Stages)	EXTL2, EXTL3, NOTUM
Bladder Cancer Signaling	CCND1, CDH1, CDK4, KRAS
IL-10 Signaling	FOS, IL4R, STAT3
Adipogenesis pathway	CEBPD, EBF1, HDAC3, PER2, TBL1XR1
Purine Nucleotides Degradation II (Aerobic)	NT5E
Valine Degradation I	BCAT2
PFKFB4 Signaling Pathway	NCOA3, TGFB2
PPAR Signaling	FOS, KRAS, NRIP1, SOS2
Retinol Biosynthesis	AKR1C3, DHRS9
Agranulocyte Adhesion and Diapedesis	CCL2, CLDN2, CLDN4, GNAI3, MYH11, PODXL, SELPLG
Amyotrophic Lateral Sclerosis Signaling	CAPN10, CASP9, NEFH, PIK3R1
NER Pathway	COPS3, DDB1, HIST1H4C, POLE3
Chondroitin Sulfate Degradation (Metazoa)	CEMIP2
Parkinson's Signaling	CASP9
IL-23 Signaling Pathway	PIK3R1, STAT3
Role of IL-17F in Allergic Inflammatory Airway Diseases	CCL2, IL11
Stearate Biosynthesis I (Animals)	ACOT8, DHCR24

iNOS Signaling	FOS, IRF1
Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza	CCL2, IL12A
D-myo-inositol (1, 4, 5)-trisphosphate Degradation	INPPL1
Histamine Degradation	ALDH9A1
Melatonin Signaling	GNAI3, NOTUM, PRKCA
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	IL12A, TLR6
Antigen Presentation Pathway	TAP2
Apelin Adipocyte Signaling Pathway	ADCY9, GNAI3
Apelin Pancreas Signaling Pathway	PIK3R1
Assembly of RNA Polymerase II Complex	TAF7L
Atherosclerosis Signaling	CCL2, F3, SELPLG
Autophagy	SQSTM1, WIPI1
BMP signaling pathway	KRAS, NOG
Basal Cell Carcinoma Signaling	TCF7L2
CDK5 Signaling	ADCY9, BDNF, KRAS
Caveolar-mediated Endocytosis Signaling	MAP3K2, PRKCA
Chondroitin Sulfate Biosynthesis	XYLT1
Communication between Innate and Adaptive Immune Cells	IL12A, TLR6
Complement System	C1QBP
Crosstalk between Dendritic Cells and Natural Killer Cells	IL12A
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	CASP9
Death Receptor Signaling	CASP9, TNFRSF21
Dendritic Cell Maturation	IL12A, IRF8, NOTUM, PIK3R1
Dermatan Sulfate Biosynthesis (Late Stages)	DSEL
Eicosanoid Signaling	AKR1C3, ALOX5AP
FXR/RXR Activation	VTN
Fatty Acid β-oxidation I	SCP2
G Protein Signaling Mediated by Tubby	GNB1
Glutamate Receptor Signaling	GNB1
Granulocyte Adhesion and Diapedesis	CCL2, CLDN2, CLDN4, GNAI3, SELPLG
Gαs Signaling	ADCY9, ADRB1, GNB1
HIF1α Signaling	KRAS, PIK3R1, SLC2A3
Hepatic Cholestasis	ADCY9, IL11, IL12A, PRKCA, TGFB2, TNFSF9
Hypoxia Signaling in the Cardiovascular System	UBE2L6, UBE2Z
Induction of Apoptosis by HIV1	CASP9, TRAF1
Inhibition of Angiogenesis by TSP1	TGFBR2
Intrinsic Prothrombin Activation Pathway	THBD
LPS/IL-1 Mediated Inhibition of RXR Function	ALDH9A1, MAOB
LXR/RXR Activation	CCL2, VTN
MIF Regulation of Innate Immunity	FOS
Melatonin Degradation I	CYP1A1
Netrin Signaling	PPP3R1
Neuroprotective Role of THOP1 in Alzheimer's Disease	TPP1
Nicotine Degradation II	CYP1A1
Nicotine Degradation III	CYP1A1

Oxidative Phosphorylation	ATP5PB
PCP pathway	LGR4, ROR2
Phospholipases	NOTUM, PLD6
Protein Ubiquitination Pathway	CBL, DNAJC16, DNAJC3, HSPA13, TAP2, UBE2L6, UBE2Z, USP39, USP43
Reelin Signaling in Neurons	CRKL, PIK3R1
Role of BRCA1 in DNA Damage Response	CHEK1, FANCE
Role of Cytokines in Mediating Communication between Immune Cells	IL12A
Role of JAK2 in Hormone-like Cytokine Signaling	STAT3
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	NR2F6
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	CASP9, CBL, FOS, IL11, PIK3R1, PPP3R1, TCF7L2
Role of RIG1-like Receptors in Antiviral Innate Immunity	TRIM25
Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza	NCOA3, TCF7L2
Superpathway of Melatonin Degradation	CYP1A1, MAOB
Systemic Lupus Erythematosus Signaling	CBL, FOS, IL6R, KRAS, PIK3R1, SOS2
Th17 Activation Pathway	IL12A, IL6R, STAT3
Thyroid Hormone Metabolism II (via Conjugation and/or Degradation)	DIO2
Triacylglycerol Biosynthesis	AGPAT1
Triacylglycerol Degradation	NOTUM
Type I Diabetes Mellitus Signaling	CASP9, IL12A, IRF1
Type II Diabetes Mellitus Signaling	PDPK1, PIK3R1, PRKCA, SMPD1
Wnt/Ca+ pathway	NOTUM, PRKCA
Xenobiotic Metabolism Signaling	ALDH9A1, CYP1A1, KRAS, MAOB, MAP3K2, MAP3K3, NRIP1, PIK3R1, PRKCA
iCOS-iCOSL Signaling in T Helper Cells	PDPK1, PIK3R1, PPP3R1
tRNA Charging	LARS2

Table 8 - A549 lung cancer downregulated pathways and associated genes

Pathway Name	**Gene**
HGF Signaling	CCND1, CDK2, CRKL, ELK3, ETS1, FOS, KRAS, MAP3K2, MAP3K3, PIK3R1, PRKCA, PTK2, SOS2, STAT3
Signaling by Rho Family GTPases	ACTR3, ARPC2, ARPC5, CDC42EP2, CDH1, CDH16, CDH8, FOS, GNAI3, GNAZ, GNB1, MYLK, PAK4, PARD6A, PIK3R1, PIP4K2C, PTK2, RHOU, STMN1
Small Cell Lung Cancer Signaling	CASP9, CCND1, CDK2, CDK4, CDK6, MAX, PIK3R1, PTK2, TRAF1
IGF-1 Signaling	CASP9, FOS, KRAS, PDPK1, PIK3R1, PTK2, RPS6KB2, SFN, SOS2, STAT3, YWHAZ
Non-Small Cell Lung Cancer Signaling	CASP9, CCND1, CDK4, CDK6, KRAS, PDPK1, PIK3R1, PRKCA, SOS2
Synaptogenesis Signaling Pathway	ACTR3, ADCY9, AP2M1, ARPC2, ARPC5, BDNF, CADM1, CDH1, CDH16, CDH8, CRKL, EIF4EBP2, EPHB2, EPHB3, GOSR2, KRAS, NSF, PIK3R1, RPS6KB2, SOS2, STX1B, SYT1
Cardiac Hypertrophy Signaling (Enhanced)	ADCY9, ADRB1, ATP2A1, GNAI3, GNB1, HDAC3, IL11, IL12A, IL17RD, IL4R, IL6R,

	KRAS, MAP3K2, MAP3K3, NOTUM, NPR1, PDE3A, PDE4D, PDE8A, PIK3R1, PLD6, PPP3R1, PRKCA, PTK2, RPS6KB2, STAT3, TGFB2, TGFBR2, TGFBR3, TNFSF9
Ephrin Receptor Signaling	ACTR3, ARPC2, ARPC5, BCAR1, CRKL, EPHB2, EPHB3, GNAI3, GNAZ, GNB1, KRAS, PAK4, PTK2, SOS2, STAT3
Neuregulin Signaling	CRKL, ERBIN, ERRFI1, KRAS, PDPK1, PIK3R1, PRKCA, PSEN1, RPS6KB2, SOS2
Regulation of Cellular Mechanics by Calpain Protease	CAPN10, CCNA2, CCND1, CDK2, CDK4, CDK6, KRAS, PTK2
ErbB4 Signaling	APH1B, KRAS, PDPK1, PIK3R1, PRKCA, PSEN1, SOS2, YAP1
Ephrin B Signaling	CBL, EPHB2, EPHB3, GNAI3, GNAZ, GNB1, PTK2, VAV3
Aryl Hydrocarbon Receptor Signaling	ALDH9A1, CCNA2, CCND1, CDK2, CDK4, CDK6, CHEK1, CYP1A1, FOS, NCOA3, NRIP1, TGFB2
Glioma Invasiveness Signaling	KRAS, PIK3R1, PLAU, PLAUR, PTK2, RHOU, TIMP4, VTN
14-3-3-mediated Signaling	CBL, FOS, KRAS, NOTUM, PIK3R1, PRKCA, SFN, TUBA1B, TUBA4A, YAP1, YWHAZ
B Cell Receptor Signaling	EBF1, ETS1, INPPL1, KRAS, MAP3K2, MAP3K3, PDPK1, PIK3AP1, PIK3R1, PPP3R1, PTK2, RPS6KB2, SOS2, VAV3
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	ACTR3, ARPC2, ARPC5, CBL, PIK3R1, PLD6, PRKCA, RPS6KB2, VAV3
Endometrial Cancer Signaling	CASP9, CCND1, CDH1, KRAS, PDPK1, PIK3R1, SOS2
p70S6K Signaling	F2RL1, GNAI3, IL4R, KRAS, NOTUM, PDPK1, PIK3R1, PRKCA, SFN, SOS2, YWHAZ
CXCR4 Signaling	ADCY9, BCAR1, ELMO2, FOS, GNAI3, GNAZ, GNB1, KRAS, PAK4, PIK3R1, PRKCA, PTK2, RHOU
Rac Signaling	ABI2, ACTR3, ARPC2, ARPC5, KRAS, PAK4, PARD6A, PIK3R1, PIP4K2C, PTK2
IL-7 Signaling Pathway	CCND1, CDK2, EBF1, MCL1, PDPK1, PIK3R1, PTK2, SOS2
Colorectal Cancer Metastasis Signaling	ADCY9, APPL1, CASP9, CCND1, CDH1, FOS, GNB1, IL6R, KRAS, PIK3R1, RHOU, SOS2, STAT3, TCF7L2, TGFB2, TGFBR2, TLR6
Prolactin Signaling	FOS, IRF1, KRAS, PDPK1, PIK3R1, PRKCA, SOS2, STAT3
Renin-Angiotensin Signaling	ADCY9, CCL2, FOS, KRAS, PAK4, PIK3R1, PRKCA, PTK2, SOS2, STAT3
PDGF Signaling	CRKL, FOS, INPPL1, KRAS, PIK3R1, PRKCA, SOS2, STAT3
GM-CSF Signaling	CCND1, ETS1, KRAS, PIK3R1, PPP3R1, SOS2, STAT3
Tec Kinase Signaling	FOS, GNAI3, GNAZ, GNB1, PAK4, PIK3R1, PRKCA, PTK2, RHOU, STAT3, TNFRSF21, VAV3
ERK5 Signaling	FOS, KRAS, MAP3K2, MAP3K3, RPS6KB2, SFN, YWHAZ
Acute Myeloid Leukemia Signaling	CCND1, IDH2, KRAS, PIK3R1, RPS6KB2, SOS2, STAT3, TCF7L2
Estrogen-mediated S-phase Entry	CCNA2, CCND1, CDK2, CDK4

Relaxin Signaling	ADCY9, FOS, GNAI3, GNAZ, GNB1, NPR1, PDE3A, PDE4D, PDE8A, PIK3R1, PLD6
PI3K/AKT Signaling	CCND1, INPPL1, KRAS, MCL1, PDPK1, PIK3R1, RPS6KB2, SFN, SOS2, YWHAZ
ERK/MAPK Signaling	BCAR1, CRKL, ELK3, ETS1, FOS, KRAS, PAK4, PIK3R1, PRKCA, PTK2, SOS2, STAT3, YWHAZ
Integrin Signaling	ACTR3, ARF3, ARPC2, ARPC5, BCAR1, CAPN10, CRKL, KRAS, MYLK, PAK4, PIK3R1, PTK2, RHOU, SOS2
Role of NFAT in Cardiac Hypertrophy	ADCY9, GNAI3, GNB1, HDAC3, IL11, KRAS, NOTUM, PIK3R1, PPP3R1, PRKCA, RCAN3, SOS2, TGFB2, TGFBR2
Cardiac Hypertrophy Signaling	ADCY9, ADRB1, GNAI3, GNAZ, GNB1, IL6R, KRAS, MAP3K2, MAP3K3, NOTUM, PIK3R1, PPP3R1, RHOU, TGFB2, TGFBR2
Actin Cytoskeleton Signaling	ABI2, ACTR3, ARPC2, ARPC5, BCAR1, CRKL, KRAS, MYH11, MYLK, PAK4, PIK3R1, PTK2, SOS2, VAV3
UVA-Induced MAPK Signaling	CASP9, FOS, KRAS, NOTUM, PIK3R1, PRKCA, RPS6KB2, SMPD1
fMLP Signaling in Neutrophils	ACTR3, ARPC2, ARPC5, GNAI3, GNB1, KRAS, PIK3R1, PPP3R1, PRKCA
IL-3 Signaling	CRKL, FOS, KRAS, PIK3R1, PPP3R1, PRKCA, STAT3
PI3K Signaling in B Lymphocytes	CBL, FOS, IL4R, KRAS, NOTUM, PDPK1, PIK3AP1, PIK3R1, PPP3R1, VAV3
Cyclins and Cell Cycle Regulation	CCNA2, CCND1, CDK2, CDK4, CDK6, HDAC3, TGFB2
SAPK/JNK Signaling	CRKL, GNB1, KRAS, MAP3K2, MAP3K3, MAP4K5, PIK3R1, SOS2
ErbB2-ErbB3 Signaling	CCND1, KRAS, PDPK1, PIK3R1, SOS2, STAT3
HMGB1 Signaling	CCL2, FOS, HMGB1, IL11, IL12A, KRAS, PIK3R1, RHOU, SERPINE1, TGFB2, TNFSF9
Protein Kinase A Signaling	ADCY9, AKAP12, GNAI3, GNB1, HHAT, MYLK, NOTUM, PDE3A, PDE4D, PDE8A, PLD6, PPP3R1, PRKCA, PTK2, PTPN9, PTPRA, SFN, TCF7L2, TGFB2, TGFBR2, YWHAZ
Remodeling of Epithelial Adherens Junctions	ACTR3, ARPC2, ARPC5, CDH1, TUBA1B, TUBA4A
Melanoma Signaling	CCND1, CDH1, CDK4, KRAS, PIK3R1
Telomerase Signaling	ELK3, ETS1, HDAC3, KRAS, PDPK1, PIK3R1, SOS2, TPP1
GNRH Signaling	ADCY9, FOS, GNAI3, GNB1, KRAS, MAP3K2, MAP3K3, PAK4, PRKCA, PTK2, SOS2
Glioma Signaling	CCND1, CDK4, CDK6, IDH2, KRAS, PIK3R1, PRKCA, SOS2
Actin Nucleation by ARP-WASP Complex	ACTR3, ARPC2, ARPC5, KRAS, RHOU, SOS2
Growth Hormone Signaling	FOS, PDPK1, PIK3R1, PRKCA, RPS6KB2, STAT3
Regulation of Actin-based Motility by Rho	ACTR3, ARPC2, ARPC5, MYLK, PAK4, PIP4K2C, RHOU
EGF Signaling	FOS, PIK3R1, PRKCA, SOS2, STAT3
NGF Signaling	KRAS, MAP3K2, MAP3K3, PDPK1, PIK3R1, RPS6KB2, SMPD1, SOS2
ErbB Signaling	FOS, KRAS, PAK4, PDPK1, PIK3R1, PRKCA, SOS2

Aldosterone Signaling in Epithelial Cells	DNAJC16, DNAJC3, HSPA13, KRAS, NOTUM, PDPK1, PIK3R1, PIP4K2C, PRKCA, SOS2
Apelin Endothelial Signaling Pathway	ADCY9, CCL2, FOS, GNAI3, KRAS, PIK3R1, PRKCA, RPS6KB2
Th2 Pathway	APH1B, BHLHE41, IL12A, IL4R, NOTCH2, PIK3R1, PSEN1, TGFBR2, TGFBR3
Neurotrophin/TRK Signaling	BDNF, FOS, KRAS, PDPK1, PIK3R1, SOS2
Sphingosine-1-phosphate Signaling	ADCY9, CASP9, GNAI3, NOTUM, PIK3R1, PTK2, RHOU, SMPD1
PAK Signaling	EPHB3, KRAS, MYLK, PAK4, PIK3R1, PTK2, SOS2
Cardiac β-adrenergic Signaling	ADCY9, ADRB1, AKAP12, ATP2A1, GNB1, PDE3A, PDE4D, PDE8A, PLD6
Agrin Interactions at Neuromuscular Junction	GABPA, GABPB1, KRAS, PAK4, PTK2, RAPSN
Thrombin Signaling	ADCY9, GNAI3, GNAZ, GNB1, KRAS, MYLK, NOTUM, PDPK1, PIK3R1, PRKCA, PTK2, RHOU
tRNA Splicing	PDE3A, PDE4D, PDE8A, PLD6
Chemokine Signaling	CCL2, FOS, GNAI3, KRAS, PRKCA, PTK2
Glioblastoma Multiforme Signaling	CCND1, CDK2, CDK4, CDK6, KRAS, NF1, NOTUM, PIK3R1, RHOU, SOS2
Th1 Pathway	APH1B, IL12A, IL6R, IRF1, NOTCH2, PIK3R1, PSEN1, STAT3
Renal Cell Carcinoma Signaling	ETS1, FOS, KRAS, PAK4, PIK3R1, SOS2
Oncostatin M Signaling	KRAS, OSMR, PLAU, STAT3
Thrombopoietin Signaling	FOS, KRAS, PIK3R1, PRKCA, STAT3
FLT3 Signaling in Hematopoietic Progenitor Cells	CBL, KRAS, PDPK1, PIK3R1, SOS2, STAT3
P2Y Purigenic Receptor Signaling Pathway	ADCY9, FOS, GNAI3, GNB1, KRAS, NOTUM, PIK3R1, PRKCA
Adrenomedullin signaling pathway	ADCY9, ADM, FOS, KRAS, MAX, MYLK, NOTUM, NPR1, PIK3R1, PTK2, SOS2
Leukocyte Extravasation Signaling	BCAR1, CLDN2, CLDN4, CRKL, GNAI3, PIK3R1, PRKCA, PTK2, SELPLG, TIMP4, VAV3
Gα12/13 Signaling	CDH1, CDH16, CDH8, F2RL1, KRAS, PIK3R1, PTK2, VAV3
IL-8 Signaling	CCND1, CDH1, FOS, GNAI3, GNB1, KRAS, PIK3R1, PLD6, PRKCA, PTK2, RHOU
RANK Signaling in Osteoclasts	CBL, FOS, MAP3K2, MAP3K3, PIK3R1, PPP3R1
STAT3 Pathway	IL17RD, IL4R, IL6R, KRAS, STAT3, TGFB2, TGFBR2, TGFBR3
Role of NFAT in Regulation of the Immune Response	FOS, GNAI3, GNAZ, GNB1, KRAS, ORAI1, PIK3R1, PPP3R1, RCAN3, SOS2
UVC-Induced MAPK Signaling	FOS, KRAS, PRKCA, SMPD1
Endocannabinoid Developing Neuron Pathway	ADCY9, CCND1, GNAI3, GNB1, KRAS, PIK3R1, STAT3
Insulin Receptor Signaling	CBL, CRKL, INPPL1, KRAS, PDPK1, PIK3R1, RPS6KB2, SOS2
Endothelin-1 Signaling	ADCY9, CASP9, FOS, GNAI3, GNAZ, KRAS, NOTUM, PIK3R1, PLD6, PRKCA
TGF-β Signaling	FOS, KRAS, SERPINE1, SOS2, TGFB2, TGFBR2
Huntington's Disease Signaling	ATP5PB, BDNF, CAPN10, CASP9, GNB1, GOSR2, HDAC3, NSF, PDPK1, PIK3R1, PRKCA, SOS2
Fc Epsilon RI Signaling	INPPL1, KRAS, PDPK1, PIK3R1, PRKCA, SOS2, VAV3

Cholecystokinin/Gastrin-mediated Signaling	BCAR1, FOS, KRAS, PRKCA, PTK2, RHOU, SOS2
Lymphotoxin β Receptor Signaling	CASP9, PDPK1, PIK3R1, TRAF1
GP6 Signaling Pathway	COL20A1, COL6A3, LAMC2, PDPK1, PIK3R1, PRKCA, PTK2
CD28 Signaling in T Helper Cells	ACTR3, ARPC2, ARPC5, FOS, PDPK1, PIK3R1, PPP3R1
G Beta Gamma Signaling	GNAI3, GNAZ, GNB1, KRAS, PDPK1, PRKCA, SOS2
RhoA Signaling	ACTR3, ARPC2, ARPC5, CDC42EP2, MYLK, PIP4K2C, PTK2
Apelin Cardiomyocyte Signaling Pathway	ATP2A1, GNAI3, MYLK, NOTUM, PIK3R1, PRKCA
VEGF Signaling	KRAS, PIK3R1, PRKCA, PTK2, SFN, SOS2
CCR3 Signaling in Eosinophils	GNAI3, GNB1, KRAS, MYLK, PAK4, PIK3R1, PRKCA
IL-6 Signaling	FOS, IL6R, KRAS, MCL1, PIK3R1, SOS2, STAT3
Neuroinflammation Signaling Pathway	APH1B, BDNF, CCL2, FOS, HMGB1, IL12A, IL6R, PIK3R1, PPP3R1, PSEN1, TGFB2, TGFBR2, TGFBR3, TLR6
JAK/Stat Signaling	FOS, KRAS, PIK3R1, SOS2, STAT3
Acute Phase Response Signaling	FOS, IL6R, KRAS, OSMR, PDPK1, PIK3R1, SERPINE1, SOS2, STAT3
CNTF Signaling	KRAS, PIK3R1, RPS6KB2, STAT3
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	IL11, IL12A, PIK3R1, PRKCA, RIPK2, TGFB2, TLR6, TNFSF9
PKCθ Signaling in T Lymphocytes	FOS, KRAS, MAP3K2, MAP3K3, PIK3R1, PPP3R1, SOS2, VAV3
IL-2 Signaling	FOS, KRAS, PIK3R1, SOS2
FGF Signaling	CRKL, PIK3R1, PRKCA, SOS2, STAT3
VEGF Family Ligand-Receptor Interactions	FOS, KRAS, PIK3R1, PRKCA, SOS2
Paxillin Signaling	BCAR1, KRAS, PAK4, PIK3R1, PTK2, SOS2
mTOR Signaling	EIF4B, KRAS, PDPK1, PIK3R1, PLD6, PRKCA, PRR5L, RHOU, RPS17, RPS6KB2
Pyridoxal 5'-phosphate Salvage Pathway	CDK2, CDK4, CDK6, FAM20B
Dopamine-DARPP32 Feedback in cAMP Signaling	ADCY9, ATP2A1, CAMKK1, GNAI3, KCNJ16, NOTUM, PPP3R1, PRKCA
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	FOS, HOXA10, IRF1, IRF8, MAP3K2, MAP3K3, PIK3R1, PRKCA, RHOU
Cdc42 Signaling	ACTR3, ARPC2, ARPC5, CDC42EP2, FOS, MYLK, PAK4, PARD6A
Sperm Motility	DSTYK, EPHB2, EPHB3, NOTUM, NPR1, PDE4D, PRKCA, PTK2, ROR2, TWF1
SPINK1 General Cancer Pathway	IL6R, KRAS, PIK3R1, STAT3
Melanocyte Development and Pigmentation Signaling	ADCY9, KRAS, PIK3R1, RPS6KB2, SOS2
Superpathway of Inositol Phosphate Compounds	HACD2, INPPL1, ITPKB, NUDT15, NUDT3, PIK3R1, PIP4K2C, PPTC7, SET
Salvage Pathways of Pyrimidine Ribonucleotides	AK7, CDK2, CDK4, CDK6, FAM20B
cAMP-mediated signaling	ADCY9, ADRB1, AKAP12, GNAI3, PDE3A, PDE4D, PDE8A, PLD6, PPP3R1, STAT3
Systemic Lupus Erythematosus In T Cell Signaling Pathway	CASP9, CBL, FOS, GNAI3, KRAS, ORAI1, PIK3R1, PPP3R1, PTK2, RHOU, RPS6KB2, SELPLG, SOS2, STAT3
Gαi Signaling	ADCY9, GNAI3, GNB1, KRAS, SOS2, STAT3

Estrogen-Dependent Breast Cancer Signaling	CCND1, FOS, KRAS, PIK3R1
TREM1 Signaling	CCL2, LAT2, STAT3, TLR6
Neuropathic Pain Signaling In Dorsal Horn Neurons	BDNF, FOS, NOTUM, PIK3R1, PRKCA
GDNF Family Ligand-Receptor Interactions	FOS, KRAS, PIK3R1, SOS2
CREB Signaling in Neurons	ADCY9, GNAI3, GNAZ, GNB1, KRAS, NOTUM, PIK3R1, PRKCA, SOS2
Mouse Embryonic Stem Cell Pluripotency	KRAS, PIK3R1, SOS2, STAT3, TCF7L2
Sirtuin Signaling Pathway	ACSS2, ATP5PB, CDH1, CPS1, GABPA, GABPB1, IDH2, STAT3, TOMM20, TUBA1B, TUBA4A, ZBTB14
Heparan Sulfate Biosynthesis	EXTL2, EXTL3, NOTUM, XYLT1
LPS-stimulated MAPK Signaling	FOS, KRAS, PIK3R1, PRKCA
PEDF Signaling	BDNF, KRAS, PIK3R1, TCF7L2
NRF2-mediated Oxidative Stress Response	DNAJC16, DNAJC3, FOS, GSR, KRAS, PIK3R1, PRKCA, SQSTM1
ILK Signaling	CCND1, CDH1, FOS, MYH11, PDPK1, PIK3R1, PTK2, RHOU
3-phosphoinositide Biosynthesis	HACD2, NUDT15, NUDT3, PIK3R1, PIP4K2C, PPTC7, SET
Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency	KRAS, PIK3R1, SOS2, STAT3
Opioid Signaling Pathway	ADCY9, AP2M1, FOS, GNAI3, GNB1, KRAS, PPP3R1, PRKCA, RPS6KB2, SOS2
Ovarian Cancer Signaling	CCND1, CDK4, KRAS, PIK3R1, RPS6KB2, TCF7L2
NF-κB Signaling	KRAS, MAP3K3, PIK3R1, TGFBR2, TGFBR3, TLR6
Calcium Signaling	ATP2A1, ATP2B4, CAMKK1, HDAC3, MYH11, PPP3R1, RCAN3
Wnt/β-catenin Signaling	APPL1, CCND1, CDH1, TCF7L2, TGFB2, TGFBR2, TGFBR3
GPCR-Mediated Nutrient Sensing in Enteroendocrine Cells	ADCY9, GNAI3, NOTUM, PRKCA
D-myo-inositol (1, 4, 5, 6)-Tetrakisphosphate Biosynthesis	HACD2, NUDT15, NUDT3, PPTC7, SET
D-myo-inositol (3, 4, 5, 6)-tetrakisphosphate Biosynthesis	HACD2, NUDT15, NUDT3, PPTC7, SET
Phospholipase C Signaling	ADCY9, GNB1, HDAC3, KRAS, PLD6, PPP3R1, PRKCA, RHOU, SOS2
EIF2 Signaling	CCND1, EIF2AK1, KRAS, PDPK1, PIK3R1, RPL26, RPS17, SOS2
3-phosphoinositide Degradation	HACD2, INPPL1, NUDT15, NUDT3, PPTC7, SET
D-myo-inositol-5-phosphate Metabolism	HACD2, NUDT15, NUDT3, PIP4K2C, PPTC7, SET
Endocannabinoid Neuronal Synapse Pathway	ADCY9, GNAI3, GNB1, NOTUM, PPP3R1
eNOS Signaling	ADCY9, CASP9, CCNA2, PDPK1, PIK3R1, PRKCA
Nitric Oxide Signaling in the Cardiovascular System	ADRB1, ATP2A1, PIK3R1, PRKCA
Gαq Signaling	GNB1, PIK3R1, PLD6, PPP3R1, PRKCA, RHOU
Regulation of eIF4 and p70S6K Signaling	EIF4EBP2, KRAS, PDPK1, PIK3R1, RPS17, SOS2
Osteoarthritis Pathway	CASP9, HDAC3, HMGB1, TCF7L2, TGFBR2
Synaptic Long Term Depression	GNAI3, GNAZ, KRAS, NOTUM, NPR1, PRKCA

Synaptic Long Term Potentiation	KRAS, NOTUM, PPP3R1, PRKCA

Table 9 – BT549 breast cancer upregulated pathways and associated genes

Pathway Name	**Gene**
PTEN Signaling	BCAR1, BMPR2, CBL, CCND1, INPPL1, ITGA2, KRAS, MAGI3, NGFR, PDGFRB, PDPK1, PIK3R1, PTK2, RPS6KB2, SOS2, SYNJ2, TGFBR3
RhoGDI Signaling	ACTG2, ARHGDIB, ARHGEF1, ARHGEF9, ARPC2, ARPC5, CREBBP, GNAI1, GNAI3, GNB1L, ITGA2, PAK4, PIP4K2C, PRKCA, RHOU, RND1, RND3
Cell Cycle: G1/S Checkpoint Regulation	ABL1, CCND1, CDC25A, CDK4, CDK6, E2F8, MAX, MDM2, SKP2
Sumoylation Pathway	ARHGDIB, CREBBP, ETS1, MDM2, MYB, RFC4, RHOU, RND1, RND3, SENP1
PPARα/RXRα Activation	ADCY7, BMPR2, CREBBP, HELZ2, IL1B, JAK2, KRAS, NCOA3, PLCB2, PLCD1, PLCD3, PRKCA, SOS2, TGFBR3
Endocannabinoid Cancer Inhibition Pathway	ADCY7, CCND1, CREBBP, GNAI1, GNAI3, GNB1L, PIK3R1, PTK2, SMPD1, TCF4
PPAR Signaling	CREBBP, IL1B, KRAS, NGFR, PDGFD, PDGFRB, SOS2, TNFRSF1B
HIPPO signaling	FAT4, FRMD6, LATS2, LLGL1, SKP2, YAP1, YWHAZ
Antioxidant Action of Vitamin C	CSF2, JAK2, PLCB2, PLCD1, PLCD3, PLD6, SLC23A2, SLC2A3
GPCR-Mediated Integration of Enteroendocrine Signaling Exemplified by an L Cell	ADCY7, GNAI1, GNAI3, PLCB2, PLCD1, PLCD3
Apoptosis Signaling	APAF1, KRAS, MCL1, PRKCA, TNFRSF1B

Table 10 - BT549 breast cancer aberrant pathways and associated genes

Pathway Name	**Gene**
Molecular Mechanisms of Cancer	ABL1, ADCY7, APAF1, ARHGEF1, ARHGEF9, BMPR2, CBL, CCND1, CDC25A, CDK4, CDK6, CREBBP, E2F8, GAB2, GNAI1, GNAI3, ITGA2, JAK2, KRAS, LRP5, MAX, MDM2, PAK4, PIK3R1, PLCB2, PRKCA, PSEN1, PTCH1, PTK2, RHOU, RND1, RND3, SOS2, TCF4
Axonal Guidance Signaling	ABL1, ADAM22, ADAMTS1, ADAMTS15, ADAMTS18, ARPC2, ARPC5, BCAR1, CRKL, ERAP2, ERBB2, GIT1, GNAI1, GNAI3, GNB1L, ITGA2, KRAS, LNPEP, MMP1, MMP14, NGFR, PAK4, PDGFD, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, PTCH1, PTK2, RND1, SOS2
Estrogen-mediated S-phase Entry	CCNA2, CCND1, CDC25A, CDK4, E2F8, SKP2
HER-2 Signaling in Breast Cancer	CCND1, CDK6, ERBB2, ITGB3, KRAS, MDM2, PARD6A, PIK3R1, PRKCA, SOS2
Chronic Myeloid Leukemia Signaling	ABL1, CCND1, CDK4, CDK6, CRKL, E2F8, GAB2, KRAS, MDM2, PIK3R1, SOS2
Bladder Cancer Signaling	ABL1, CCND1, CDK4, CXCL8, DAPK1, ERBB2, KRAS, MDM2, MMP1, MMP14
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	CCND1, CEBPD, CREBBP, CSF2, CXCL8, F2RL1, IL1B, JAK2, KRAS, LRP5, MMP1, NGFR, PDGFD, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, TCF4, TNFRSF1B, TRAF1

Clathrin-mediated Endocytosis Signaling	ACTG2, AP2M1, ARPC2, ARPC5, CBL, DAB2, DNM3, ITGB3, MDM2, PDGFD, PIK3R1, RAB5B, SNAP91, SNX9, STAM
Role of Tissue Factor in Cancer	CSF2, CXCL8, F2RL1, IL1B, ITGB3, JAK2, KRAS, MMP1, PIK3R1, PLAUR, PRKCA
G-Protein Coupled Receptor Signaling	ADCY7, CREBBP, DUSP4, GNAI1, GNAI3, HTR7, KRAS, LPAR1, PDE3A, PDE4D, PDE5A, PDPK1, PIK3R1, PLCB2, PLD6, PRKCA, RGS2, SOS2
FAK Signaling	ACTG2, BCAR1, ITGA2, KRAS, PAK4, PDPK1, PIK3R1, PTK2, SOS2
Breast Cancer Regulation by Stathmin1	ADCY7, ARHGEF1, ARHGEF9, E2F8, GNAI1, GNAI3, GNB1L, KRAS, PIK3R1, PLCB2, PRKCA, SOS2, STMN1, UHMK1
TR/RXR Activation	AKR1C3, DIO2, GPS2, MDM2, NCOA3, PIK3R1, SREBF2, THRB
Phenylalanine Degradation I (Aerobic)	PCBD1, QDPR
Prostate Cancer Signaling	ABL1, CCND1, CREBBP, KRAS, MDM2, PDPK1, PIK3R1, SOS2
Regulation of the Epithelial-Mesenchymal Transition Pathway	ETS1, HMGA2, JAK2, KRAS, LOX, NOTCH2, PARD6A, PDGFD, PDGFRB, PIK3R1, PSEN1, SOS2, TCF4
NAD biosynthesis II (from tryptophan)	ABL1, IDO1, TDO2
Germ Cell-Sertoli Cell Junction Signaling	ACTG2, BCAR1, ITGA2, KRAS, MAP3K3, PAK4, PDPK1, PIK3R1, PTK2, RHOU, RND1, RND3
Leptin Signaling in Obesity	ADCY7, JAK2, PDE3A, PIK3R1, PLCB2, PLCD1, PLCD3
Erythropoietin Signaling	CBL, JAK2, KRAS, PDPK1, PIK3R1, PRKCA, SOS2
Granulocyte Adhesion and Diapedesis	CCL20, CXCL2, CXCL8, GNAI1, GNAI3, IL1B, ITGA2, ITGB3, MMP1, MMP14, NGFR, TNFRSF1B
Reelin Signaling in Neurons	ARHGEF1, ARHGEF9, CDK5R1, CRKL, ITGA2, ITGB3, PIK3R1
G Protein Signaling Mediated by Tubby	ABL1, GNB1L, JAK2, PLCB2
1D-myo-inositol Hexakisphosphate Biosynthesis II (Mammalian)	INPPL1, ITPKA, SYNJ2
D-myo-inositol (1, 3, 4)-trisphosphate Biosynthesis	INPPL1, ITPKA, SYNJ2
Tryptophan Degradation to 2-amino-3-carboxymuconate Semialdehyde	IDO1, TDO2
Phagosome Formation	ITGA2, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, RHOU, RND1, RND3
IL-4 Signaling	INPPL1, JAK2, KRAS, PIK3R1, RPS6KB2, SOS2, SYNJ2
Virus Entry via Endocytic Pathways	ABL1, ACTG2, AP2M1, ITGA2, ITGB3, KRAS, PIK3R1, PRKCA
Cellular Effects of Sildenafil (Viagra)	ACTG2, ADCY7, CACNG4, PDE3A, PDE4D, PDE5A, PLCB2, PLCD1, PLCD3
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	BMPR2, CBL, CSF2, IL1B, ITGA2, ITGB3, LRP5, MMP1, MMP14, NGFR, PIK3R1, TCF4, TNFRSF1B
Airway Pathology in Chronic Obstructive Pulmonary Disease	CXCL8, MMP1
Salvage Pathways of Pyrimidine Deoxyribonucleotides	APOBEC3G, TK2

Gap Junction Signaling	ACTG2, ADCY7, GNAI1, GNAI3, KRAS, LPAR1, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, SOS2
IL-15 Signaling	CSF2, CXCL8, JAK2, KRAS, PIK3R1, PTK2
Caveolar-mediated Endocytosis Signaling	ABL1, ACTG2, ITGA2, ITGB3, PRKCA, RAB5B
HIF1α Signaling	CREBBP, KRAS, MAPK15, MDM2, MMP1, MMP14, PIK3R1, SLC2A3
Leucine Degradation I	BCAT2, HMGCLL1
Polyamine Regulation in Colon Cancer	KRAS, MAX, TCF4
Docosahexaenoic Acid (DHA) Signaling	APAF1, IL1B, PDPK1, PIK3R1
Hereditary Breast Cancer Signaling	CCND1, CDK4, CDK6, CREBBP, DPF1, H2AFX, KRAS, PIK3R1, RFC4
Superpathway of D-myo-inositol (1, 4, 5)-trisphosphate Metabolism	INPPL1, ITPKA, SYNJ2
Glucocorticoid Receptor Signaling	CREBBP, CSF2, CXCL8, DPF1, IL1B, JAK2, KRAS, KRT10, KRT15, KRT79, MMP1, NCOA3, PIK3R1, PLAU, POU2F2, SOS2, TAF9B
Semaphorin Signaling in Neurons	PAK4, PTK2, RHOU, RND1, RND3
Agranulocyte Adhesion and Diapedesis	ACTG2, AOC3, CCL20, CXCL2, CXCL8, GNAI1, GNAI3, IL1B, ITGA2, MMP1, MMP14
RAR Activation	ADCY7, AKR1C3, CREBBP, DPF1, JAK2, MMP1, NR2F2, NSD1, PDPK1, PIK3R1, PRKCA
Serotonin Receptor Signaling	ADCY7, HTR7, PCBD1, QDPR
Relaxin Signaling	ADCY7, GNAI1, GNAI3, GNB1L, PDE3A, PDE4D, PDE5A, PIK3R1, PLD6
Epithelial Adherens Junction Signaling	ACTG2, ARPC2, ARPC5, BMPR2, DLL1, KRAS, NOTCH2, TCF4, TGFBR3
Gustation Pathway	ADCY7, CACNG4, PDE3A, PDE4D, PDE5A, PLCB2, PLD6, SCNN1A, TAS2R14
Hematopoiesis from Multipotent Stem Cells	CSF2, KITLG
Myc Mediated Apoptosis Signaling	APAF1, KRAS, PIK3R1, SOS2, YWHAZ
Glycine Biosynthesis I	SHMT2
Guanine and Guanosine Salvage I	HPRT1
L-cysteine Degradation III	MPST
Bile Acid Biosynthesis, Neutral Pathway	AKR1C3, SCP2
Role of IL-17A in Psoriasis	CCL20, CXCL8
Ephrin A Signaling	BCAR1, NGFR, PIK3R1, PTK2
Remodeling of Epithelial Adherens Junctions	ACTG2, ARPC2, ARPC5, DNM3, RAB5B
Hematopoiesis from Pluripotent Stem Cells	CSF2, CXCL8, KITLG, LIF
Iron homeostasis signaling pathway	ATP6V1B2, BMPR2, ERFE, GDF15, HFE, JAK2, PDGFRB, SKP2
Factors Promoting Cardiogenesis in Vertebrates	BMPR2, LRP5, NKX2-5, PRKCA, TCF4, TGFBR3
Thyroid Cancer Signaling	CCND1, CXCL8, KRAS, TCF4
Ephrin B Signaling	CBL, GNAI1, GNAI3, GNB1L, PTK2
Natural Killer Cell Signaling	INPPL1, KRAS, PAK4, PIK3R1, PRKCA, SOS2, SYNJ2
ATM Signaling	ABL1, CDC25A, CREBBP, H2AFX, MDM2, RAD17
p53 Signaling	APAF1, CCND1, CDK4, MDM2, PIK3R1, TP53INP1
Granzyme B Signaling	APAF1, LMNB1
Vitamin-C Transport	SLC23A2, SLC2A3
L-carnitine Biosynthesis	ALDH9A1
N-acetylglucosamine Degradation I	GNPDA1

Thiosulfate Disproportionation III (Rhodanese)	MPST
Thyroid Hormone Metabolism I (via Deiodination)	DIO2
Thyronamine and Iodothyronamine Metabolism	DIO2
Tyrosine Biosynthesis IV	PCBD1
Protein Ubiquitination Pathway	CBL, DNAJB9, DNAJC3, HSPA13, HSPB7, MDM2, PSMB8, SKP2, UBE2L6, USP18, USP27X, USP39, USP40
Macropinocytosis Signaling	ITGB3, KRAS, PDGFD, PIK3R1, PRKCA
Role of IL-17A in Arthritis	CCL20, CXCL8, MMP1, PIK3R1
Unfolded protein response	CEBPD, DNAJB9, DNAJC3, SREBF2
D-myo-inositol (1, 4, 5)-trisphosphate Degradation	INPPL1, SYNJ2
Dermatan Sulfate Degradation (Metazoa)	HYAL2, IDS
Role of CHK Proteins in Cell Cycle Checkpoint Control	CDC25A, E2F8, RAD17, RFC4
Differential Regulation of Cytokine Production in Macrophages and T Helper Cells by IL-17A and IL-17F	CSF2, IL1B
Cell Cycle Regulation by BTG Family Proteins	CCND1, CDK4, E2F8
Notch Signaling	DLL1, NOTCH2, PSEN1
GADD45 Signaling	CCND1, CDK4
Oxidative Ethanol Degradation III	ACSS2, ALDH9A1
Acetate Conversion to Acetyl-CoA	ACSS2
N-acetylglucosamine Degradation II	GNPDA1
Phenylethylamine Degradation I	AOC3
Cardiomyocyte Differentiation via BMP Receptors	BMPR2, NKX2-5
Hepatic Fibrosis / Hepatic Stellate Cell Activation	COL5A1, CXCL8, EDNRA, IL1B, MMP1, NGFR, PDGFD, PDGFRB, TNFRSF1B
Mechanisms of Viral Exit from Host Cells	ACTG2, LMNB1, PRKCA
Pyrimidine Ribonucleotides Interconversion	AK4, NUDT18, SMARCA1
Folate Polyglutamylation	SHMT2
Protein Citrullination	PADI2
dTMP De Novo Biosynthesis	SHMT2
Role of PI3K/AKT Signaling in the Pathogenesis of Influenza	CRKL, GNAI1, GNAI3, PIK3R1
Pyrimidine Deoxyribonucleotides De Novo Biosynthesis I	AK4, RRM2
Tryptophan Degradation III (Eukaryotic)	IDO1, TDO2
Pyrimidine Ribonucleotides De Novo Biosynthesis	AK4, NUDT18, SMARCA1
Tight Junction Signaling	ACTG2, CDK4, LLGL1, NGFR, NSF, NUDT21, PARD6A, TNFRSF1B
Differential Regulation of Cytokine Production in Intestinal Epithelial Cells by IL-17A and IL-17F	CSF2, IL1B
Ethanol Degradation IV	ACSS2, ALDH9A1
Stearate Biosynthesis I (Animals)	ACOT8, ACSL5, DHCR24
iNOS Signaling	CREBBP, IRF1, JAK2
Adenine and Adenosine Salvage III	HPRT1
Glycogen Biosynthesis II (from UDP-D-Glucose)	GBE1
UDP-N-acetyl-D-glucosamine Biosynthesis II	GFPT1
CCR5 Signaling in Macrophages	CACNG4, GNAI1, GNAI3, GNB1L, PRKCA
PFKFB4 Signaling Pathway	CREBBP, HK2, NCOA3
Role of JAK1 and JAK3 in γc Cytokine Signaling	IL7R, JAK2, KRAS, PIK3R1

GABA Receptor Signaling	ADCY7, ALDH9A1, AP2M1, CACNG4, NSF
Th1 and Th2 Activation Pathway	BMPR2, DLL1, IRF1, JAK2, NOTCH2, PIK3R1, PSEN1, TGFBR3
IL-15 Production	ABL1, ERBB2, IRF1, JAK2, PDGFRB, PTK2
IL-17A Signaling in Gastric Cells	CCL20, CXCL8
Role of JAK family kinases in IL-6-type Cytokine Signaling	JAK2, OSMR
Antiproliferative Role of TOB in T Cell Signaling	CCNA2, SKP2
NAD Salvage Pathway II	NT5E, PXYLP1
GDP-glucose Biosynthesis	PGM5
NAD Biosynthesis from 2-amino-3-carboxymuconate Semialdehyde	ABL1
Superpathway of Serine and Glycine Biosynthesis I	SHMT2
UVC-Induced MAPK Signaling	KRAS, PRKCA, SMPD1
FcγRIIB Signaling in B Lymphocytes	CACNG4, KRAS, PDPK1, PIK3R1
Hepatic Cholestasis	ADCY7, CSF2, CXCL8, IL1B, LIF, NGFR, PRKCA, TNFRSF1B
Glucose and Glucose-1-phosphate Degradation	PGM5
Sphingomyelin Metabolism	SMPD1
VDR/RXR Activation	CSF2, LRP5, NCOA3, PRKCA
Role of Cytokines in Mediating Communication between Immune Cells	CSF2, CXCL8, IL1B
T Cell Receptor Signaling	CBL, KRAS, PAG1, PIK3R1, SOS2
Role of p14/p19ARF in Tumor Suppression	MDM2, PIK3R1
TNFR2 Signaling	TNFRSF1B, TRAF1
Folate Transformations I	SHMT2
Sucrose Degradation V (Mammalian)	TKFC
UDP-N-acetyl-D-galactosamine Biosynthesis II	GNPDA1
IL-17 Signaling	CXCL8, JAK2, KRAS, PIK3R1
Human Embryonic Stem Cell Pluripotency	BMPR2, PDGFD, PDGFRB, PDPK1, PIK3R1, TCF4
EGF Signaling	PIK3R1, PRKCA, SOS2
Estrogen Receptor Signaling	CREBBP, KRAS, MED21, NCOA3, SOS2, TAF9B
Ethanol Degradation II	ACSS2, ALDH9A1
Fatty Acid β-oxidation I	ACSL5, SCP2
Dolichyl-diphosphooligosaccharide Biosynthesis	DPM3
Embryonic Stem Cell Differentiation into Cardiac Lineages	NKX2-5
Glycine Betaine Degradation	SHMT2
Ketogenesis	HMGCLL1
Cancer Drug Resistance By Drug Efflux	KRAS, MDM2, PIK3R1
Dopamine Degradation	ALDH9A1
Sonic Hedgehog Signaling	PTCH1
MSP-RON Signaling Pathway	ACTG2, JAK2, PIK3R1
Retinoic acid Mediated Apoptosis Signaling	APAF1, IRF1, PARP14
Superpathway of Cholesterol Biosynthesis	DHCR24
Coagulation System	PLAU, PLAUR
IL-17A Signaling in Fibroblasts	CEBPD, MMP1
TWEAK Signaling	APAF1, TRAF1
Autophagy	CTSO, SQSTM1
IL-2 Signaling	KRAS, PIK3R1, SOS2

SPINK1 Pancreatic Cancer Pathway	CPA4, F2RL1
Apelin Liver Signaling Pathway	PDGFRB
Lipid Antigen Presentation by CD1	AP2M1
Nur77 Signaling in T Lymphocytes	APAF1, MAP3K3
Cleavage and Polyadenylation of Pre-mRNA	NUDT21
Glycogen Degradation II	PGM5
Guanosine Nucleotides Degradation III	NT5E
IL-1 Signaling	ADCY7, GNAI1, GNAI3, GNB1L
Atherosclerosis Signaling	CXCL8, IL1B, MMP1, PDGFD
Tryptophan Degradation X (Mammalian, via Tryptamine)	ALDH9A1
CTLA4 Signaling in Cytotoxic T Lymphocytes	AP2M1, JAK2, PIK3R1
Role of JAK1, JAK2 and TYK2 in Interferon Signaling	JAK2
Tumoricidal Function of Hepatic Natural Killer Cells	APAF1
Crosstalk between Dendritic Cells and Natural Killer Cells	ACTG2, CSF2, TNFRSF1B
RANK Signaling in Osteoclasts	CBL, MAP3K3, PIK3R1
Sertoli Cell-Sertoli Cell Junction Signaling	ACTG2, BCAR1, ITGA2, KRAS, MAP3K3, TGFBR3
IL-17A Signaling in Airway Cells	CCL20, JAK2, PIK3R1
Cell Cycle Control of Chromosomal Replication	CDK4, CDK6
Acyl-CoA Hydrolysis	ACOT8
Cholesterol Biosynthesis I	DHCR24
Cholesterol Biosynthesis II (via 24, 25-dihydrolanosterol)	DHCR24
Cholesterol Biosynthesis III (via Desmosterol)	DHCR24
Fatty Acid Activation	ACSL5
NAD Phosphorylation and Dephosphorylation	PXYLP1
Urate Biosynthesis/Inosine 5'-phosphate Degradation	NT5E
Inhibition of Matrix Metalloproteases	MMP1, MMP14
Phosphatidylglycerol Biosynthesis II (Non-plastidic)	AGPAT1
Androgen Biosynthesis	AKR1C3
DNA Double-Strand Break Repair by Homologous Recombination	ABL1
Glycogen Degradation III	PGM5
Isoleucine Degradation I	BCAT2
CD27 Signaling in Lymphocytes	APAF1, MAP3K3
UVB-Induced MAPK Signaling	PIK3R1, PRKCA
Role of PKR in Interferon Induction and Antiviral Response	APAF1, IRF1
Endoplasmic Reticulum Stress Pathway	DNAJC3
Putrescine Degradation III	ALDH9A1
LPS-stimulated MAPK Signaling	KRAS, PIK3R1, PRKCA
PEDF Signaling	KRAS, PIK3R1, TCF4
Amyloid Processing	CDK5R1, PSEN1
SPINK1 General Cancer Pathway	JAK2, KRAS, PIK3R1
Adenosine Nucleotides Degradation II	NT5E
Choline Biosynthesis III	PLD6
Retinol Biosynthesis	AKR1C3, LIPE
CDP-diacylglycerol Biosynthesis I	AGPAT1

Fatty Acid α-oxidation	ALDH9A1
Granzyme A Signaling	CREBBP
Inflammasome pathway	IL1B
The Visual Cycle	AKR1C3
iCOS-iCOSL Signaling in T Helper Cells	GAB2, PDPK1, PIK3R1, PLEKHA2
TNFR1 Signaling	APAF1, PAK4
Role of BRCA1 in DNA Damage Response	DPF1, E2F8, RFC4
Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza	CXCL8, IL1B
Chondroitin Sulfate Degradation (Metazoa)	HYAL2
Mismatch Repair in Eukaryotes	RFC4
DNA damage-induced 14-3-3σ Signaling	RAD17
NER Pathway	COPS3, DDB1, POLE3, RFC4
Antiproliferative Role of Somatostatin Receptor 2	GNB1L, KRAS, PIK3R1
Hypoxia Signaling in the Cardiovascular System	CREBBP, MDM2, UBE2L6
Adipogenesis pathway	BMPR2, CEBPD, EBF1, KLF3, NR2F2
Dopamine Receptor Signaling	ADCY7, PCBD1, QDPR
FAT10 Signaling Pathway	SQSTM1
Methylglyoxal Degradation III	AKR1C3
Purine Nucleotides Degradation II (Aerobic)	NT5E
Valine Degradation I	BCAT2
Histamine Degradation	ALDH9A1
Mitochondrial L-carnitine Shuttle Pathway	ACSL5
RAN Signaling	KPNA5
γ-linolenate Biosynthesis II (Animals)	ACSL5
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	NR2F2, NR6A1
4-1BB Signaling in T Lymphocytes	TRAF1
Activation of IRF by Cytosolic Pattern Recognition Receptors	CREBBP
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	CSF2, IL1B
Antigen Presentation Pathway	PSMB8
Apelin Pancreas Signaling Pathway	PIK3R1
April Mediated Signaling	TRAF1
Assembly of RNA Polymerase II Complex	TAF9B
B Cell Activating Factor Signaling	TRAF1
B Cell Development	IL7R
BAG2 Signaling Pathway	MDM2
Basal Cell Carcinoma Signaling	PTCH1, TCF4
CD40 Signaling	PIK3R1, TRAF1
Calcium Signaling	CACNG4, CREBBP, RCAN1
Calcium-induced T Lymphocyte Apoptosis	PRKCA
Circadian Rhythm Signaling	CREBBP
Communication between Innate and Adaptive Immune Cells	CSF2, CXCL8, IL1B
Complement System	C1QBP
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	APAF1
DNA Methylation and Transcriptional Repression Signaling	MTA2
Eicosanoid Signaling	AKR1C3

Estrogen Biosynthesis	AKR1C3
FXR/RXR Activation	CREBBP, IL1B
Graft-versus-Host Disease Signaling	IL1B
Heparan Sulfate Biosynthesis	EXTL2, LIPE
Heparan Sulfate Biosynthesis (Late Stages)	EXTL2, LIPE
IL-10 Signaling	IL1B
IL-12 Signaling and Production in Macrophages	IRF1, PIK3R1, PRKCA
IL-9 Signaling	PIK3R1
LPS/IL-1 Mediated Inhibition of RXR Function	ACSL5, ALDH9A1, IL1B, NGFR, TNFRSF1B
LXR/RXR Activation	IL1B, NGFR, TNFRSF1B
Mitochondrial Dysfunction	ATP5PB, PSEN1
Mitotic Roles of Polo-Like Kinase	CDC25A
Netrin Signaling	CACNG4
Neuroprotective Role of THOP1 in Alzheimer's Disease	TPP1
Nitric Oxide Signaling in the Cardiovascular System	PDE5A, PIK3R1, PRKCA
Noradrenaline and Adrenaline Degradation	ALDH9A1
Oxidative Phosphorylation	ATP5PB
PCP pathway	LGR4
Phagosome Maturation	ATP6V1B2, CTSO, NSF, RAB5B
Primary Immunodeficiency Signaling	IL7R
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	KRAS, SOS2
Retinoate Biosynthesis I	AKR1C3
Role of JAK2 in Hormone-like Cytokine Signaling	JAK2
Role of MAPK Signaling in the Pathogenesis of Influenza	KRAS, PRKCA
Role of RIG1-like Receptors in Antiviral Innate Immunity	CREBBP
Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza	NCOA3, TCF4
Serotonin Degradation	ALDH9A1
Systemic Lupus Erythematosus Signaling	CBL, IL1B, KRAS, PIK3R1, PRPF40B, SOS2
T Helper Cell Differentiation	NGFR, TNFRSF1B
Thyroid Hormone Metabolism II (via Conjugation and/or Degradation)	DIO2
Toll-like Receptor Signaling	IL1B, TRAF1
Transcriptional Regulatory Network in Embryonic Stem Cells	PAX6
Triacylglycerol Biosynthesis	AGPAT1
Triacylglycerol Degradation	LIPE
Xenobiotic Metabolism Signaling	ALDH9A1, CREBBP, IL1B, KRAS, MAP3K3, PIK3R1, PRKCA
nNOS Signaling in Neurons	PRKCA
nNOS Signaling in Skeletal Muscle Cells	CACNG4
tRNA Charging	LARS2

Table 11 - BT549 breast cancer downregulated pathways and associated genes

Pathway Name	**Gene**
Protein Kinase A Signaling	ADCY7, AKAP12, CDC14B, CDC25A, CREBBP, DUSP16, DUSP2, DUSP4, EPM2A, GNAI1, GNAI3, GNB1L, LIPE, NGFR, PDE3A,

	PDE4D, PDE5A, PLCB2, PLCD1, PLCD3, PLD6, PRKCA, PTCH1, PTK2, PTPN21, PTPN3, PTPN9, PTPRA, PTPRE, PTPRZ1, TCF4, YWHAZ
Neuregulin Signaling	CDK5R1, CRKL, ERBB2, ERBIN, ERRFI1, GRB7, ITGA2, KRAS, PDPK1, PIK3R1, PRKCA, PSEN1, RPS6KB2, SOS2
PI3K/AKT Signaling	CCND1, GAB2, GDF15, INPPL1, ITGA2, JAK2, KRAS, MCL1, MDM2, PDPK1, PIK3R1, RPS6KB2, SOS2, SYNJ2, YWHAZ
Sphingosine-1-phosphate Signaling	ADCY7, GNAI1, GNAI3, PDGFD, PDGFRB, PIK3R1, PLCB2, PLCD1, PLCD3, PTK2, RHOU, RND1, RND3, SMPD1
Glioma Signaling	ABL1, CCND1, CDK4, CDK6, E2F8, IDH1, KRAS, MDM2, PDGFD, PDGFRB, PIK3R1, PRKCA, SOS2
Integrin Signaling	ABL1, ACTG2, ARF3, ARPC2, ARPC5, BCAR1, CRKL, GIT1, GRB7, ITGA2, ITGB3, KRAS, PAK4, PIK3R1, PTK2, RHOU, RND1, RND3, SOS2
Glioblastoma Multiforme Signaling	CCND1, CDK4, CDK6, E2F8, KRAS, MDM2, PDGFD, PDGFRB, PIK3R1, PLCB2, PLCD1, PLCD3, RHOU, RND1, RND3, SOS2
Small Cell Lung Cancer Signaling	ABL1, APAF1, CCND1, CDK4, CDK6, MAX, PIK3R1, PTK2, SKP2, TRAF1
Cardiac Hypertrophy Signaling (Enhanced)	ADCY7, BMPR2, CSF2, CXCL8, EDNRA, GNAI1, GNAI3, HSPB7, IL17RD, IL1B, IL7R, ITGA2, JAK2, KRAS, LIF, MAP3K3, NGFR, NKX2-5, PDE3A, PDE4D, PDE5A, PIK3R1, PLCB2, PLCD1, PLCD3, PLD6, PRKCA, PTK2, RCAN1, RPS6KB2, TGFBR3, TNFRSF1B
CXCR4 Signaling	ADCY7, BCAR1, ELMO2, ELMO3, GNAI1, GNAI3, GNB1L, KRAS, PAK4, PIK3R1, PLCB2, PRKCA, PTK2, RHOU, RND1, RND3
B Cell Receptor Signaling	ABL1, CREBBP, EBF1, ETS1, GAB2, INPPL1, KRAS, MAP3K3, PAG1, PAX5, PDPK1, PIK3R1, POU2F2, PTK2, RPS6KB2, SOS2, SYNJ2
PDGF Signaling	ABL1, CRKL, INPPL1, JAK2, KRAS, PDGFD, PDGFRB, PIK3R1, PRKCA, SOS2, SYNJ2
Signaling by Rho Family GTPases	ACTG2, ARHGEF1, ARHGEF9, ARPC2, ARPC5, CDC42EP2, CDC42EP3, GNAI1, GNAI3, GNB1L, ITGA2, PAK4, PARD6A, PIK3R1, PIP4K2C, PTK2, RHOU, RND1, RND3, STMN1
Non-Small Cell Lung Cancer Signaling	ABL1, CCND1, CDK4, CDK6, ERBB2, KRAS, PDPK1, PIK3R1, PRKCA, SOS2
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	ACTG2, ARPC2, ARPC5, CBL, CSF2, DGKB, GAB2, PIK3R1, PLD6, PRKCA, RPS6KB2
IL-7 Signaling Pathway	CCND1, CDC25A, EBF1, IL7R, MCL1, PAX5, PDPK1, PIK3R1, PTK2, SOS2
Ephrin Receptor Signaling	ABL1, ARPC2, ARPC5, BCAR1, CREBBP, CRKL, GNAI1, GNAI3, GNB1L, ITGA2, JAK2, KRAS, PAK4, PDGFD, PTK2, SOS2
Superpathway of Inositol Phosphate Compounds	CDC25A, DUSP16, DUSP2, HACD2, INPPL1, ITPKA, NUDT3, PIK3R1, PIP4K2A, PIP4K2C, PLCB2, PLCD1, PLCD3, PPM1H, PPTC7, PXYLP1, SYNJ2

Thrombin Signaling	ADCY7, ARHGEF1, ARHGEF9, GNAI1, GNAI3, GNB1L, KRAS, PDPK1, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, PTK2, RHOU, RND1, RND3
ERK/MAPK Signaling	BCAR1, CREBBP, CRKL, DUSP2, DUSP4, ELK3, ETS1, HSPB7, ITGA2, KRAS, PAK4, PIK3R1, PRKCA, PTK2, SOS2, YWHAZ
Aldosterone Signaling in Epithelial Cells	DNAJB9, DNAJC3, HSPA13, HSPB7, KRAS, PDPK1, PIK3R1, PIP4K2C, PLCB2, PLCD1, PLCD3, PRKCA, SCNN1A, SOS2
Glioma Invasiveness Signaling	ITGB3, KRAS, PIK3R1, PLAU, PLAUR, PTK2, RHOU, RND1, RND3
P2Y Purigenic Receptor Signaling Pathway	ADCY7, CREBBP, GNAI1, GNAI3, GNB1L, ITGB3, KRAS, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA
Tec Kinase Signaling	ACTG2, GNAI1, GNAI3, GNB1L, ITGA2, JAK2, PAK4, PIK3R1, PRKCA, PTK2, RHOU, RND1, RND3, TNFRSF21
Agrin Interactions at Neuromuscular Junction	ACTG2, ERBB2, GABPA, ITGA2, ITGB3, KRAS, LAMC1, PAK4, PTK2
HGF Signaling	CCND1, CRKL, ELK3, ETS1, ITGA2, KRAS, MAP3K3, PIK3R1, PRKCA, PTK2, SOS2
p70S6K Signaling	F2RL1, GNAI1, GNAI3, KRAS, PDPK1, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, SOS2, YWHAZ
D-myo-inositol (1, 4, 5)-Trisphosphate Biosynthesis	PIP4K2A, PIP4K2C, PLCB2, PLCD1, PLCD3
D-myo-inositol-5-phosphate Metabolism	CDC25A, DUSP16, DUSP2, HACD2, NUDT3, PIP4K2A, PIP4K2C, PLCB2, PLCD1, PLCD3, PPM1H, PPTC7, PXYLP1
Insulin Receptor Signaling	CBL, CRKL, INPPL1, JAK2, KRAS, LIPE, PDPK1, PIK3R1, RPS6KB2, SCNN1A, SOS2, SYNJ2
RhoA Signaling	ACTG2, ARHGEF1, ARPC2, ARPC5, CDC42EP2, CDC42EP3, LPAR1, LPAR2, PIP4K2C, PTK2, RND3
IL-8 Signaling	CCND1, CXCL8, GNAI1, GNAI3, GNB1L, ITGB3, KRAS, PIK3R1, PLCB2, PLD6, PRKCA, PTK2, RHOU, RND1, RND3
Actin Nucleation by ARP-WASP Complex	ARPC2, ARPC5, ITGA2, KRAS, RHOU, RND1, RND3, SOS2
Pancreatic Adenocarcinoma Signaling	ABL1, CCND1, CDK4, E2F8, ERBB2, JAK2, KRAS, MDM2, PIK3R1, PLD6
Rac Signaling	ARPC2, ARPC5, CDK5R1, ITGA2, KRAS, PAK4, PARD6A, PIK3R1, PIP4K2C, PTK2
Regulation of Actin-based Motility by Rho	ACTG2, ARPC2, ARPC5, ITGA2, PAK4, PIP4K2C, RHOU, RND1, RND3
Phospholipase C Signaling	ADCY7, ARHGEF1, ARHGEF9, CREBBP, GNB1L, ITGA2, KRAS, PLCB2, PLCD1, PLCD3, PLD6, PRKCA, RHOU, RND1, RND3, SOS2, TGM2
Role of NFAT in Cardiac Hypertrophy	ADCY7, CACNG4, GNAI1, GNAI3, GNB1L, KRAS, LIF, NKX2-5, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, RCAN1, SOS2
Endocannabinoid Developing Neuron Pathway	ADCY7, CCND1, CREBBP, GNAI1, GNAI3, GNB1L, KRAS, MAPK15, PAX6, PIK3R1
PAK Signaling	GIT1, ITGA2, KRAS, PAK4, PDGFD, PDGFRB, PIK3R1, PTK2, SOS2

UVA-Induced MAPK Signaling	KRAS, PARP14, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, RPS6KB2, SMPD1
Cyclins and Cell Cycle Regulation	ABL1, CCNA2, CCND1, CDC25A, CDK4, CDK6, E2F8, SKP2
Prolactin Signaling	CREBBP, IRF1, JAK2, KRAS, PDPK1, PIK3R1, PRKCA, SOS2
Apelin Cardiomyocyte Signaling Pathway	GNAI1, GNAI3, MAPK15, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, SLC9A3
Cholecystokinin/Gastrin-mediated Signaling	BCAR1, IL1B, KRAS, PLCB2, PRKCA, PTK2, RHOU, RND1, RND3, SOS2
Regulation of Cellular Mechanics by Calpain Protease	CCNA2, CCND1, CDK4, CDK6, ITGA2, KRAS, PTK2
Interferon Signaling	IFIT3, IRF1, JAK2, MX1, PSMB8
Aryl Hydrocarbon Receptor Signaling	ALDH9A1, APAF1, CCNA2, CCND1, CDK4, CDK6, HSPB7, IL1B, MDM2, NCOA3, TGM2
ErbB4 Signaling	KRAS, PDPK1, PIK3R1, PRKCA, PSEN1, SOS2, YAP1
IL-6 Signaling	CXCL8, HSPB7, IL1B, JAK2, KRAS, MCL1, NGFR, PIK3R1, SOS2, TNFRSF1B
GM-CSF Signaling	CCND1, CSF2, ETS1, JAK2, KRAS, PIK3R1, SOS2
Acute Myeloid Leukemia Signaling	CCND1, IDH1, KITLG, KRAS, PIK3R1, RPS6KB2, SOS2, TCF4
Melatonin Signaling	GNAI1, GNAI3, PLCB2, PLCD1, PLCD3, PRKCA, RORA
Paxillin Signaling	ACTG2, BCAR1, ITGA2, ITGB3, KRAS, PAK4, PIK3R1, PTK2, SOS2
GNRH Signaling	ADCY7, CACNG4, CREBBP, GNAI1, GNAI3, KRAS, MAP3K3, PAK4, PLCB2, PRKCA, PTK2, SOS2
Cardiac Hypertrophy Signaling	ADCY7, CREBBP, GNAI1, GNAI3, GNB1L, KRAS, MAP3K3, NKX2-5, PIK3R1, PLCB2, PLCD1, PLCD3, RHOU, RND1, RND3
Actin Cytoskeleton Signaling	ACTG2, ARHGEF1, ARPC2, ARPC5, BCAR1, CRKL, GIT1, ITGA2, KRAS, PAK4, PDGFD, PIK3R1, PTK2, SOS2
STAT3 Pathway	BMPR2, CDC25A, IL17RD, IL1B, IL7R, JAK2, KRAS, NGFR, PDGFRB, TGFBR3
Leukocyte Extravasation Signaling	ABL1, ACTG2, BCAR1, CRKL, GNAI1, GNAI3, ITGA2, ITGB3, MMP1, MMP14, PIK3R1, PRKCA, PTK2
NGF Signaling	CREBBP, KRAS, MAP3K3, NGFR, PDPK1, PIK3R1, RPS6KB2, SMPD1, SOS2
Oncostatin M Signaling	JAK2, KRAS, MMP1, OSMR, PLAU
fMLP Signaling in Neutrophils	ARPC2, ARPC5, GNAI1, GNAI3, GNB1L, KRAS, PIK3R1, PLCB2, PRKCA
Salvage Pathways of Pyrimidine Ribonucleotides	AK4, APOBEC3F, APOBEC3G, CDK4, CDK6, DAPK1, FAM20B, UPRT
Endometrial Cancer Signaling	CCND1, ERBB2, KRAS, PDPK1, PIK3R1, SOS2
IL-23 Signaling Pathway	CSF2, IL1B, JAK2, PIK3R1, RORA
FAT10 Cancer Signaling Pathway	BMPR2, NGFR, TCF4, TGFBR3, TNFRSF1B
CREB Signaling in Neurons	ADCY7, CACNG4, CREBBP, GNAI1, GNAI3, GNB1L, KRAS, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, SOS2
Colorectal Cancer Metastasis Signaling	ADCY7, APPL1, CCND1, GNB1L, JAK2, KRAS, LRP5, MMP1, MMP14, PIK3R1, RHOU, RND1, RND3, SOS2, TCF4

Endothelin-1 Signaling	ADCY7, EDNRA, GNAI1, GNAI3, KRAS, MAPK15, PIK3R1, PLCB2, PLCD1, PLCD3, PLD6, PRKCA
HMGB1 Signaling	CSF2, CXCL8, IL1B, KRAS, LIF, NGFR, PIK3R1, RHOU, RND1, RND3, TNFRSF1B
Mouse Embryonic Stem Cell Pluripotency	BMPR2, CREBBP, JAK2, KRAS, LIF, PIK3R1, SOS2, TCF4
FLT3 Signaling in Hematopoietic Progenitor Cells	CBL, CREBBP, GAB2, KRAS, PDPK1, PIK3R1, SOS2
ErbB2-ErbB3 Signaling	CCND1, ERBB2, KRAS, PDPK1, PIK3R1, SOS2
IGF-1 Signaling	JAK2, KRAS, PDPK1, PIK3R1, PTK2, RPS6KB2, SOS2, YWHAZ
Huntington's Disease Signaling	APAF1, ATP5PB, CDK5R1, CREBBP, DNM3, GNB1L, NSF, PDPK1, PIK3R1, PLCB2, PRKCA, SOS2, TAF9B, TGM2
14-3-3-mediated Signaling	CBL, KRAS, PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA, YAP1, YWHAZ
CDK5 Signaling	ABL1, ADCY7, CDK5R1, ITGA2, KRAS, LAMC1, MAPK15, NGFR
Telomerase Signaling	ABL1, ELK3, ETS1, KRAS, PDPK1, PIK3R1, SOS2, TPP1
Melanoma Signaling	CCND1, CDK4, KRAS, MDM2, PIK3R1
3-phosphoinositide Degradation	CDC25A, DUSP16, DUSP2, HACD2, INPPL1, NUDT3, PPM1H, PPTC7, PXYLP1, SYNJ2
Death Receptor Signaling	ACTG2, APAF1, ARHGDIB, HSPB7, PARP14, TNFRSF1B, TNFRSF21
ERK5 Signaling	CREBBP, KRAS, LIF, MAP3K3, RPS6KB2, YWHAZ
GPCR-Mediated Nutrient Sensing in Enteroendocrine Cells	ADCY7, CACNG4, GNAI1, GNAI3, PLCB2, PLCD1, PLCD3, PRKCA
Lymphotoxin β Receptor Signaling	APAF1, CREBBP, PDPK1, PIK3R1, TRAF1
cAMP-mediated signaling	ADCY7, AKAP12, CREBBP, DUSP4, GNAI1, GNAI3, HTR7, LPAR1, PDE3A, PDE4D, PDE5A, PLD6, RGS2
PI3K Signaling in B Lymphocytes	ABL1, CBL, KRAS, PDPK1, PIK3R1, PLCB2, PLCD1, PLCD3, PLEKHA2
ErbB Signaling	ERBB2, KRAS, PAK4, PDPK1, PIK3R1, PRKCA, SOS2
Melanocyte Development and Pigmentation Signaling	ADCY7, CREBBP, KITLG, KRAS, PIK3R1, RPS6KB2, SOS2
Apelin Endothelial Signaling Pathway	ADCY7, GNAI1, GNAI3, KRAS, PIK3R1, PLCB2, PRKCA, RPS6KB2
Fc Epsilon RI Signaling	CSF2, INPPL1, KRAS, PDPK1, PIK3R1, PRKCA, SOS2, SYNJ2
Renin-Angiotensin Signaling	ADCY7, JAK2, KRAS, PAK4, PIK3R1, PRKCA, PTK2, SOS2
Neurotrophin/TRK Signaling	CREBBP, KRAS, NGFR, PDPK1, PIK3R1, SOS2
GP6 Signaling Pathway	COL5A1, ITGB3, LAMC1, LAMC2, PDPK1, PIK3R1, PRKCA, PTK2
mTOR Signaling	EIF4A1, EIF4B, GNB1L, KRAS, PDPK1, PIK3R1, PLD6, PRKCA, RHOU, RND1, RND3, RPS6KB2
3-phosphoinositide Biosynthesis	CDC25A, DUSP16, DUSP2, HACD2, NUDT3, PIK3R1, PIP4K2C, PPM1H, PPTC7, PXYLP1

Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	CREBBP, IRF1, JAK2, MAP3K3, NGFR, PIK3R1, PRKCA, RHOU, RND1, RND3, TNFRSF1B
G Beta Gamma Signaling	CACNG4, GNAI1, GNAI3, GNB1L, KRAS, PDPK1, PRKCA, SOS2
Chemokine Signaling	GNAI1, GNAI3, KRAS, PLCB2, PRKCA, PTK2
IL-3 Signaling	CRKL, GAB2, JAK2, KRAS, PIK3R1, PRKCA
Renal Cell Carcinoma Signaling	CREBBP, ETS1, KRAS, PAK4, PIK3R1, SOS2
tRNA Splicing	PDE3A, PDE4D, PDE5A, PLD6
CCR3 Signaling in Eosinophils	GNAI1, GNAI3, GNB1L, KRAS, PAK4, PIK3R1, PLCB2, PRKCA
SAPK/JNK Signaling	CRKL, DUSP4, KRAS, MAP3K3, MAP4K5, PIK3R1, SOS2
Wnt/Ca+ pathway	CREBBP, PLCB2, PLCD1, PLCD3, PRKCA
Endocannabinoid Neuronal Synapse Pathway	ADCY7, CACNG4, GNAI1, GNAI3, MAPK15, PLCB2, PLCD1, PLCD3
Adrenomedullin signaling pathway	ADCY7, IL1B, KRAS, MAPK15, MAX, PIK3R1, PLCB2, PLCD1, PLCD3, PTK2, SOS2
Thrombopoietin Signaling	GAB2, JAK2, KRAS, PIK3R1, PRKCA
Role of IL-17F in Allergic Inflammatory Airway Diseases	CREBBP, CSF2, CXCL8, IL1B
PD-1, PD-L1 cancer immunotherapy pathway	JAK2, LATS2, NGFR, PIK3R1, SKP2, TNFRSF1B, YAP1
Acute Phase Response Signaling	IL1B, JAK2, KRAS, NGFR, OSMR, PDPK1, PIK3R1, SOS2, TCF4, TNFRSF1B
NF-κB Signaling	BMPR2, CREBBP, IL1B, KRAS, MAP3K3, NGFR, PDGFRB, PIK3R1, TGFBR3, TNFRSF1B
Gαq Signaling	GNB1L, PIK3R1, PLCB2, PLD6, PRKCA, RGS2, RHOU, RND1, RND3
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	ABL1, MDM2, SKP2, YWHAZ
Dendritic Cell Maturation	CREBBP, CSF2, IL1B, JAK2, NGFR, PIK3R1, PLCB2, PLCD1, PLCD3, TNFRSF1B
Ovarian Cancer Signaling	ABL1, CCND1, CDK4, EDNRA, KRAS, PIK3R1, RPS6KB2, TCF4
AMPK Signaling	AK4, CCNA2, CCND1, CREBBP, DPF1, GNB1L, LIPE, PDPK1, PIK3R1, PPM1F, PPM1H
D-myo-inositol (1, 4, 5, 6)-Tetrakisphosphate Biosynthesis	CDC25A, DUSP16, DUSP2, HACD2, NUDT3, PPM1H, PPTC7, PXYLP1
D-myo-inositol (3, 4, 5, 6)-tetrakisphosphate Biosynthesis	CDC25A, DUSP16, DUSP2, HACD2, NUDT3, PPM1H, PPTC7, PXYLP1
Growth Hormone Signaling	JAK2, PDPK1, PIK3R1, PRKCA, RPS6KB2
α-Adrenergic Signaling	ADCY7, GNAI1, GNAI3, GNB1L, KRAS, PRKCA
ILK Signaling	ACTG2, CCND1, CREBBP, ITGB3, PDPK1, PIK3R1, PTK2, RHOU, RND1, RND3
Type II Diabetes Mellitus Signaling	ACSL5, CACNG4, NGFR, PDPK1, PIK3R1, PRKCA, SMPD1, TNFRSF1B
Corticotropin Releasing Hormone Signaling	ADCY7, ARPC5, CACNG4, CREBBP, GNAI1, GNAI3, PRKCA, PTCH1
Angiopoietin Signaling	GRB7, KRAS, PAK4, PIK3R1, PTK2
VEGF Signaling	ACTG2, KRAS, PIK3R1, PRKCA, PTK2, SOS2
Gαi Signaling	ADCY7, GNAI1, GNAI3, GNB1L, KRAS, LPAR1, SOS2
Apelin Adipocyte Signaling Pathway	ADCY7, GNAI1, GNAI3, LIPE, MAPK15

Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	CSF2, CXCL8, IL1B, LIF, OAS2, PIK3R1, PRKCA, RIPK2
Gα12/13 Signaling	ARHGEF1, F2RL1, KRAS, LPAR1, LPAR2, PIK3R1, PTK2
NF-κB Activation by Viruses	ITGA2, ITGB3, KRAS, PIK3R1, PRKCA
CNTF Signaling	JAK2, KRAS, PIK3R1, RPS6KB2
Induction of Apoptosis by HIV1	APAF1, NGFR, TNFRSF1B, TRAF1
Phospholipases	PLCB2, PLCD1, PLCD3, PLD6
FGF Signaling	CREBBP, CRKL, PIK3R1, PRKCA, SOS2
Androgen Signaling	CACNG4, CCND1, CREBBP, GNAI1, GNAI3, GNB1L, PRKCA
Type I Diabetes Mellitus Signaling	APAF1, IL1B, IRF1, JAK2, NGFR, TNFRSF1B
Dopamine-DARPP32 Feedback in cAMP Signaling	ADCY7, CREBBP, GNAI1, GNAI3, PLCB2, PLCD1, PLCD3, PRKCA
Th2 Pathway	BMPR2, DLL1, JAK2, NOTCH2, PIK3R1, PSEN1, TGFBR3
Pyridoxal 5'-phosphate Salvage Pathway	CDK4, CDK6, DAPK1, FAM20B
Ceramide Signaling	KRAS, NGFR, PIK3R1, SMPD1, TNFRSF1B
NRF2-mediated Oxidative Stress Response	ACTG2, BACH1, CREBBP, DNAJB9, DNAJC3, KRAS, PIK3R1, PRKCA, SQSTM1
Cardiac β-adrenergic Signaling	ADCY7, AKAP12, GNB1L, PDE3A, PDE4D, PDE5A, PLD6
Th17 Activation Pathway	CCL20, CSF2, IL1B, JAK2, RORA
Sperm Motility	ABL1, ERBB2, JAK2, PDE4D, PDGFRB, PLCB2, PLCD1, PLCD3, PRKCA, PTK2
Opioid Signaling Pathway	ADCY7, AP2M1, CACNG4, CREBBP, GNAI1, GNAI3, KRAS, MAPK15, PRKCA, RPS6KB2, SOS2
p38 MAPK Signaling	CREBBP, HSPB7, IL1B, MAX, RPS6KB2, TNFRSF1B
Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency	BMPR2, JAK2, KRAS, LIF, PIK3R1, SOS2
Wnt/β-catenin Signaling	APPL1, BMPR2, CCND1, CREBBP, LRP5, MDM2, TCF4, TGFBR3
TGF-β Signaling	BMPR2, CREBBP, KRAS, NKX2-5, SOS2
Synaptogenesis Signaling Pathway	ADCY7, AP2M1, ARPC2, ARPC5, CREBBP, CRKL, EIF4EBP2, KRAS, NSF, PIK3R1, RAB5B, RPS6KB2, SOS2
Th1 Pathway	DLL1, IRF1, JAK2, NOTCH2, PIK3R1, PSEN1
Estrogen-Dependent Breast Cancer Signaling	CCND1, CREBBP, KRAS, PIK3R1
TREM1 Signaling	CSF2, CXCL8, IL1B, JAK2
Role of NFAT in Regulation of the Immune Response	GNAI1, GNAI3, GNB1L, KRAS, PIK3R1, PLCB2, RCAN1, SOS2
Neuropathic Pain Signaling In Dorsal Horn Neurons	PIK3R1, PLCB2, PLCD1, PLCD3, PRKCA
Synaptic Long Term Potentiation	CREBBP, KRAS, PLCB2, PLCD1, PLCD3, PRKCA
GDNF Family Ligand-Receptor Interactions	DOK3, KRAS, PIK3R1, SOS2
Osteoarthritis Pathway	BMPR2, CREBBP, CXCL8, IL1B, ITGA2, MMP1, PTCH1, TCF4, TNFRSF1B
Regulation of eIF4 and p70S6K Signaling	EIF4A1, EIF4EBP2, ITGA2, KRAS, PDPK1, PIK3R1, SOS2
Synaptic Long Term Depression	CACNG4, GNAI1, GNAI3, KRAS, PLCB2, PLCD1, PLCD3, PRKCA
eNOS Signaling	ADCY7, CCNA2, LPAR1, LPAR2, PDPK1, PIK3R1, PRKCA

Gαs Signaling	ADCY7, CREBBP, GNB1L, HTR7, RGS2
JAK/Stat Signaling	JAK2, KRAS, PIK3R1, SOS2
Systemic Lupus Erythematosus In T Cell Signaling Pathway	CBL, CREBBP, GNAI1, GNAI3, GNB1L, KRAS, PIK3R1, PTK2, RHOU, RND1, RND3, RPS6KB2, SOS2
Cdc42 Signaling	ARPC2, ARPC5, CDC42EP2, ITGA2, LLGL1, PAK4, PARD6A
BMP signaling pathway	BMPR2, CREBBP, KRAS, NKX2-5
VEGF Family Ligand-Receptor Interactions	KRAS, PIK3R1, PRKCA, SOS2
PKCθ Signaling in T Lymphocytes	CACNG4, KRAS, MAP3K3, PIK3R1, SOS2
CD28 Signaling in T Helper Cells	ARPC2, ARPC5, PDPK1, PIK3R1
Amyotrophic Lateral Sclerosis Signaling	APAF1, HECW1, PIK3R1, RAB5B
EIF2 Signaling	ACTG2, CCND1, EIF4A1, KRAS, PDPK1, PIK3R1, SOS2
Neuroinflammation Signaling Pathway	BMPR2, CREBBP, CXCL8, IL1B, JAK2, MAPK15, PIK3R1, PSEN1, TGFBR3
Sirtuin Signaling Pathway	ACSS2, ATP5PB, CXCL8, GABPA, MAPK15, SCNN1A
T Cell Exhaustion Signaling Pathway	BMPR2, JAK2, KRAS, PIK3R1, TGFBR3

Table 12 – H460 lung cancer upregulated pathways and associated genes

Pathway Name	**Gene**
PTEN Signaling	CASP9, CBL, CCND1, CDKN1A, FGFR2, INPPL1, KRAS, PDGFRB, PDPK1, PIK3R1, PIK3R3, PTK2, SYNJ2, TGFBR3
Endocannabinoid Cancer Inhibition Pathway	ADCY1, ADCY9, CASP2, CASP7, CASP9, CCND1, CDKN1A, GNAI3, LEF1, PIK3R1, PIK3R3, PRKAA2, PTK2, SMPD1, TRIB3
Pancreatic Adenocarcinoma Signaling	CASP9, CCND1, CDK2, CDKN1A, HMOX1, KRAS, MAPK8, NOTCH1, PIK3R1, PIK3R3, PLD1
PPARα/RXRα Activation	ABCA1, ADCY1, ADCY9, FASN, GNA15, HELZ2, IL1RAP, IL1RL1, KRAS, MAPK8, PLCD3, PRKAA2, TGFBR3
AMPK Signaling	ACTB, AK8, CCNA2, CCND1, CDKN1A, CPT1C, FASN, MAPK13, PDPK1, PIK3R1, PIK3R3, PPAT, PPM1F, PRKAA2
RhoGDI Signaling	ACTB, ARPC2, ARPC4, ARPC5, GNA15, GNAI3, GNB1, PAK4, PIP4K2C, RHOB, RHOV
Antioxidant Action of Vitamin C	HMOX1, MAPK13, MAPK8, PLCD3, PLD1, SLC23A2, SLC2A3
Cell Cycle: G1/S Checkpoint Regulation	CCND1, CDK2, CDK6, CDKN1A, MAX
GPCR-Mediated Integration of Enteroendocrine Signaling Exemplified by an L Cell	ADCY1, ADCY9, GNA15, GNAI3, PLCD3
PPAR Signaling	FOS, IL1RAP, IL1RL1, KRAS, PDGFRB, TNFRSF1B
HIPPO signaling	LATS2, TEAD3, TEAD4, WWTR1, YWHAZ
Systemic Lupus Erythematosus In T Cell Signaling Pathway	CASP2, CASP7, CASP9, CBL, FOS, GNAI3, HLA-DMA, KRAS, ORAI1, PIK3R1, PIK3R3, PPP3R1, PTK2, RHOB, RHOV

LXR/RXR Activation	ABCA1, FASN, IL1RAP, IL1RL1, TNFRSF1B

Table 13 - H460 lung cancer aberrant pathways and associated genes

Pathway Name	**Gene**
Molecular Mechanisms of Cancer	ADCY1, ADCY9, APH1B, BMP6, CAMK2B, CASP7, CASP9, CBL, CCND1, CDK2, CDK6, CDKN1A, CHEK1, FOS, FZD8, GNA15, GNAI3, HHAT, KRAS, LEF1, MAPK13, MAPK8, MAX, NOTCH1, PAK4, PIK3R1, PIK3R3, PMAIP1, PRKCH, PSEN1, PTK2, RHOB, RHOV, WNT5A, WNT9A
Regulation of the Epithelial-Mesenchymal Transition Pathway	APH1B, EGR1, ETS1, FGFR2, FGFRL1, FZD8, JAG1, JAG2, KRAS, LEF1, NOTCH1, NOTCH2, NOTCH3, PARD6A, PDGFRB, PIK3R1, PIK3R3, PSEN1, WNT5A, WNT9A
Role of IL-17A in Arthritis	CXCL1, CXCL3, CXCL5, CXCL8, MAPK13, MAPK8, MMP1, PIK3R1, PIK3R3
Th1 and Th2 Activation Pathway	APH1B, HLA-DMA, ICAM1, IL18R1, IL1RL1, IL4R, IL6R, IRF1, JAG1, JAG2, NOTCH1, NOTCH2, NOTCH3, PIK3R1, PIK3R3, PSEN1, TGFBR3
Axonal Guidance Signaling	ADAMTS16, ARPC2, ARPC4, ARPC5, BMP6, CRKL, EFNB1, EFNB2, FZD8, GLI2, GNA15, GNAI3, GNB1, KALRN, KRAS, MMP1, PAK4, PAPPA2, PIK3R1, PIK3R3, PLCD3, PLXNA1, PLXNA2, PPP3R1, PRKCH, PTK2, PXN, RASSF5, TUBB, TUBG1, WNT5A, WNT9A
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	C5, CAMK2B, CCND1, CXCL8, F2RL1, FOS, FZD8, ICAM1, IL18R1, IL1RAP, IL1RL1, IL6R, KRAS, LEF1, MMP1, PIK3R1, PIK3R3, PLCD3, PPP3R1, PRKCH, TNFRSF1B, WNT5A, WNT9A
Role of IL-17A in Psoriasis	CXCL1, CXCL3, CXCL5, CXCL8
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	BMP6, CASP9, CBL, FOS, FZD8, IL18R1, IL1RAP, IL1RL1, LEF1, MAPK8, MMP1, PIK3R1, PIK3R3, PPP3R1, TNFRSF1B, WNT5A, WNT9A
Airway Pathology in Chronic Obstructive Pulmonary Disease	CXCL3, CXCL8, MMP1
HER-2 Signaling in Breast Cancer	CASP9, CCND1, CDK6, CDKN1A, KRAS, PARD6A, PIK3R1, PIK3R3, PRKCH
TR/RXR Activation	AKR1C3, FASN, KLF9, PIK3R1, PIK3R3, SREBF2, TBL1XR1, THRA, THRB
Germ Cell-Sertoli Cell Junction Signaling	ACTB, KRAS, MAP3K3, MAPK8, PAK4, PDPK1, PIK3R1, PIK3R3, PTK2, PXN, RHOB, RHOV, TUBB, TUBG1
Role of Tissue Factor in Cancer	CXCL1, CXCL8, EGR1, F2RL1, GNA15, KRAS, MAPK13, MMP1, PIK3R1, PIK3R3, PLAUR
Serotonin Receptor Signaling	ADCY1, ADCY9, GCH1, PCBD1, QDPR, SMOX
Granulocyte Adhesion and Diapedesis	C5, CCL26, CXCL1, CXCL2, CXCL3, CXCL5, CXCL8, GNAI3, ICAM1, IL1RAP, IL1RL1, MMP1, SDC1, TNFRSF1B
Breast Cancer Regulation by Stathmin1	ADCY1, ADCY9, CAMK2B, CDK2, CDKN1A, GNAI3, GNB1, KRAS, PIK3R1, PIK3R3, PRKCH, STMN1, TUBB, TUBG1, UHMK1
Prostate Cancer Signaling	CASP9, CCND1, CDK2, CDKN1A, KRAS, LEF1, PDPK1, PIK3R1, PIK3R3

Hepatic Fibrosis / Hepatic Stellate Cell Activation	COL5A2, COL5A3, CXCL3, CXCL8, FGFR2, ICAM1, IL1RAP, IL1RL1, IL4R, IL6R, MMP1, PDGFRB, SERPINE1, TNFRSF1B
FAK Signaling	ACTB, ARHGAP26, KRAS, PAK4, PDPK1, PIK3R1, PIK3R3, PTK2, PXN
Acetate Conversion to Acetyl-CoA	ACSS2, ACSS3
Phenylalanine Degradation I (Aerobic)	PCBD1, QDPR
IL-17 Signaling	CXCL1, CXCL5, CXCL8, KRAS, MAPK13, MAPK8, PIK3R1, PIK3R3
Epithelial Adherens Junction Signaling	ACTB, ARPC2, ARPC4, ARPC5, KRAS, LEF1, NOTCH1, NOTCH2, NOTCH3, TGFBR3, TUBB, TUBG1
RAR Activation	ACTB, ADCY1, ADCY9, AKR1C3, ALDH1A3, FOS, MAPK13, MAPK8, MMP1, NR2F6, PDPK1, PIK3R1, PIK3R3, PRKCH
Human Embryonic Stem Cell Pluripotency	BMP6, FGFR2, FGFRL1, FZD8, LEF1, PDGFRB, PDPK1, PIK3R1, PIK3R3, WNT5A, WNT9A
Iron homeostasis signaling pathway	ABCB10, ATP6V0A2, ATP6V1B2, BMP6, CYBRD1, ERFE, HFE, HMOX1, IL6R, PCBP1, PDGFRB
Gαq Signaling	GNA15, GNB1, GRK2, HMOX1, PIK3R1, PIK3R3, PLD1, PPP3R1, PRKCH, RGS2, RHOB, RHOV
IL-10 Signaling	FOS, HMOX1, IL1RAP, IL1RL1, IL4R, MAPK13, MAPK8
Role of JAK family kinases in IL-6-type Cytokine Signaling	IL6R, MAPK13, MAPK8, OSMR
Cell Cycle Control of Chromosomal Replication	CDC45, CDC6, CDK2, CDK6, CDT1, MCM2
Glucocorticoid Receptor Signaling	ACTB, CDKN1A, CXCL3, CXCL8, FOS, HMGB1, ICAM1, KRAS, KRT80, MAPK13, MAPK8, MED14, MMP1, PIK3R1, PIK3R3, PLAU, PPP3R1, PRKAA2, SERPINE1, TAF4B
Parkinson's Signaling	CASP9, MAPK13, MAPK8
Erythropoietin Signaling	CBL, FOS, KRAS, PDPK1, PIK3R1, PIK3R3, PRKCH
Gap Junction Signaling	ACTB, ADCY1, ADCY9, GJB2, GNAI3, KRAS, PIK3R1, PIK3R3, PLCD3, PPP3R1, PRKCH, TUBB, TUBG1
Hereditary Breast Cancer Signaling	ACTB, CCND1, CDK6, CDKN1A, CHEK1, KRAS, PIK3R1, PIK3R3, RFC3, TUBG1
GADD45 Signaling	CCND1, CDK2, CDKN1A
Myc Mediated Apoptosis Signaling	CASP9, KRAS, MAPK8, PIK3R1, PIK3R3, YWHAZ
Sphingomyelin Metabolism	SGMS1, SMPD1
IL-4 Signaling	HLA-DMA, IL4R, INPPL1, KRAS, PIK3R1, PIK3R3, SYNJ2
T Cell Receptor Signaling	CBL, FOS, KRAS, MAPK8, PAG1, PIK3R1, PIK3R3, PPP3R1
IL-17A Signaling in Fibroblasts	CXCL5, FOS, MAPK13, MMP1
Methylglyoxal Degradation VI	LDHD
Endoplasmic Reticulum Stress Pathway	CASP7, CASP9, MAPK8
Putrescine Degradation III	ALDH1A3, ALDH9A1, SMOX
Agranulocyte Adhesion and Diapedesis	ACTB, C5, CCL26, CXCL1, CXCL2, CXCL3, CXCL5, CXCL8, GNAI3, ICAM1, MMP1, PODXL

Clathrin-mediated Endocytosis Signaling	ACTB, AP2M1, ARPC2, ARPC4, ARPC5, CBL, HIP1, PIK3R1, PIK3R3, PPP3R1, RAB5B, STON2
IL-15 Signaling	CXCL8, KRAS, MAPK13, PIK3R1, PIK3R3, PTK2
Apelin Cardiac Fibroblast Signaling Pathway	APLN, PRKAA2, SERPINE1
Factors Promoting Cardiogenesis in Vertebrates	BMP6, CDC6, CDK2, FZD8, LEF1, PRKCH, TGFBR3
Leptin Signaling in Obesity	ADCY1, ADCY9, PDE3A, PIK3R1, PIK3R3, PLCD3
Docosahexaenoic Acid (DHA) Signaling	CASP9, PDPK1, PIK3R1, PIK3R3
Role of CHK Proteins in Cell Cycle Checkpoint Control	CDK2, CDKN1A, CHEK1, MDC1, RFC3
Tumoricidal Function of Hepatic Natural Killer Cells	CASP7, CASP9, ICAM1
Angiopoietin Signaling	CASP9, KRAS, PAK4, PIK3R1, PIK3R3, PTK2
Dopamine Receptor Signaling	ADCY1, ADCY9, GCH1, PCBD1, QDPR, SMOX
G-Protein Coupled Receptor Signaling	ADCY1, ADCY9, CAMK2B, GNA15, GNAI3, GRK2, KRAS, PDE3A, PDE4D, PDE9A, PDPK1, PIK3R1, PIK3R3, PTGER2, RGS2
Tryptophan Degradation X (Mammalian, via Tryptamine)	ALDH1A3, ALDH9A1, SMOX
Semaphorin Signaling in Neurons	PAK4, PLXNA1, PTK2, RHOB, RHOV
Cleavage and Polyadenylation of Pre-mRNA	NUDT21, PAPOLA
4-hydroxyproline Degradation I	HOGA1
Fatty Acid Biosynthesis Initiation II	FASN
Glycine Biosynthesis I	SHMT2
Guanine and Guanosine Salvage I	HPRT1
L-cysteine Degradation III	MPST
Palmitate Biosynthesis I (Animals)	FASN
Chronic Myeloid Leukemia Signaling	CCND1, CDK6, CDKN1A, CRKL, KRAS, PIK3R1, PIK3R3
Bile Acid Biosynthesis, Neutral Pathway	AKR1C3, SCP2
Role of PI3K/AKT Signaling in the Pathogenesis of Influenza	CASP9, CRKL, GNAI3, PIK3R1, PIK3R3
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	ETS2, FBXO15, KDM5B, NR2F6
PD-1, PD-L1 cancer immunotherapy pathway	CDK2, HLA-DMA, LATS2, PDCD4, PIK3R1, PIK3R3, TNFRSF1B
Dopamine Degradation	ALDH1A3, ALDH9A1, SMOX
TNFR2 Signaling	FOS, MAPK8, TNFRSF1B
Choline Biosynthesis III	HMOX1, PLD1
5-aminoimidazole Ribonucleotide Biosynthesis I	PPAT
L-carnitine Biosynthesis	ALDH9A1
Methylglyoxal Degradation I	GLO1
N-acetylglucosamine Degradation I	GNPDA1
Tetrahydrobiopterin Biosynthesis I	GCH1
Tetrahydrobiopterin Biosynthesis II	GCH1
Thiosulfate Disproportionation III (Rhodanese)	MPST
Tyrosine Biosynthesis IV	PCBD1
Thyroid Cancer Signaling	CCND1, CXCL8, KRAS, LEF1
HIF1α Signaling	KRAS, MAPK13, MAPK8, MMP1, PIK3R1, PIK3R3, SLC2A3
Granzyme B Signaling	CASP9, LMNB2

Vitamin-C Transport	SLC23A2, SLC2A3
T Helper Cell Differentiation	HLA-DMA, IL18R1, IL4R, IL6R, TNFRSF1B
Inhibition of Angiogenesis by TSP1	MAPK13, MAPK8, SDC1
GABA Receptor Signaling	ADCY1, ADCY9, ALDH9A1, AP2M1, CACNG6, NSF
α-Adrenergic Signaling	ADCY1, ADCY9, GNAI3, GNB1, KRAS, PRKCH
D-myo-inositol (1, 4, 5)-trisphosphate Degradation	INPPL1, SYNJ2
Dermatan Sulfate Degradation (Metazoa)	FGFRL1, IDS
Histamine Degradation	ALDH1A3, ALDH9A1
Ovarian Cancer Signaling	CCND1, FZD8, KRAS, LEF1, PIK3R1, PIK3R3, WNT5A, WNT9A
Coagulation System	PLAU, PLAUR, SERPINE1
Noradrenaline and Adrenaline Degradation	ALDH1A3, ALDH9A1, SMOX
Natural Killer Cell Signaling	INPPL1, KRAS, PAK4, PIK3R1, PIK3R3, PRKCH, SYNJ2
1D-myo-inositol Hexakisphosphate Biosynthesis II (Mammalian)	INPPL1, SYNJ2
D-myo-inositol (1, 3, 4)-trisphosphate Biosynthesis	INPPL1, SYNJ2
FAT10 Signaling Pathway	SQSTM1, UBE2Z
Interferon Signaling	IRF1, MED14, PSMB8
Heme Degradation	HMOX1
Melatonin Degradation II	SMOX
N-acetylglucosamine Degradation II	GNPDA1
Spermine and Spermidine Degradation I	SMOX
Cell Cycle Regulation by BTG Family Proteins	BTG2, CCND1, CDK2
Apelin Muscle Signaling Pathway	APLN, PRKAA2
Role of BRCA1 in DNA Damage Response	ACTB, CDKN1A, CHEK1, MDC1, RFC3
Nur77 Signaling in T Lymphocytes	CASP9, HLA-DMA, MAP3K3, PPP3R1
CDP-diacylglycerol Biosynthesis I	AGPAT1, CDS1
Fatty Acid α-oxidation	ALDH1A3, ALDH9A1
April Mediated Signaling	FOS, MAPK13, MAPK8
Inhibition of Matrix Metalloproteases	MMP1, SDC1, TFPI2
Folate Polyglutamylation	SHMT2
dTMP De Novo Biosynthesis	SHMT2
Gustation Pathway	ADCY1, ADCY9, CACNG6, GNB1, P2RX5, PDE3A, PDE4D, PDE9A
B Cell Activating Factor Signaling	FOS, MAPK13, MAPK8
Mechanisms of Viral Exit from Host Cells	ACTB, LMNB2, PRKCH
Cellular Effects of Sildenafil (Viagra)	ACTB, ADCY1, ADCY9, CACNG6, PDE3A, PDE4D, PLCD3
Virus Entry via Endocytic Pathways	ACTB, AP2M1, KRAS, PIK3R1, PIK3R3, PRKCH
Phosphatidylglycerol Biosynthesis II (Non-plastidic)	AGPAT1, CDS1
Polyamine Regulation in Colon Cancer	KRAS, MAX
Pyrimidine Deoxyribonucleotides De Novo Biosynthesis	AK8, NME5
Pyrimidine Ribonucleotides Interconversion	AK8, NME5, NUDT15
tRNA Splicing	PDE3A, PDE4D, PDE9A
IL-12 Signaling and Production in Macrophages	FOS, IRF1, MAPK13, MAPK8, PIK3R1, PIK3R3, PRKCH

Superpathway of D-myo-inositol (1, 4, 5)-trisphosphate Metabolism	INPPL1, SYNJ2
Adenine and Adenosine Salvage III	HPRT1
UDP-N-acetyl-D-glucosamine Biosynthesis II	GFPT1
Urea Cycle	CPS1
Hepatic Cholestasis	ADCY1, ADCY9, CXCL8, IL1RAP, IL1RL1, LIF, MAPK8, PRKCH, TNFRSF1B
Pyrimidine Ribonucleotides De Novo Biosynthesis	AK8, NME5, NUDT15
Calcium-induced T Lymphocyte Apoptosis	HLA-DMA, ORAI1, PPP3R1, PRKCH
IL-22 Signaling	MAPK13, MAPK8
TCA Cycle II (Eukaryotic)	IDH3A, MDH1B
Role of IL-17F in Allergic Inflammatory Airway Diseases	CXCL1, CXCL5, CXCL8
iNOS Signaling	FOS, IRF1, MAPK13
D-myo-inositol (1, 4, 5)-Trisphosphate Biosynthesis	PIP4K2C, PLCD3
Aspartate Degradation II	MDH1B
Superpathway of Serine and Glycine Biosynthesis I	SHMT2
Role of JAK1 and JAK3 in γc Cytokine Signaling	IL4R, KRAS, PIK3R1, PIK3R3
Antiproliferative Role of TOB in T Cell Signaling	CCNA2, CDK2
Gluconeogenesis I	ENO4, MDH1B
NAD Salvage Pathway II	NT5E, PXYLP1
Ephrin A Signaling	PIK3R1, PIK3R3, PTK2
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	CDKN1A, CHEK1, YWHAZ
Histidine Degradation III	AMDHD1
Salvage Pathways of Pyrimidine Deoxyribonucleotides	TK2
IL-15 Production	FGFR2, IRF1, PDGFRB, PTK2, PTK7, ROR1
Bladder Cancer Signaling	CCND1, CDKN1A, CXCL8, KRAS, MMP1
Amyloid Processing	APH1B, MAPK13, PSEN1
Superpathway of Cholesterol Biosynthesis	DHCR24
Toll-like Receptor Signaling	FOS, IL1RL1, MAPK13, MAPK8
Folate Transformations I	SHMT2
Leucine Degradation I	BCAT2
UDP-N-acetyl-D-galactosamine Biosynthesis II	GNPDA1
Phagosome Formation	PIK3R1, PIK3R3, PLCD3, PRKCH, RHOB, RHOV
Role of p14/p19ARF in Tumor Suppression	PIK3R1, PIK3R3
Sonic Hedgehog Signaling	GLI2, GRK2
Glycolysis I	ENO4
Lipid Antigen Presentation by CD1	AP2M1
Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza	FZD8, LEF1, WNT5A, WNT9A
Reelin Signaling in Neurons	CRKL, MAPK8, PIK3R1, PIK3R3
Unfolded protein response	MAPK8, SREBF2
Dolichyl-diphosphooligosaccharide Biosynthesis	DPM3
Glycine Betaine Degradation	SHMT2
Xenobiotic Metabolism Signaling	ALDH1A3, ALDH9A1, CAMK2B, HMOX1, KRAS, MAP3K3, MAPK13, MAPK8, PIK3R1, PIK3R3, PRKCH, SMOX
4-1BB Signaling in T Lymphocytes	MAPK13, MAPK8

Transcriptional Regulatory Network in Embryonic Stem Cells	HIST1H4H, SET
Differential Regulation of Cytokine Production in Intestinal Epithelial Cells by IL-17A and IL-17F	CXCL1
Phototransduction Pathway	GNB1, OPN3
Mitochondrial Dysfunction	APH1B, ATP5PB, CASP9, CPT1C, MAPK8, PSEN1
Purine Nucleotides De Novo Biosynthesis II	PPAT
Sertoli Cell-Sertoli Cell Junction Signaling	ACTB, KRAS, MAP3K3, MAPK13, MAPK8, TGFBR3, TUBB, TUBG1
Cancer Drug Resistance By Drug Efflux	KRAS, PIK3R1, PIK3R3
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	CASP7, CASP9
DNA Methylation and Transcriptional Repression Signaling	HIST1H4H, MTA2
IL-9 Signaling	PIK3R1, PIK3R3
Retinoate Biosynthesis I	AKR1C3, ALDH1A3
Role of JAK2 in Hormone-like Cytokine Signaling	SH2B2, SH2B3
Androgen Signaling	CACNG6, CCND1, GNA15, GNAI3, GNB1, PRKCH
MSP-RON Signaling Pathway	ACTB, PIK3R1, PIK3R3
Primary Immunodeficiency Signaling	RFX5, UNG
TWEAK Signaling	CASP7, CASP9
Guanosine Nucleotides Degradation III	NT5E
Role of MAPK Signaling in the Pathogenesis of Influenza	KRAS, MAPK13, MAPK8
VDR/RXR Activation	CDKN1A, IL1RL1, PRKCH
Hematopoiesis from Pluripotent Stem Cells	CXCL8, LIF
Granzyme A Signaling	SET
The Visual Cycle	AKR1C3
CNTF Signaling	KRAS, PIK3R1, PIK3R3
Induction of Apoptosis by HIV1	CASP9, MAPK8, TNFRSF1B
Phospholipases	HMOX1, PLCD3, PLD1
Adipogenesis pathway	FGFR2, FGFRL1, FZD8, TBL1XR1, WNT5A
Cholesterol Biosynthesis I	DHCR24
Cholesterol Biosynthesis II (via 24, 25-dihydrolanosterol)	DHCR24
Cholesterol Biosynthesis III (via Desmosterol)	DHCR24
NAD Phosphorylation and Dephosphorylation	PXYLP1
Urate Biosynthesis/Inosine 5'-phosphate Degradation	NT5E
nNOS Signaling in Neurons	PPP3R1, PRKCH
DNA damage-induced 14-3-3σ Signaling	CDK2
Complement System	C1QBP, C5
Tight Junction Signaling	ACTB, FOS, HSF1, NSF, NUDT21, PARD6A, TNFRSF1B
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	FOS, KRAS, MAPK8, PPP3R1
FAT10 Cancer Signaling Pathway	TGFBR3, TNFRSF1B
Differential Regulation of Cytokine Production in Macrophages and T Helper Cells by IL-17A and IL-17F	CXCL1
Methylglyoxal Degradation III	AKR1C3

Purine Nucleotides Degradation II (Aerobic)	NT5E
Valine Degradation I	BCAT2
IL-23 Signaling Pathway	PIK3R1, PIK3R3
Stearate Biosynthesis I (Animals)	DHCR24, FASN
Androgen Biosynthesis	AKR1C3
Isoleucine Degradation I	BCAT2
Phenylalanine Degradation IV (Mammalian, via Side Chain)	SMOX
Antigen Presentation Pathway	HLA-DMA, PSMB8
tRNA Charging	FARSA, LARS2
Mitochondrial L-carnitine Shuttle Pathway	CPT1C
RAN Signaling	TNPO1
Adenosine Nucleotides Degradation II	NT5E
Histidine Degradation VI	AMDHD1
Superpathway of Citrulline Metabolism	CPS1
Serotonin Degradation	ALDH1A3, ALDH9A1, SMOX
Role of PKR in Interferon Induction and Antiviral Response	CASP9, IRF1
MIF Regulation of Innate Immunity	FOS, MAPK8
Mismatch Repair in Eukaryotes	RFC3
Phagosome Maturation	ATP6V0A2, ATP6V1B2, NSF, RAB5B, TUBB, TUBG1
Activation of IRF by Cytosolic Pattern Recognition Receptors	MAPK8
Allograft Rejection Signaling	HLA-DMA
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	HLA-DMA
Assembly of RNA Polymerase II Complex	TAF4B
Atherosclerosis Signaling	COL5A3, CXCL8, ICAM1, MMP1
Autoimmune Thyroid Disease Signaling	HLA-DMA
Autophagy	SQSTM1
B Cell Development	HLA-DMA
BAG2 Signaling Pathway	CDKN1A
CTLA4 Signaling in Cytotoxic T Lymphocytes	AP2M1, PIK3R1, PIK3R3
Calcium Signaling	CACNG6, CAMK2B, PPP3R1
Caveolar-mediated Endocytosis Signaling	ACTB, RAB5B
Circadian Rhythm Signaling	BHLHE40
Communication between Innate and Adaptive Immune Cells	CXCL8
Crosstalk between Dendritic Cells and Natural Killer Cells	ACTB, CAMK2B, TNFRSF1B
Dermatan Sulfate Biosynthesis	CHST14
Dermatan Sulfate Biosynthesis (Late Stages)	CHST14
Eicosanoid Signaling	AKR1C3, PTGER2
Estrogen Biosynthesis	AKR1C3
Estrogen Receptor Signaling	KRAS, MED14, MED21, TAF4B
FXR/RXR Activation	FASN, MAPK8, SDC1
Fatty Acid β-oxidation I	SCP2
G Protein Signaling Mediated by Tubby	GNB1
Glutamate Receptor Signaling	GNB1
Graft-versus-Host Disease Signaling	HLA-DMA
Hypoxia Signaling in the Cardiovascular System	UBE2L6, UBE2Z

Intrinsic Prothrombin Activation Pathway	COL5A3
Netrin Signaling	CACNG6, PPP3R1
Nitric Oxide Signaling in the Cardiovascular System	PIK3R1, PIK3R3, PRKCH
OX40 Signaling Pathway	HLA-DMA, MAPK8
Oxidative Phosphorylation	ATP5PB
PFKFB4 Signaling Pathway	HK2
Protein Ubiquitination Pathway	CBL, DNAJB5, HSPA13, HSPB8, PSMB8, UBE2L6, UBE2Z, USP39, USP49
Retinoic acid Mediated Apoptosis Signaling	CASP9, IRF1
Retinol Biosynthesis	AKR1C3
Role of Cytokines in Mediating Communication between Immune Cells	CXCL8
Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza	CXCL8
Role of RIG1-like Receptors in Antiviral Innate Immunity	TRIM25
SPINK1 Pancreatic Cancer Pathway	F2RL1
Superpathway of Melatonin Degradation	SMOX
Systemic Lupus Erythematosus Signaling	C5, CBL, FOS, IL6R, KRAS, LSM14B, PIK3R1, PIK3R3
Th17 Activation Pathway	IL6R, PTGER2
Triacylglycerol Biosynthesis	AGPAT1
nNOS Signaling in Skeletal Muscle Cells	CACNG6

Table 14 - H460 lung cancer downregulated pathways and associated genes

Pathway Name	**Gene**
HGF Signaling	CCND1, CDK2, CDKN1A, CRKL, ELF4, ELK3, ETS1, ETS2, FOS, KRAS, MAP3K3, MAPK8, PIK3R1, PIK3R3, PRKCH, PTK2, PXN
CXCR4 Signaling	ADCY1, ADCY9, EGR1, ELMO2, FOS, GNA15, GNAI3, GNB1, KRAS, MAPK8, PAK4, PIK3R1, PIK3R3, PRKCH, PTK2, PXN, RHOB, RHOV
Sphingosine-1-phosphate Signaling	ADCY1, ADCY9, CASP2, CASP7, CASP9, GNAI3, PDGFRB, PIK3R1, PIK3R3, PLCD3, PTK2, RHOB, RHOV, SMPD1
Endothelin-1 Signaling	ADCY1, ADCY9, CASP2, CASP7, CASP9, FOS, GNA15, GNAI3, HMOX1, KRAS, MAPK13, MAPK8, PIK3R1, PIK3R3, PLCD3, PLD1, PRKCH, PTGER2
GNRH Signaling	ADCY1, ADCY9, CACNG6, CAMK2B, EGR1, FOS, GNA15, GNAI3, GNB1, KRAS, MAP3K3, MAPK13, MAPK8, PAK4, PRKCH, PTK2, PXN
Rac Signaling	ABI2, ARPC2, ARPC4, ARPC5, KRAS, MAPK8, PAK4, PARD6A, PIK3R1, PIK3R3, PIP4K2C, PLD1, PTK2
IL-8 Signaling	CCND1, CXCL1, CXCL8, FOS, GNAI3, GNB1, HMOX1, ICAM1, KRAS, LASP1, MAPK8, PIK3R1, PIK3R3, PLD1, PRKCH, PTK2, RHOB, RHOV
Colorectal Cancer Metastasis Signaling	ADCY1, ADCY9, APPL1, CASP9, CCND1, FOS, FZD8, GNB1, GRK2, IL6R, KRAS, LEF1, MAPK8, MMP1, PIK3R1, PIK3R3, PTGER2, RHOB, RHOV, WNT5A, WNT9A
Notch Signaling	APH1B, JAG1, JAG2, NOTCH1, NOTCH2, NOTCH3, PSEN1

Th2 Pathway	APH1B, HLA-DMA, ICAM1, IL1RL1, IL4R, JAG1, JAG2, NOTCH1, NOTCH2, NOTCH3, PIK3R1, PIK3R3, PSEN1, TGFBR3
Signaling by Rho Family GTPases	ACTB, ARPC2, ARPC4, ARPC5, CDC42EP2, FOS, GNA15, GNAI3, GNB1, MAPK8, PAK4, PARD6A, PIK3R1, PIK3R3, PIP4K2C, PLD1, PTK2, RHOB, RHOV, STMN1
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	ACTB, ARPC2, ARPC4, ARPC5, CBL, HMOX1, PIK3R1, PIK3R3, PLD1, PRKCH, PXN
Cardiac Hypertrophy Signaling (Enhanced)	ADCY1, ADCY9, CAMK2B, CXCL8, FGFR2, FGFRL1, FZD8, GNA15, GNAI3, GNB1, IL18R1, IL1RL1, IL4R, IL6R, KRAS, LIF, MAP3K3, MAPK13, MAPK8, PDE3A, PDE4D, PDE9A, PIK3R1, PIK3R3, PLCD3, PPP3R1, PRKCH, PTK2, TGFBR3, TNFRSF1B, WNT5A, WNT9A
Glioblastoma Multiforme Signaling	CCND1, CDK2, CDK6, CDKN1A, FZD8, KRAS, LEF1, PDGFRB, PIK3R1, PIK3R3, PLCD3, RHOB, RHOV, WNT5A, WNT9A
Apelin Endothelial Signaling Pathway	ADCY1, ADCY9, APLN, FOS, GNAI3, ICAM1, KRAS, MAPK8, PIK3R1, PIK3R3, PRKAA2, PRKCH
B Cell Receptor Signaling	CAMK2B, EGR1, ETS1, INPPL1, KRAS, MAP3K3, MAPK13, MAPK8, PAG1, PDPK1, PIK3R1, PIK3R3, PPP3R1, PTK2, RASSF5, SYNJ2
Ephrin B Signaling	CBL, EFNB1, EFNB2, GNA15, GNAI3, GNB1, KALRN, PTK2, PXN
Renin-Angiotensin Signaling	ADCY1, ADCY9, FOS, KRAS, MAPK13, MAPK8, PAK4, PIK3R1, PIK3R3, PRKCH, PTGER2, PTK2
Thrombin Signaling	ADCY1, ADCY9, CAMK2B, GATA2, GNA15, GNAI3, GNB1, KRAS, MAPK13, PDPK1, PIK3R1, PIK3R3, PLCD3, PRKCH, PTK2, RHOB, RHOV
Th1 Pathway	APH1B, HLA-DMA, ICAM1, IL18R1, IL6R, IRF1, NOTCH1, NOTCH2, NOTCH3, PIK3R1, PIK3R3, PSEN1
IL-17A Signaling in Gastric Cells	CXCL1, CXCL8, FOS, MAPK13, MAPK8
IL-6 Signaling	CXCL8, FOS, IL1RAP, IL1RL1, IL6R, KRAS, MAPK13, MAPK8, MCL1, PIK3R1, PIK3R3, TNFRSF1B
Glioma Signaling	CAMK2B, CCND1, CDK6, CDKN1A, IDH1, IDH2, KRAS, PDGFRB, PIK3R1, PIK3R3, PRKCH
Superpathway of Inositol Phosphate Compounds	DUSP5, HACD2, INPPL1, NUDT15, NUDT3, NUDT4, PIK3R1, PIK3R3, PIP4K2C, PLCD3, PPP4R1, PPTC7, PXYLP1, SET, SSH3, SYNJ2
14-3-3-mediated Signaling	CBL, FOS, KRAS, MAPK8, PIK3R1, PIK3R3, PLCD3, PRKCH, TP73, TUBB, TUBG1, YWHAZ
Tec Kinase Signaling	ACTB, FOS, GNA15, GNAI3, GNB1, MAPK8, PAK4, PIK3R1, PIK3R3, PRKCH, PTK2, RHOB, RHOV, TNFRSF21
ATM Signaling	CBX1, CDK2, CDKN1A, CHEK1, HP1BP3, MAPK13, MAPK8, MDC1, RNF168, TP73
Salvage Pathways of Pyrimidine Ribonucleotides	AK8, CDK2, CDK6, FAM20B, GRK5, MAPK8, NME5, PRKAA2, PRKCH, UPP1

HMGB1 Signaling	CXCL8, FOS, HMGB1, ICAM1, KRAS, LIF, MAPK13, MAPK8, PIK3R1, PIK3R3, RHOB, RHOV, SERPINE1, TNFRSF1B
STAT3 Pathway	BMP6, CDKN1A, FGFR2, IL18R1, IL1RL1, IL4R, IL6R, KRAS, MAPK13, MAPK8, PDGFRB, TGFBR3
PDGF Signaling	CRKL, FOS, INPPL1, KRAS, MAPK8, PDGFRB, PIK3R1, PIK3R3, SYNJ2
Small Cell Lung Cancer Signaling	CASP9, CCND1, CDK2, CDK6, MAX, PIK3R1, PIK3R3, PTK2
IGF-1 Signaling	CASP9, FOS, KRAS, MAPK8, PDPK1, PIK3R1, PIK3R3, PTK2, PXN, YWHAZ
Oxidative Ethanol Degradation III	ACSS2, ACSS3, ALDH1A3, ALDH9A1
Integrin Signaling	ACTB, ARF3, ARHGAP26, ARPC2, ARPC4, ARPC5, CRKL, KRAS, MAPK8, PAK4, PIK3R1, PIK3R3, PTK2, PXN, RHOB, RHOV
Acute Phase Response Signaling	C5, FOS, HMOX1, IL1RAP, IL6R, KRAS, MAPK13, MAPK8, OSMR, PDPK1, PIK3R1, PIK3R3, SERPINE1, TNFRSF1B
Non-Small Cell Lung Cancer Signaling	CASP9, CCND1, CDK6, KRAS, PDPK1, PIK3R1, PIK3R3, RASSF5
Ephrin Receptor Signaling	ARPC2, ARPC4, ARPC5, CRKL, EFNB1, EFNB2, GNA15, GNAI3, GNB1, KALRN, KRAS, PAK4, PTK2, PXN
IL-1 Signaling	ADCY1, ADCY9, FOS, GNA15, GNAI3, GNB1, IL1RAP, MAPK13, MAPK8
Aryl Hydrocarbon Receptor Signaling	ALDH1A3, ALDH9A1, CCNA2, CCND1, CDK2, CDK6, CDKN1A, CHEK1, FOS, MAPK8, TGM2, TP73
Glioma Invasiveness Signaling	KRAS, PIK3R1, PIK3R3, PLAU, PLAUR, PTK2, RHOB, RHOV
Telomerase Signaling	CDKN1A, ELF4, ELK3, ETS1, ETS2, KRAS, PDPK1, PIK3R1, PIK3R3, TERT
Endometrial Cancer Signaling	CASP9, CCND1, KRAS, LEF1, PDPK1, PIK3R1, PIK3R3
3-phosphoinositide Biosynthesis	DUSP5, HACD2, NUDT15, NUDT3, NUDT4, PIK3R1, PIK3R3, PIP4K2C, PPP4R1, PPTC7, PXYLP1, SET, SSH3
Agrin Interactions at Neuromuscular Junction	ACTB, GABPA, GABPB1, KRAS, MAPK8, PAK4, PTK2, PXN
p70S6K Signaling	F2RL1, GNAI3, IL4R, KRAS, PDPK1, PIK3R1, PIK3R3, PLCD3, PLD1, PRKCH, YWHAZ
ErbB Signaling	FOS, KRAS, MAPK13, MAPK8, PAK4, PDPK1, PIK3R1, PIK3R3, PRKCH
IL-7 Signaling Pathway	CCND1, CDK2, MAPK13, MCL1, PDPK1, PIK3R1, PIK3R3, PTK2
Neuregulin Signaling	CRKL, ERBIN, ERRFI1, KRAS, PDPK1, PIK3R1, PIK3R3, PRKCH, PSEN1
UVA-Induced MAPK Signaling	CASP9, FOS, KRAS, MAPK13, MAPK8, PIK3R1, PIK3R3, PLCD3, SMPD1
p53 Signaling	CCND1, CDK2, CDKN1A, CHEK1, MAPK8, PIK3R1, PIK3R3, PMAIP1, TP73
Endocannabinoid Developing Neuron Pathway	ADCY1, ADCY9, CCND1, GNAI3, GNB1, KRAS, MAPK13, MAPK8, PIK3R1, PIK3R3
IL-17A Signaling in Airway Cells	CXCL1, CXCL3, CXCL5, MAPK13, MAPK8, PIK3R1, PIK3R3
Pyridoxal 5'-phosphate Salvage Pathway	CDK2, CDK6, FAM20B, GRK5, MAPK8, PRKAA2, PRKCH

TNFR1 Signaling	CASP2, CASP7, CASP9, FOS, MAPK8, PAK4
Ethanol Degradation IV	ACSS2, ACSS3, ALDH1A3, ALDH9A1
fMLP Signaling in Neutrophils	ARPC2, ARPC4, ARPC5, GNAI3, GNB1, KRAS, PIK3R1, PIK3R3, PPP3R1, PRKCH
Osteoarthritis Pathway	CASP2, CASP7, CASP9, CXCL8, FZD8, GLI2, HMGB1, IL1RAP, IL1RL1, JAG1, LEF1, MMP1, NOTCH1, PRKAA2, TNFRSF1B
Regulation of Cellular Mechanics by Calpain Protease	CCNA2, CCND1, CDK2, CDK6, KRAS, PTK2, PXN
3-phosphoinositide Degradation	DUSP5, HACD2, INPPL1, NUDT15, NUDT3, NUDT4, PPP4R1, PPTC7, PXYLP1, SET, SSH3, SYNJ2
UVC-Induced MAPK Signaling	FOS, KRAS, MAPK13, MAPK8, PRKCH, SMPD1
Role of NFAT in Cardiac Hypertrophy	ADCY1, ADCY9, CACNG6, CAMK2B, GNAI3, GNB1, KRAS, LIF, MAPK13, MAPK8, PIK3R1, PIK3R3, PLCD3, PPP3R1, PRKCH
D-myo-inositol-5-phosphate Metabolism	DUSP5, HACD2, NUDT15, NUDT3, NUDT4, PIP4K2C, PLCD3, PPP4R1, PPTC7, PXYLP1, SET, SSH3
CD28 Signaling in T Helper Cells	ARPC2, ARPC4, ARPC5, FOS, HLA-DMA, MAPK8, PDPK1, PIK3R1, PIK3R3, PPP3R1
ErbB4 Signaling	APH1B, KRAS, PDPK1, PIK3R1, PIK3R3, PRKCH, PSEN1
Remodeling of Epithelial Adherens Junctions	ACTB, ARPC2, ARPC4, ARPC5, RAB5B, TUBB, TUBG1
UVB-Induced MAPK Signaling	FOS, MAPK13, MAPK8, PIK3R1, PIK3R3, PRKCH
Mouse Embryonic Stem Cell Pluripotency	FZD8, ID1, ID3, KRAS, LEF1, LIF, MAPK13, PIK3R1, PIK3R3
Cardiac Hypertrophy Signaling	ADCY1, ADCY9, GNA15, GNAI3, GNB1, IL6R, KRAS, MAP3K3, MAPK13, MAPK8, PIK3R1, PIK3R3, PLCD3, PPP3R1, RHOB, RHOV
GM-CSF Signaling	CAMK2B, CCND1, ETS1, KRAS, PIK3R1, PIK3R3, PPP3R1
Apelin Liver Signaling Pathway	APLN, COL5A3, MAPK8, PDGFRB
Estrogen-mediated S-phase Entry	CCNA2, CCND1, CDK2, CDKN1A
RANK Signaling in Osteoclasts	CBL, FOS, MAP3K3, MAPK13, MAPK8, PIK3R1, PIK3R3, PPP3R1
Endocannabinoid Neuronal Synapse Pathway	ADCY1, ADCY9, CACNG6, GNA15, GNAI3, GNB1, MAPK13, MAPK8, PLCD3, PPP3R1
P2Y Purigenic Receptor Signaling Pathway	ADCY1, ADCY9, FOS, GNAI3, GNB1, KRAS, PIK3R1, PIK3R3, PLCD3, PRKCH
Paxillin Signaling	ACTB, KRAS, MAPK13, MAPK8, PAK4, PIK3R1, PIK3R3, PTK2, PXN
Relaxin Signaling	ADCY1, ADCY9, FOS, GNA15, GNAI3, GNB1, PDE3A, PDE4D, PDE9A, PIK3R1, PIK3R3
Regulation of Actin-based Motility by Rho	ACTB, ARPC2, ARPC4, ARPC5, PAK4, PIP4K2C, RHOB, RHOV
NRF2-mediated Oxidative Stress Response	ACTB, DNAJB5, FOS, FOSL1, HMOX1, HSPB8, KRAS, MAFF, MAPK8, PIK3R1, PIK3R3, PRKCH, SQSTM1
PI3K/AKT Signaling	CCND1, CDKN1A, INPPL1, KRAS, MCL1, PDPK1, PIK3R1, PIK3R3, SYNJ2, YWHAZ
ERK/MAPK Signaling	CRKL, ELF4, ELK3, ETS1, ETS2, FOS, KRAS, PAK4, PIK3R1, PIK3R3, PTK2, PXN, YWHAZ
Apelin Pancreas Signaling Pathway	APLN, MAPK8, PIK3R1, PIK3R3, PRKAA2

PAK Signaling	KRAS, MAPK8, PAK4, PDGFRB, PIK3R1, PIK3R3, PTK2, PXN
Chemokine Signaling	CAMK2B, FOS, GNAI3, KRAS, MAPK13, MAPK8, PTK2
IL-3 Signaling	CRKL, FOS, KRAS, PIK3R1, PIK3R3, PPP3R1, PRKCH
Fc Epsilon RI Signaling	INPPL1, KRAS, MAPK13, MAPK8, PDPK1, PIK3R1, PIK3R3, PRKCH, SYNJ2
Apelin Adipocyte Signaling Pathway	ADCY1, ADCY9, APLN, GNAI3, MAPK13, MAPK8, PRKAA2
Leukocyte Extravasation Signaling	ACTB, CRKL, GNAI3, ICAM1, MAPK13, MAPK8, MMP1, PIK3R1, PIK3R3, PRKCH, PTK2, PXN, RASSF5
Apelin Cardiomyocyte Signaling Pathway	APLN, GNAI3, MAPK13, MAPK8, PIK3R1, PIK3R3, PLCD3, PRKCH
Prolactin Signaling	FOS, IRF1, KRAS, PDPK1, PIK3R1, PIK3R3, PRKCH
Ethanol Degradation II	ACSS2, ACSS3, ALDH1A3, ALDH9A1
LPS-stimulated MAPK Signaling	FOS, KRAS, MAPK13, MAPK8, PIK3R1, PIK3R3, PRKCH
D-myo-inositol (1, 4, 5, 6)-Tetrakisphosphate Biosynthesis	DUSP5, HACD2, NUDT15, NUDT3, NUDT4, PPP4R1, PPTC7, PXYLP1, SET, SSH3
D-myo-inositol (3, 4, 5, 6)-tetrakisphosphate Biosynthesis	DUSP5, HACD2, NUDT15, NUDT3, NUDT4, PPP4R1, PPTC7, PXYLP1, SET, SSH3
SAPK/JNK Signaling	CRKL, GNB1, KRAS, MAP3K3, MAP4K5, MAPK8, PIK3R1, PIK3R3
CD40 Signaling	FOS, ICAM1, MAPK13, MAPK8, PIK3R1, PIK3R3
FGF Signaling	CRKL, FGFR2, FGFRL1, MAPK13, MAPK8, PIK3R1, PIK3R3
RhoA Signaling	ACTB, ARPC2, ARPC4, ARPC5, CDC42EP2, PIP4K2C, PLD1, PLXNA1, PTK2
Opioid Signaling Pathway	ADCY1, ADCY9, AP2M1, CACNG6, CAMK2B, FOS, FOSB, GNAI3, GNB1, GRK2, GRK5, KRAS, OGFR, PPP3R1, PRKCH
CCR3 Signaling in Eosinophils	CCL26, GNAI3, GNB1, KRAS, MAPK13, PAK4, PIK3R1, PIK3R3, PRKCH
Melanoma Signaling	CCND1, CDKN1A, KRAS, PIK3R1, PIK3R3
mTOR Signaling	EIF4B, HMOX1, KRAS, PDPK1, PIK3R1, PIK3R3, PLD1, PRKAA2, PRKCH, RHOB, RHOV, RPS17, RPS21
Ceramide Signaling	FOS, KRAS, MAPK8, PIK3R1, PIK3R3, SMPD1, TNFRSF1B
Acute Myeloid Leukemia Signaling	CCND1, IDH1, IDH2, KRAS, LEF1, PIK3R1, PIK3R3
ILK Signaling	ACTB, CCND1, FOS, LEF1, MAPK8, PDPK1, PIK3R1, PIK3R3, PTK2, PXN, RHOB, RHOV
Death Receptor Signaling	ACTB, CASP2, CASP7, CASP9, MAPK8, TNFRSF1B, TNFRSF21
Actin Nucleation by ARP-WASP Complex	ARPC2, ARPC4, ARPC5, KRAS, RHOB, RHOV
ERK5 Signaling	FOS, FOSL1, KRAS, LIF, MAP3K3, YWHAZ
Lymphotoxin β Receptor Signaling	CASP9, CXCL1, PDPK1, PIK3R1, PIK3R3
Huntington's Disease Signaling	ATP5PB, CASP2, CASP7, CASP9, GNA15, GNB1, HIP1, MAPK8, NSF, PDPK1, PIK3R1, PIK3R3, PRKCH, TGM2
Basal Cell Carcinoma Signaling	BMP6, FZD8, GLI2, LEF1, WNT5A, WNT9A

Protein Kinase A Signaling	ADCY1, ADCY9, AKAP12, AKAP6, CAMK2B, DUSP18, DUSP5, GNAI3, GNB1, HHAT, LEF1, PDE3A, PDE4D, PDE9A, PLCD3, PPP3R1, PRKCH, PTK2, PTPRA, PXN, YWHAZ
Actin Cytoskeleton Signaling	ABI2, ACTB, ARPC2, ARPC4, ARPC5, CRKL, KRAS, PAK4, PIK3R1, PIK3R3, PTK2, PXN, SSH3
Adrenomedullin signaling pathway	ADCY1, ADCY9, FOS, GNA15, KRAS, MAPK13, MAPK8, MAX, PIK3R1, PIK3R3, PLCD3, PTK2
EGF Signaling	FOS, MAPK13, MAPK8, PIK3R1, PIK3R3
Estrogen-Dependent Breast Cancer Signaling	CCND1, FOS, KRAS, PIK3R1, PIK3R3, TERT
CCR5 Signaling in Macrophages	CACNG6, FOS, GNAI3, GNB1, MAPK13, MAPK8, PRKCH
PKCθ Signaling in T Lymphocytes	CACNG6, CAMK2B, FOS, HLA-DMA, KRAS, MAP3K3, MAPK8, PIK3R1, PIK3R3, PPP3R1
Synaptogenesis Signaling Pathway	ADCY1, ADCY9, AP2M1, ARPC2, ARPC4, ARPC5, CAMK2B, CRKL, EFNB1, EFNB2, KALRN, KRAS, NSF, PIK3R1, PIK3R3, RAB5B, THBS4
FcγRIIB Signaling in B Lymphocytes	CACNG6, KRAS, MAPK8, PDPK1, PIK3R1, PIK3R3
Aldosterone Signaling in Epithelial Cells	DNAJB5, HSPA13, HSPB8, KRAS, PDPK1, PIK3R1, PIK3R3, PIP4K2C, PLCD3, PRKCH
Neurotrophin/TRK Signaling	FOS, KRAS, MAPK8, PDPK1, PIK3R1, PIK3R3
PI3K Signaling in B Lymphocytes	CAMK2B, CBL, FOS, IL4R, KRAS, PDPK1, PIK3R1, PLCD3, PPP3R1
cAMP-mediated signaling	ADCY1, ADCY9, AKAP12, AKAP6, CAMK2B, GNAI3, GRK2, PDE3A, PDE4D, PDE9A, PPP3R1, PTGER2, RGS2
Cardiac β-adrenergic Signaling	ADCY1, ADCY9, AKAP12, AKAP6, GNB1, GRK2, PDE3A, PDE4D, PDE9A
Insulin Receptor Signaling	CBL, CRKL, INPPL1, KRAS, MAPK8, PDPK1, PIK3R1, PIK3R3, SYNJ2
Cholecystokinin/Gastrin-mediated Signaling	FOS, KRAS, MAPK8, PRKCH, PTK2, PXN, RHOB, RHOV
Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency	BMP6, FZD8, KRAS, LIF, PIK3R1, PIK3R3, WNT5A, WNT9A
Apoptosis Signaling	CASP2, CASP7, CASP9, KRAS, MAPK8, MCL1, TNFRSF1B
Oncostatin M Signaling	KRAS, MMP1, OSMR, PLAU
CREB Signaling in Neurons	ADCY1, ADCY9, CACNG6, CAMK2B, GNA15, GNAI3, GNB1, KRAS, PIK3R1, PIK3R3, PLCD3, PRKCH
PCP pathway	EFNB1, FZD8, MAPK8, WNT5A, WNT9A
Type II Diabetes Mellitus Signaling	CACNG6, MAPK8, PDPK1, PIK3R1, PIK3R3, PRKAA2, PRKCH, SMPD1, TNFRSF1B
IL-2 Signaling	FOS, KRAS, MAPK8, PIK3R1, PIK3R3
G Beta Gamma Signaling	ADCY1, CACNG6, GNA15, GNAI3, GNB1, KRAS, PDPK1, PRKCH
Renal Cell Carcinoma Signaling	ETS1, FOS, KRAS, PAK4, PIK3R1, PIK3R3
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	FOS, IRF1, MAP3K3, MAPK13, MAPK8, PIK3R1, PIK3R3, PRKCH, RHOB, RHOV, TNFRSF1B
Corticotropin Releasing Hormone Signaling	ADCY1, ADCY9, ARPC5, CACNG6, FOS, GLI2, GNAI3, MAPK13, PRKCH
Sumoylation Pathway	ETS1, FOS, MAPK8, RFC3, RHOB, RHOV, SENP1

Cdc42 Signaling	ARPC2, ARPC4, ARPC5, CDC42EP2, FOS, HLA-DMA, MAPK13, MAPK8, PAK4, PARD6A
Thrombopoietin Signaling	FOS, KRAS, PIK3R1, PIK3R3, PRKCH
FLT3 Signaling in Hematopoietic Progenitor Cells	CBL, KRAS, MAPK13, PDPK1, PIK3R1, PIK3R3
ErbB2-ErbB3 Signaling	CCND1, KRAS, PDPK1, PIK3R1, PIK3R3
Wnt/β-catenin Signaling	APPL1, CCND1, FZD8, LEF1, SOX18, SOX6, SOX7, TGFBR3, WNT5A, WNT9A
CDK5 Signaling	ADCY1, ADCY9, EGR1, FOSB, KRAS, MAPK13, MAPK8
Sirtuin Signaling Pathway	ABCA1, ACSS2, ATP5PB, CPS1, CPT1C, CXCL8, GABPA, GABPB1, HSF1, IDH2, LDHD, PRKAA2, TOMM20, TOMM34, TP73
Type I Diabetes Mellitus Signaling	CASP9, HLA-DMA, IL1RAP, IRF1, MAPK13, MAPK8, TNFRSF1B
GPCR-Mediated Nutrient Sensing in Enteroendocrine Cells	ADCY1, ADCY9, CACNG6, GNA15, GNAI3, PLCD3, PRKCH
Role of NFAT in Regulation of the Immune Response	FOS, GNA15, GNAI3, GNB1, HLA-DMA, KRAS, ORAI1, PIK3R1, PIK3R3, PPP3R1
Growth Hormone Signaling	FOS, PDPK1, PIK3R1, PIK3R3, PRKCH
Neuroinflammation Signaling Pathway	APH1B, CXCL8, FOS, HLA-DMA, HMGB1, HMOX1, ICAM1, IL6R, MAPK13, MAPK8, PIK3R1, PIK3R3, PPP3R1, PSEN1, TGFBR3
NGF Signaling	KRAS, MAP3K3, MAPK8, PDPK1, PIK3R1, PIK3R3, SMPD1
eNOS Signaling	ADCY1, ADCY9, CASP9, CCNA2, PDPK1, PIK3R1, PIK3R3, PRKAA2, PRKCH
CD27 Signaling in Lymphocytes	CASP9, FOS, MAP3K3, MAPK8
Melanocyte Development and Pigmentation Signaling	ADCY1, ADCY9, KRAS, PIK3R1, PIK3R3, SH2B2
GP6 Signaling Pathway	COL5A2, COL5A3, PDPK1, PIK3R1, PIK3R3, PRKCH, PTK2
Amyotrophic Lateral Sclerosis Signaling	CASP7, CASP9, NEFH, PIK3R1, PIK3R3, RAB5B
GDNF Family Ligand-Receptor Interactions	FOS, KRAS, MAPK8, PIK3R1, PIK3R3
Antiproliferative Role of Somatostatin Receptor 2	CDKN1A, GNB1, KRAS, PIK3R1, PIK3R3
VEGF Signaling	ACTB, KRAS, PIK3R1, PIK3R3, PTK2, PXN
Neuropathic Pain Signaling In Dorsal Horn Neurons	CAMK2B, FOS, PIK3R1, PIK3R3, PLCD3, PRKCH
Cyclins and Cell Cycle Regulation	CCNA2, CCND1, CDK2, CDK6, CDKN1A
JAK/Stat Signaling	CDKN1A, FOS, KRAS, PIK3R1, PIK3R3
PEDF Signaling	CASP7, KRAS, MAPK13, PIK3R1, PIK3R3
Synaptic Long Term Potentiation	ADCY1, CAMK2B, GNA15, KRAS, PLCD3, PPP3R1, PRKCH
Wnt/Ca+ pathway	FZD8, PLCD3, ROR1, WNT5A
Gα12/13 Signaling	F2RL1, KRAS, MAPK8, PIK3R1, PIK3R3, PTK2, PXN
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	C5, CXCL8, LIF, MAPK8, PIK3R1, PIK3R3, PRKCH, PTX3
VEGF Family Ligand-Receptor Interactions	FOS, KRAS, PIK3R1, PIK3R3, PRKCH
NF-κB Signaling	FGFR2, KRAS, MAP3K3, MAPK8, PDGFRB, PIK3R1, PIK3R3, TGFBR3, TNFRSF1B
Phospholipase C Signaling	ADCY1, ADCY9, GNB1, HMOX1, KRAS, PLCD3, PLD1, PPP3R1, PRKCH, RHOB, RHOV, TGM2

Dendritic Cell Maturation	COL5A3, HLA-DMA, ICAM1, MAPK13, MAPK8, PIK3R1, PIK3R3, PLCD3, TNFRSF1B
iCOS-iCOSL Signaling in T Helper Cells	CAMK2B, HLA-DMA, PDPK1, PIK3R1, PIK3R3, PPP3R1
SPINK1 General Cancer Pathway	IL6R, KRAS, PIK3R1, PIK3R3
Melatonin Signaling	CAMK2B, GNAI3, PLCD3, PRKCH
TGF-β Signaling	FOS, KRAS, MAPK13, MAPK8, SERPINE1
TREM1 Signaling	CXCL3, CXCL8, ICAM1, IL1RL1
T Cell Exhaustion Signaling Pathway	FOS, HLA-DMA, IL6R, KRAS, MAPK8, PIK3R1, PIK3R3, TGFBR3
Macropinocytosis Signaling	KRAS, PIK3R1, PIK3R3, PRKCH
NER Pathway	COPS3, DDB1, HIST1H4H, POLE3, RFC3
Regulation of eIF4 and p70S6K Signaling	KRAS, MAPK13, PDPK1, PIK3R1, PIK3R3, RPS17, RPS21
Gαs Signaling	ADCY1, ADCY9, GNB1, PTGER2, RGS2
NF-κB Activation by Viruses	KRAS, PIK3R1, PIK3R3, PRKCH
BMP signaling pathway	BMP6, KRAS, MAPK13, MAPK8
Sperm Motility	FGFR2, PDE4D, PDGFRB, PLCD3, PRKCH, PTK2, PTK7, ROR1
Dopamine-DARPP32 Feedback in cAMP Signaling	ADCY1, ADCY9, GNAI3, PLCD3, PPP3R1, PRKCH
LPS/IL-1 Mediated Inhibition of RXR Function	ABCA1, ALDH1A3, ALDH9A1, CPT1C, IL1RAP, IL1RL1, MAPK8, SMOX, TNFRSF1B
EIF2 Signaling	ACTB, CCND1, KRAS, PDPK1, PIK3R1, PIK3R3, RPS17, RPS21, TRIB3
p38 MAPK Signaling	IL1RAP, IL1RL1, MAPK13, MAX, TNFRSF1B
Gαi Signaling	ADCY1, ADCY9, GNAI3, GNB1, KRAS
Synaptic Long Term Depression	CACNG6, GNA15, GNAI3, KRAS, PLCD3, PRKCH

Table 15 – HEP3B liver cancer upregulated pathways and associated genes

Pathway Name	**Gene**
PTEN Signaling	BCAR1, CBL, CCND1, INPP5B, INPPL1, KRAS, MAGI3, PDGFRB, PDPK1, PIK3R1, PTK2, RPS6KB2, RRAS, SOS2, TGFBR2, TGFBR3
PPARα/RXRα Activation	ABCA1, ADCY9, CREBBP, CYP2C8, EP300, KRAS, MAPK8, NOTUM, PLCD3, PPARGC1A, PRKAA2, RRAS, SMAD3, SOS2, TGFB2, TGFBR2, TGFBR3
Sumoylation Pathway	CREBBP, EP300, ETS1, MAPK8, MDM2, MYB, RHOH, RND3, RNF4, SENP5
RhoGDI Signaling	ACTB, ARHGEF12, ARPC2, ARPC5, CREBBP, DLC1, EP300, GNAI3, PAK4, PIP4K2C, PIP5K1A, RHOH, RND3
Endocannabinoid Cancer Inhibition Pathway	ADCY9, CASP2, CASP7, CCND1, CREBBP, GNAI3, LEF1, PIK3R1, PRKAA2, PTK2, SMPD1
Apelin Cardiac Fibroblast Signaling Pathway	CCN2, PRKAA2, SERPINE1, TGFB2
HIPPO signaling	AJUBA, DLG1, FAT4, SMAD3, TEAD4, YAP1, YWHAZ
Regulation of Cellular Mechanics by Calpain Protease	CCNA2, CCND1, CDK6, KRAS, PTK2, RRAS
Cell Cycle: G1/S Checkpoint Regulation	CCND1, CDK6, MAX, MDM2, SMAD3, TGFB2
GPCR-Mediated Integration of Enteroendocrine Signaling Exemplified by an L Cell	ADCY9, GNAI3, NOTUM, PLCD3

Table 16 - HEP3B liver cancer aberrant pathways and associated genes

Pathway Name	**Gene**
Molecular Mechanisms of Cancer	ADCY9, ARHGEF12, CASP7, CBL, CCND1, CDK6, CREBBP, EP300, FZD5, GNAI3, HHAT, KRAS, LEF1, MAPK8, MAX, MDM2, NF1, NOTCH1, PAK4, PIK3R1, PSEN1, PTK2, RHOH, RND3, RRAS, SMAD3, SOS2, TGFB2, TGFBR2
Chronic Myeloid Leukemia Signaling	CCND1, CDK6, CRKL, KRAS, MDM2, PIK3R1, RRAS, SMAD3, SOS2, TGFB2, TGFBR2
Germ Cell-Sertoli Cell Junction Signaling	ACTB, BCAR1, KRAS, MAPK8, PAK4, PDPK1, PIK3R1, PTK2, RHOH, RND3, RRAS, TGFB2, TGFBR2, TUBB4A
Antiproliferative Role of TOB in T Cell Signaling	CCNA2, SMAD3, TGFB2, TGFBR2, TWSG1
Glucocorticoid Receptor Signaling	ACTB, CREBBP, DUSP1, EP300, KRAS, KRT17, KRT80, MAPK8, PBX1, PHF10, PIK3R1, PRKAA2, RRAS, SERPINE1, SMAD3, SMARCA2, SOS2, TAF4B, TGFB2, TGFBR2, TSC22D3
Prostate Cancer Signaling	CCND1, CREBBP, KRAS, LEF1, MDM2, PDPK1, PIK3R1, RRAS, SOS2
RAR Activation	ACTB, ADCY9, CREBBP, DUSP1, EP300, MAPK8, NR2F6, PDPK1, PHF10, PIK3R1, PPARGC1A, SMAD3, SMARCA2, TGFB2
Regulation of the Epithelial-Mesenchymal Transition Pathway	ETS1, FZD5, KRAS, LEF1, LOX, NOTCH1, PDGFRB, PIK3R1, PSEN1, RRAS, SMAD3, SOS2, TGFB2, TGFBR2
FAK Signaling	ACTB, BCAR1, KRAS, PAK4, PDPK1, PIK3R1, PTK2, RRAS, SOS2
Hereditary Breast Cancer Signaling	ACTB, CCND1, CDK6, CREBBP, EP300, GADD45B, KRAS, PHF10, PIK3R1, RRAS, SMARCA2
Acetate Conversion to Acetyl-CoA	ACSS2, ACSS3
Epithelial Adherens Junction Signaling	ACTB, ARPC2, ARPC5, KRAS, LEF1, NOTCH1, RRAS, TGFB2, TGFBR2, TGFBR3, TUBB4A
Hypoxia Signaling in the Cardiovascular System	CREBBP, EDN1, EP300, MDM2, UBE2F, UBE2J1, UBE2L6
Erythropoietin Signaling	CBL, KRAS, PDPK1, PIK3R1, RRAS, SOCS3, SOS2
p53 Signaling	CCND1, EP300, GADD45B, MAPK8, MDM2, PIK3R1, TNFRSF10B, TP53INP1
Axonal Guidance Signaling	ADAMTS1, ARHGEF12, ARPC2, ARPC5, BCAR1, CRKL, CXCR4, EFNA4, EFNB1, EFNB2, EPHA2, FZD5, GLIS2, GNAI3, KRAS, NOTUM, NRP2, PAK4, PIK3R1, PLCD3, PTK2, RRAS, SOS2, TUBB4A
HER-2 Signaling in Breast Cancer	CCND1, CDK6, KRAS, MDM2, PIK3R1, RRAS, SOS2
Ephrin A Signaling	BCAR1, EFNA4, EPHA2, PIK3R1, PTK2
Myc Mediated Apoptosis Signaling	KRAS, MAPK8, PIK3R1, RRAS, SOS2, YWHAZ
IL-4 Signaling	INPP5B, INPPL1, KRAS, PIK3R1, RPS6KB2, RRAS, SOS2
Superpathway of Serine and Glycine Biosynthesis I	PHGDH, SHMT2
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	KRAS, MAPK8, RRAS, SMAD3, SOS2, TGFB2, TGFBR2

Oxidative Ethanol Degradation III	ACSS2, ACSS3, ALDH9A1
Factors Promoting Cardiogenesis in Vertebrates	CER1, FZD5, LEF1, NPPB, TGFB2, TGFBR2, TGFBR3
HIF1α Signaling	CREBBP, EDN1, EP300, KRAS, MAPK8, MDM2, PIK3R1, RRAS
Estrogen Receptor Signaling	CREBBP, EP300, KRAS, MED21, PPARGC1A, RBFOX2, RRAS, SOS2, TAF4B
Sphingomyelin Metabolism	SGMS1, SMPD1
Leptin Signaling in Obesity	ADCY9, NOTUM, PDE3A, PIK3R1, PLCD3, SOCS3
Thio-molybdenum Cofactor Biosynthesis	MOCOS
Ethanol Degradation IV	ACSS2, ACSS3, ALDH9A1
Semaphorin Signaling in Neurons	ARHGEF12, PAK4, PTK2, RHOH, RND3
D-myo-inositol (1, 4, 5)-Trisphosphate Biosynthesis	PIP4K2C, PIP5K1A, PLCD3
Role of JAK family kinases in IL-6-type Cytokine Signaling	IL6R, MAPK8, SOCS3
T Cell Receptor Signaling	CBL, KRAS, MAPK8, PAG1, PIK3R1, RRAS, SOS2
Apelin Liver Signaling Pathway	EDN1, MAPK8, PDGFRB
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	IGF2BP1, NR2F6, NR6A1, SPP1
Human Embryonic Stem Cell Pluripotency	FZD5, LEF1, PDGFRB, PDPK1, PIK3R1, SMAD3, TGFB2, TGFBR2
Iron homeostasis signaling pathway	ATP6V1B2, GDF15, HFE, HJV, IL6R, PDGFRB, SMAD3, TWSG1
Remodeling of Epithelial Adherens Junctions	ACTB, ARPC2, ARPC5, RAB5B, TUBB4A
Glycine Biosynthesis I	SHMT2
Guanine and Guanosine Salvage I	HPRT1
L-cysteine Degradation III	MPST
Thyroid Cancer Signaling	CCND1, KRAS, LEF1, RRAS
Natural Killer Cell Signaling	INPP5B, INPPL1, KRAS, PAK4, PIK3R1, RRAS, SOS2
Gap Junction Signaling	ACTB, ADCY9, GNAI3, KRAS, NOTUM, PIK3R1, PLCD3, RRAS, SOS2, TUBB4A
Th1 and Th2 Activation Pathway	CXCR4, IL6R, IRF1, NOTCH1, PIK3R1, PSEN1, SOCS3, TGFBR2, TGFBR3
Apoptosis Signaling	CASP2, CASP7, KRAS, MAPK8, MCL1, RRAS
Lymphotoxin β Receptor Signaling	CREBBP, EP300, PDPK1, PIK3R1
Reelin Signaling in Neurons	ARHGEF12, CDK5R1, CRKL, MAPK8, PIK3R1
L-carnitine Biosynthesis	ALDH9A1
Methylglyoxal Degradation I	GLO1
N-acetylglucosamine Degradation I	GNPDA1
S-adenosyl-L-methionine Biosynthesis	MAT1A
Tetrahydrobiopterin Biosynthesis I	GCH1
Tetrahydrobiopterin Biosynthesis II	GCH1
Thiosulfate Disproportionation III (Rhodanese)	MPST
Tyrosine Biosynthesis IV	PCBD1
D-myo-inositol (1, 4, 5)-trisphosphate Degradation	INPP5B, INPPL1
RAN Signaling	KPNA2, KPNA5
Cancer Drug Resistance By Drug Efflux	KRAS, MDM2, PIK3R1, RRAS
Cellular Effects of Sildenafil (Viagra)	ACTB, ADCY9, MYLK, NOTUM, PDE3A, PDE4D, PLCD3

1D-myo-inositol Hexakisphosphate Biosynthesis II (Mammalian)	INPP5B, INPPL1
D-myo-inositol (1, 3, 4)-trisphosphate Biosynthesis	INPP5B, INPPL1
Virus Entry via Endocytic Pathways	ACTB, AP2M1, FLNC, KRAS, PIK3R1, RRAS
Hepatic Fibrosis / Hepatic Stellate Cell Activation	CCN2, EDN1, IGFBP4, IL6R, PDGFRB, SERPINE1, SMAD3, TGFB2, TGFBR2
Apelin Muscle Signaling Pathway	PPARGC1A, PRKAA2
GADD45 Signaling	CCND1, GADD45B
TR/RXR Activation	EP300, MDM2, PIK3R1, PPARGC1A, TBL1XR1
G-Protein Coupled Receptor Signaling	ADCY9, CREBBP, DUSP1, GNAI3, KRAS, PDE3A, PDE4D, PDPK1, PIK3R1, RGS2, RRAS, SOS2
Glutathione Redox Reactions II	GSR
N-acetylglucosamine Degradation II	GNPDA1
Phenylalanine Degradation I (Aerobic)	PCBD1
CDP-diacylglycerol Biosynthesis I	AGPAT1, CDS1
Fatty Acid α-oxidation	ALDH9A1, BCO2
Granzyme A Signaling	CREBBP, EP300
Clathrin-mediated Endocytosis Signaling	ACTB, AP2M1, ARPC2, ARPC5, CBL, CD2AP, MDM2, PIK3R1, RAB5B
Ceramide Signaling	KRAS, MAPK8, PIK3R1, RRAS, SMPD1
Endoplasmic Reticulum Stress Pathway	CASP7, MAPK8
tRNA Splicing	PDE3A, PDE4D, TSEN2
Serotonin Receptor Signaling	ADCY9, GCH1, PCBD1
Phosphatidylglycerol Biosynthesis II (Non-plastidic)	AGPAT1, CDS1
Polyamine Regulation in Colon Cancer	KRAS, MAX
Folate Polyglutamylation	SHMT2
Serine Biosynthesis	PHGDH
dTMP De Novo Biosynthesis	SHMT2
Breast Cancer Regulation by Stathmin1	ADCY9, ARHGEF12, GNAI3, KRAS, PIK3R1, RRAS, SOS2, STMN1, TUBB4A
Superpathway of D-myo-inositol (1, 4, 5)-trisphosphate Metabolism	INPP5B, INPPL1
Apelin Pancreas Signaling Pathway	MAPK8, PIK3R1, PRKAA2
Stearate Biosynthesis I (Animals)	ACOT8, ACSL4, DHCR24
GABA Receptor Signaling	ADCY9, ALDH9A1, AP2M1, NSF, SLC6A12
Role of JAK1 and JAK3 in γc Cytokine Signaling	KRAS, PIK3R1, RRAS, SOCS3
Glutathione Redox Reactions I	GPX2, GSR
IL-22 Signaling	MAPK8, SOCS3
Tumoricidal Function of Hepatic Natural Killer Cells	CASP7, M6PR
ATM Signaling	CBX1, CREBBP, GADD45B, MAPK8, MDM2
Adenine and Adenosine Salvage III	HPRT1
Chondroitin and Dermatan Biosynthesis	CHSY1
UDP-N-acetyl-D-glucosamine Biosynthesis II	GFPT1
IL-15 Signaling	KRAS, PIK3R1, PTK2, RRAS
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	EP300, MDM2, YWHAZ
Estrogen-mediated S-phase Entry	CCNA2, CCND1
NAD Salvage Pathway II	NT5E, PXYLP1
Sertoli Cell-Sertoli Cell Junction Signaling	ACTB, BCAR1, DLG1, KRAS, MAPK8, RRAS, TGFBR3, TUBB4A

Protein Ubiquitination Pathway	CBL, CRYAA/CRYAA2, DNAJA1, HSPA13, HSPB8, MDM2, UBE2F, UBE2J1, UBE2L6, USP39, USP53
Superpathway of Cholesterol Biosynthesis	DHCR24, MVK
VDR/RXR Activation	EP300, HR, SPP1, TGFB2
Salvage Pathways of Pyrimidine Deoxyribonucleotides	TK2
IL-17 Signaling	KRAS, MAPK8, PIK3R1, RRAS
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	CCND1, CREBBP, FRZB, FZD5, IL6R, KRAS, LEF1, NOTUM, PIK3R1, PLCD3, RRAS, SOCS3
Role of p14/p19ARF in Tumor Suppression	MDM2, PIK3R1
EGF Signaling	MAPK8, PIK3R1, SOS2
PEDF Signaling	CASP7, KRAS, PIK3R1, RRAS
Folate Transformations I	SHMT2
Leucine Degradation I	BCAT2
Phosphatidylethanolamine Biosynthesis II	ETNK1
UDP-N-acetyl-D-galactosamine Biosynthesis II	GNPDA1
4-1BB Signaling in T Lymphocytes	MAPK8, TNFSF9
Fatty Acid β-oxidation I	ACSL4, SCP2
Circadian Rhythm Signaling	CREBBP, GRIN2D
Glycine Betaine Degradation	SHMT2
DNA Methylation and Transcriptional Repression Signaling	MECP2, MTA2
IL-9 Signaling	PIK3R1, SOCS3
Inhibition of Angiogenesis by TSP1	MAPK8, TGFBR2
Noradrenaline and Adrenaline Degradation	ADH1A, ALDH9A1
Phagosome Maturation	ATP6V1B2, M6PR, NCF2, NSF, RAB5B, TUBB4A
IL-15 Production	EPHA2, ERBB4, IRF1, PDGFRB, PTK2
Acetone Degradation I (to Methylglyoxal)	CYP2C8
Dopamine Degradation	ALDH9A1
Sonic Hedgehog Signaling	GLIS2
TNFR2 Signaling	MAPK8
Thrombopoietin Signaling	KRAS, PIK3R1, RRAS
CD40 Signaling	MAPK8, PIK3R1
Complement System	C1QBP, C8A
Role of PI3K/AKT Signaling in the Pathogenesis of Influenza	CRKL, GNAI3, PIK3R1
Cleavage and Polyadenylation of Pre-mRNA	NUDT21
Guanosine Nucleotides Degradation III	NT5E
IL-17A Signaling in Airway Cells	MAPK8, PIK3R1
Nicotine Degradation II	CYP2C8, UGT2B7
PXR/RXR Activation	CYP2C8, PPARGC1A
Superpathway of Melatonin Degradation	CYP2C8, UGT2B7
Notch Signaling	NOTCH1, PSEN1
α-Adrenergic Signaling	ADCY9, GNAI3, KRAS, RRAS
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	IL11, MAPK8, PIK3R1, PTX3, TGFB2, TNFSF9
Activation of IRF by Cytosolic Pattern Recognition Receptors	CREBBP, MAPK8
Phagosome Formation	NOTUM, PIK3R1, PLCD3, RHOH, RND3
Serotonin Degradation	ADH1A, ALDH9A1, UGT2B7

Docosahexaenoic Acid (DHA) Signaling	PDPK1, PIK3R1
Acyl-CoA Hydrolysis	ACOT8
Bile Acid Biosynthesis, Neutral Pathway	SCP2
Cholesterol Biosynthesis I	DHCR24
Cholesterol Biosynthesis II (via 24, 25-dihydrolanosterol)	DHCR24
Cholesterol Biosynthesis III (via Desmosterol)	DHCR24
Fatty Acid Activation	ACSL4
Mevalonate Pathway I	MVK
NAD Phosphorylation and Dephosphorylation	PXYLP1
Urate Biosynthesis/Inosine 5'-phosphate Degradation	NT5E
Bladder Cancer Signaling	CCND1, KRAS, MDM2, RRAS
Induction of Apoptosis by HIV1	CXCR4, MAPK8
Phospholipases	NOTUM, PLCD3
Lipid Antigen Presentation by CD1	AP2M1
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	CBL, FRZB, FZD5, IL11, LEF1, MAPK8, PIK3R1, SPP1
Melatonin Degradation I	CYP2C8, UGT2B7
Retinoic acid Mediated Apoptosis Signaling	IRF1, TNFRSF10B
SPINK1 Pancreatic Cancer Pathway	SMAD3, TGFBR2
Bupropion Degradation	CYP2C8
IL-17A Signaling in Gastric Cells	MAPK8
Tryptophan Degradation X (Mammalian, via Tryptamine)	ALDH9A1
MSP-RON Signaling Pathway	ACTB, PIK3R1
Isoleucine Degradation I	BCAT2
FXR/RXR Activation	APOH, CREBBP, MAPK8, PPARGC1A
eNOS Signaling	ADCY9, CCNA2, PDPK1, PIK3R1, PRKAA2
Xenobiotic Metabolism Signaling	ALDH9A1, CREBBP, CYP2C8, EP300, KRAS, MAPK8, PIK3R1, PPARGC1A, RRAS, UGT2B7
Cysteine Biosynthesis III (mammalia)	MAT1A
Pyrimidine Ribonucleotides Interconversion	ENTPD7, NUDT15
IL-1 Signaling	ADCY9, GNAI3, MAPK8
IL-12 Signaling and Production in Macrophages	EP300, IRF1, MAPK8, PIK3R1, TGFB2
Melatonin Signaling	GNAI3, NOTUM, PLCD3
Adenosine Nucleotides Degradation II	NT5E
NER Pathway	COPS3, EP300, POLD3, POLE3
Oncostatin M Signaling	KRAS, RRAS
Nicotine Degradation III	CYP2C8, UGT2B7
Basal Cell Carcinoma Signaling	FZD5, GLIS2, LEF1
Caveolar-mediated Endocytosis Signaling	ACTB, FLNC, RAB5B
RANK Signaling in Osteoclasts	CBL, MAPK8, PIK3R1
Role of IL-17A in Arthritis	MAPK8, PIK3R1
Pyrimidine Ribonucleotides De Novo Biosynthesis	ENTPD7, NUDT15
Role of RIG1-like Receptors in Antiviral Innate Immunity	CREBBP, EP300
Methionine Degradation I (to Homocysteine)	MAT1A
Role of Tissue Factor in Cancer	CCN2, KRAS, PIK3R1, RRAS
Androgen Signaling	CCND1, CREBBP, EP300, GNAI3, SMAD3
Systemic Lupus Erythematosus Signaling	C8A, CBL, IL6R, KRAS, LSM14B, PIK3R1, RRAS, SOS2

Tight Junction Signaling	ACTB, MYLK, NSF, NUDT21, TGFB2, TGFBR2
Parkinson's Signaling	MAPK8
Vitamin-C Transport	SLC23A2
Gustation Pathway	ADCY9, P2RY1, PDE3A, PDE4D, SCNN1A
IL-23 Signaling Pathway	PIK3R1, SOCS3
Role of IL-17F in Allergic Inflammatory Airway Diseases	CREBBP, IL11
iNOS Signaling	CREBBP, IRF1
UVB-Induced MAPK Signaling	MAPK8, PIK3R1
Putrescine Degradation III	ALDH9A1
Antioxidant Action of Vitamin C	MAPK8, NOTUM, PLCD3, SLC23A2
PD-1, PD-L1 cancer immunotherapy pathway	PIK3R1, SMAD3, TGFB2, YAP1
Hepatic Cholestasis	ADCY9, ATP8B1, IL11, MAPK8, TGFB2, TNFSF9
Relaxin Signaling	ADCY9, GNAI3, PDE3A, PDE4D, PIK3R1
Dopamine Receptor Signaling	ADCY9, GCH1, PCBD1
Macropinocytosis Signaling	KRAS, PIK3R1, RRAS
Dermatan Sulfate Degradation (Metazoa)	IDS
Histamine Degradation	ALDH9A1
Mitochondrial L-carnitine Shuttle Pathway	ACSL4
Superpathway of Geranylgeranyldiphosphate Biosynthesis I (via Mevalonate)	MVK
γ-linolenate Biosynthesis II (Animals)	ACSL4
Cardiomyocyte Differentiation via BMP Receptors	NPPB
Antiproliferative Role of Somatostatin Receptor 2	KRAS, PIK3R1, RRAS
Role of MAPK Signaling in the Pathogenesis of Influenza	KRAS, MAPK8, RRAS
Amyloid Processing	CDK5R1, PSEN1
NF-κB Activation by Viruses	KRAS, PIK3R1, RRAS
FAT10 Signaling Pathway	SQSTM1
Purine Nucleotides Degradation II (Aerobic)	NT5E
Valine Degradation I	BCAT2
Role of BRCA1 in DNA Damage Response	ACTB, PHF10, SMARCA2
Adipogenesis pathway	FZD5, SMAD3, TBL1XR1
Agranulocyte Adhesion and Diapedesis	ACTB, CXCR4, GNAI3
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	SPP1
April Mediated Signaling	MAPK8
Assembly of RNA Polymerase II Complex	TAF4B
Atherosclerosis Signaling	CXCR4
Autophagy	SQSTM1
B Cell Activating Factor Signaling	MAPK8
BAG2 Signaling Pathway	MDM2
CCR5 Signaling in Macrophages	GNAI3, MAPK8
CD27 Signaling in Lymphocytes	MAPK8
CTLA4 Signaling in Cytotoxic T Lymphocytes	AP2M1, PIK3R1
Calcium Signaling	CREBBP, EP300, GRIN2D
Calcium-induced T Lymphocyte Apoptosis	EP300
Cardiac β-adrenergic Signaling	ADCY9, AKAP12, PDE3A, PDE4D
Cell Cycle Control of Chromosomal Replication	CDK6
Cell Cycle Regulation by BTG Family Proteins	CCND1

Chondroitin Sulfate Biosynthesis	CHSY1
Chondroitin Sulfate Biosynthesis (Late Stages)	CHSY1
Coagulation System	SERPINE1
Corticotropin Releasing Hormone Signaling	ADCY9, ARPC5, CREBBP, GNAI3
Crosstalk between Dendritic Cells and Natural Killer Cells	ACTB
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	CASP7
Dermatan Sulfate Biosynthesis	CHSY1
Estrogen Biosynthesis	CYP2C8
Glutamate Receptor Signaling	GRIN2D
Granulocyte Adhesion and Diapedesis	CXCR4, GNAI3
Gαq Signaling	PIK3R1, RGS2, RHOH, RND3
Gαs Signaling	ADCY9, CREBBP, RGS2
Hematopoiesis from Pluripotent Stem Cells	IL11
Heparan Sulfate Biosynthesis	NOTUM
Heparan Sulfate Biosynthesis (Late Stages)	NOTUM
IL-10 Signaling	MAPK8, SOCS3
Inhibition of Matrix Metalloproteases	TIMP4
Interferon Signaling	IRF1
LXR/RXR Activation	ABCA1, APOH
MIF Regulation of Innate Immunity	MAPK8
Mechanisms of Viral Exit from Host Cells	ACTB
Mitochondrial Dysfunction	ATP5PB, GSR, MAPK8, MT-CO3, PSEN1
Neuroprotective Role of THOP1 in Alzheimer's Disease	TPP1
Nitric Oxide Signaling in the Cardiovascular System	PIK3R1
Nur77 Signaling in T Lymphocytes	EP300
OX40 Signaling Pathway	MAPK8
Oxidative Phosphorylation	ATP5PB, MT-CO3
Primary Immunodeficiency Signaling	UNG
Role of JAK2 in Hormone-like Cytokine Signaling	SOCS3
Role of PKR in Interferon Induction and Antiviral Response	IRF1
Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza	FZD5, LEF1
Superpathway of Methionine Degradation	MAT1A
T Helper Cell Differentiation	IL6R, TGFBR2
TWEAK Signaling	CASP7
Th17 Activation Pathway	IL6R, SOCS3
Thyroid Hormone Metabolism II (via Conjugation and/or Degradation)	UGT2B7
Toll-like Receptor Signaling	MAPK8
Transcriptional Regulatory Network in Embryonic Stem Cells	FOXC1
Triacylglycerol Biosynthesis	AGPAT1
Triacylglycerol Degradation	NOTUM
Type I Diabetes Mellitus Signaling	IRF1, MAPK8, SOCS3
Unfolded protein response	MAPK8
iCOS-iCOSL Signaling in T Helper Cells	PDPK1, PIK3R1
nNOS Signaling in Neurons	GRIN2D

tRNA Charging	LARS2

Table 17 - HEP3B liver cancer downregulated pathways and associated genes

Pathway Name	**Gene**
Rac Signaling	ABI2, ARPC2, ARPC5, CDK5R1, ELK4, KRAS, MAPK8, NCF2, PAK4, PIK3R1, PIP4K2C, PIP5K1A, PTK2, RRAS
RhoA Signaling	ACTB, ARHGEF12, ARPC2, ARPC5, CDC42EP2, CDC42EP3, CDC42EP4, DLC1, MYLK, NRP2, PIP4K2C, PIP5K1A, PTK2, RND3
Neuregulin Signaling	CDK5R1, CRKL, ERBB4, ERBIN, GRB7, KRAS, PDPK1, PIK3R1, PSEN1, RPS6KB2, RRAS, SOS2
Ephrin Receptor Signaling	ARPC2, ARPC5, BCAR1, CREBBP, CRKL, CXCR4, EFNA4, EFNB1, EFNB2, EPHA2, GNAI3, GRIN2D, KRAS, PAK4, PTK2, RRAS, SOS2
IGF-1 Signaling	CCN2, IGFBP4, KRAS, MAPK8, PDPK1, PIK3R1, PTK2, RPS6KB2, RRAS, SOCS3, SOS2, YWHAZ
Integrin Signaling	ACTB, ARF3, ARPC2, ARPC5, BCAR1, CRKL, GRB7, KRAS, MAPK8, MYLK, NEDD9, PAK4, PIK3R1, PTK2, RHOH, RND3, RRAS, SOS2
Agrin Interactions at Neuromuscular Junction	ACTB, ERBB4, GABPA, GABPB1, KRAS, LAMC1, MAPK8, PAK4, PTK2, RRAS
Signaling by Rho Family GTPases	ACTB, ARHGEF12, ARPC2, ARPC5, CDC42EP2, CDC42EP3, CDC42EP4, GNAI3, MAPK8, MYLK, NCF2, PAK4, PIK3R1, PIP4K2C, PIP5K1A, PTK2, RHOH, RND3, STMN1
Glioblastoma Multiforme Signaling	CCND1, CDK6, FZD5, KRAS, LEF1, MDM2, NF1, NOTUM, PDGFRB, PIK3R1, PLCD3, RHOH, RND3, RRAS, SOS2
PI3K/AKT Signaling	CCND1, GDF15, INPP5B, INPPL1, KRAS, MCL1, MDM2, PDPK1, PIK3R1, RPS6KB2, RRAS, SOS2, YWHAZ
Sphingosine-1-phosphate Signaling	ADCY9, CASP2, CASP7, GNAI3, NOTUM, PDGFRB, PIK3R1, PLCD3, PTK2, RHOH, RND3, SMPD1
Insulin Receptor Signaling	CBL, CRKL, INPP5B, INPPL1, KRAS, MAPK8, PDPK1, PIK3R1, RPS6KB2, RRAS, SCNN1A, SOCS3, SOS2
Aldosterone Signaling in Epithelial Cells	CRYAA/CRYAA2, DNAJA1, DUSP1, HSPA13, HSPB8, KRAS, NOTUM, PDPK1, PIK3R1, PIP4K2C, PIP5K1A, PLCD3, SCNN1A, SOS2
TGF-β Signaling	CREBBP, EP300, KRAS, MAPK8, RRAS, SERPINE1, SMAD3, SOS2, TGFB2, TGFBR2
Prolactin Signaling	CREBBP, EP300, IRF1, KRAS, PDPK1, PIK3R1, RRAS, SOCS3, SOS2
Superpathway of Inositol Phosphate Compounds	DUSP1, DUSP16, HACD2, INPP5B, INPPL1, NUDT15, NUDT4, PIK3R1, PIP4K2C, PIP5K1A, PLCD3, PPM1K, PPTC7, PXYLP1, SOCS3
ErbB4 Signaling	ERBB4, KRAS, PDPK1, PIK3R1, PSEN1, RRAS, SOS2, YAP1
PDGF Signaling	CRKL, INPP5B, INPPL1, KRAS, MAPK8, PDGFRB, PIK3R1, RRAS, SOS2
3-phosphoinositide Biosynthesis	DUSP1, DUSP16, HACD2, INPP5B, NUDT15, NUDT4, PIK3R1, PIP4K2C, PIP5K1A, PPM1K, PPTC7, PXYLP1, SOCS3

Acute Myeloid Leukemia Signaling	CCND1, IDH1, IDH2, KRAS, LEF1, PIK3R1, RPS6KB2, RRAS, SOS2
CXCR4 Signaling	ADCY9, BCAR1, CXCR4, ELMO2, GNAI3, KRAS, MAPK8, PAK4, PIK3R1, PTK2, RHOH, RND3, RRAS
Glioma Signaling	CCND1, CDK6, IDH1, IDH2, KRAS, MDM2, PDGFRB, PIK3R1, RRAS, SOS2
HGF Signaling	CCND1, CRKL, ELF4, ETS1, KRAS, MAPK8, PIK3R1, PTK2, RRAS, SOS2
Regulation of Actin-based Motility by Rho	ACTB, ARPC2, ARPC5, MYLK, PAK4, PIP4K2C, PIP5K1A, RHOH, RND3
ERK/MAPK Signaling	BCAR1, CREBBP, CRKL, DUSP1, ELF4, ETS1, KRAS, MYCN, PAK4, PIK3R1, PTK2, RRAS, SOS2, YWHAZ
Wnt/β-catenin Signaling	APPL1, CCND1, CREBBP, EP300, FRZB, FZD5, LEF1, MDM2, SOX5, TGFB2, TGFBR2, TGFBR3, TLE4
Endometrial Cancer Signaling	CCND1, KRAS, LEF1, PDPK1, PIK3R1, RRAS, SOS2
Actin Cytoskeleton Signaling	ABI2, ACTB, ARHGEF12, ARPC2, ARPC5, BCAR1, CRKL, KRAS, MYLK, PAK4, PIK3R1, PIP5K1A, PTK2, RRAS, SOS2
D-myo-inositol-5-phosphate Metabolism	DUSP1, DUSP16, HACD2, INPP5B, NUDT15, NUDT4, PIP4K2C, PLCD3, PPM1K, PPTC7, PXYLP1, SOCS3
PAK Signaling	KRAS, MAPK8, MYLK, PAK4, PDGFRB, PIK3R1, PTK2, RRAS, SOS2
Renal Cell Carcinoma Signaling	CREBBP, EP300, ETS1, KRAS, PAK4, PIK3R1, RRAS, SOS2
B Cell Receptor Signaling	CREBBP, ETS1, INPP5B, INPPL1, KRAS, MAPK8, PAG1, PDPK1, PIK3R1, PTK2, RPS6KB2, RRAS, SOS2
Colorectal Cancer Metastasis Signaling	ADCY9, APPL1, CCND1, FZD5, IL6R, KRAS, LEF1, MAPK8, PIK3R1, RHOH, RND3, RRAS, SMAD3, SOS2, TGFB2, TGFBR2
Protein Kinase A Signaling	ADCY9, AKAP12, CDC14B, CREBBP, DUSP1, DUSP16, FLNC, GNAI3, HHAT, LEF1, MYLK, NOTUM, PDE3A, PDE4D, PLCD3, PTK2, PTPN9, PTPRA, SMAD3, TGFB2, TGFBR2, YWHAZ
AMPK Signaling	ACTB, CAB39, CCNA2, CCND1, CREBBP, EP300, PDPK1, PFKFB4, PHF10, PIK3R1, PPARGC1A, PPM1K, PRKAA2, SMARCA2
14-3-3-mediated Signaling	CBL, KRAS, MAPK8, NOTUM, PIK3R1, PLCD3, RRAS, TUBB4A, YAP1, YWHAZ
Actin Nucleation by ARP-WASP Complex	ARPC2, ARPC5, KRAS, RHOH, RND3, RRAS, SOS2
Pancreatic Adenocarcinoma Signaling	CCND1, KRAS, MAPK8, MDM2, NOTCH1, PIK3R1, SMAD3, TGFB2, TGFBR2
Paxillin Signaling	ACTB, BCAR1, KRAS, MAPK8, PAK4, PIK3R1, PTK2, RRAS, SOS2
Cardiac Hypertrophy Signaling	ADCY9, CREBBP, EP300, GNAI3, IL6R, KRAS, MAPK8, NOTUM, PIK3R1, PLCD3, RHOH, RND3, RRAS, TGFB2, TGFBR2
Synaptogenesis Signaling Pathway	ADCY9, AP2M1, ARPC2, ARPC5, CREBBP, CRKL, EFNA4, EFNB1, EFNB2, EPHA2, GRIN2D, KRAS, NSF, PIK3R1, RAB5B, RPS6KB2, RRAS, SOS2

Non-Small Cell Lung Cancer Signaling	CCND1, CDK6, KRAS, PDPK1, PIK3R1, RRAS, SOS2
3-phosphoinositide Degradation	DUSP1, DUSP16, HACD2, INPP5B, INPPL1, NUDT15, NUDT4, PPM1K, PPTC7, PXYLP1, SOCS3
Glioma Invasiveness Signaling	KRAS, PIK3R1, PTK2, RHOH, RND3, RRAS, TIMP4
STAT3 Pathway	IL17RD, IL6R, KRAS, MAPK8, PDGFRB, RRAS, SOCS3, TGFB2, TGFBR2, TGFBR3
NGF Signaling	CREBBP, KRAS, MAPK8, PDPK1, PIK3R1, RPS6KB2, RRAS, SMPD1, SOS2
ErbB Signaling	ERBB4, KRAS, MAPK8, PAK4, PDPK1, PIK3R1, RRAS, SOS2
Melanocyte Development and Pigmentation Signaling	ADCY9, CREBBP, EP300, KRAS, PIK3R1, RPS6KB2, RRAS, SOS2
GDNF Family Ligand-Receptor Interactions	DOK7, GFRA3, KRAS, MAPK8, PIK3R1, RRAS, SOS2
Neurotrophin/TRK Signaling	CREBBP, KRAS, MAPK8, PDPK1, PIK3R1, RRAS, SOS2
Apelin Endothelial Signaling Pathway	ADCY9, GNAI3, KRAS, MAPK8, PIK3R1, PRKAA2, RPS6KB2, RRAS, SMAD3
UVA-Induced MAPK Signaling	KRAS, MAPK8, NOTUM, PIK3R1, PLCD3, RPS6KB2, RRAS, SMPD1
D-myo-inositol (1, 4, 5, 6)-Tetrakisphosphate Biosynthesis	DUSP1, DUSP16, HACD2, INPP5B, NUDT15, NUDT4, PPM1K, PPTC7, PXYLP1, SOCS3
D-myo-inositol (3, 4, 5, 6)-tetrakisphosphate Biosynthesis	DUSP1, DUSP16, HACD2, INPP5B, NUDT15, NUDT4, PPM1K, PPTC7, PXYLP1, SOCS3
Thrombin Signaling	ADCY9, ARHGEF12, GNAI3, KRAS, MYLK, NOTUM, PDPK1, PIK3R1, PLCD3, PTK2, RHOH, RND3, RRAS
Apelin Adipocyte Signaling Pathway	ADCY9, GNAI3, GPX2, MAPK8, NCF2, PPARGC1A, PRKAA2
Cardiac Hypertrophy Signaling (Enhanced)	ADCY9, DLG1, EDN1, EP300, FZD5, GNAI3, IL11, IL17RD, IL6R, KRAS, MAPK8, NOTUM, NPPB, PDE3A, PDE4D, PIK3R1, PLCD3, PTK2, RPS6KB2, RRAS, TGFB2, TGFBR2, TGFBR3, TNFSF9
FAT10 Cancer Signaling Pathway	CXCR4, SMAD3, TGFB2, TGFBR2, TGFBR3
Osteoarthritis Pathway	CASP2, CASP7, CREBBP, FRZB, FZD5, GLIS2, LEF1, NOTCH1, PPARGC1A, PRKAA2, SMAD3, SPP1, TGFBR2
SAPK/JNK Signaling	CRKL, KRAS, MAP4K5, MAPK8, MINK1, PIK3R1, RRAS, SOS2
NRF2-mediated Oxidative Stress Response	ACTB, CREBBP, DNAJA1, EP300, GPX2, GSR, HSPB8, KRAS, MAPK8, PIK3R1, RRAS, SQSTM1
FLT3 Signaling in Hematopoietic Progenitor Cells	CBL, CREBBP, KRAS, PDPK1, PIK3R1, RRAS, SOS2
Mouse Embryonic Stem Cell Pluripotency	CREBBP, FZD5, ID3, KRAS, LEF1, PIK3R1, RRAS, SOS2
Role of NFAT in Cardiac Hypertrophy	ADCY9, EP300, GNAI3, IL11, KRAS, MAPK8, NOTUM, PIK3R1, PLCD3, RRAS, SOS2, TGFB2, TGFBR2
ErbB2-ErbB3 Signaling	CCND1, KRAS, PDPK1, PIK3R1, RRAS, SOS2
Ethanol Degradation II	ACSS2, ACSS3, ADH1A, ALDH9A1
P2Y Purigenic Receptor Signaling Pathway	ADCY9, CREBBP, GNAI3, KRAS, NOTUM, P2RY1, PIK3R1, PLCD3, RRAS

Telomerase Signaling	ELF4, ETS1, KRAS, PDPK1, PIK3R1, RRAS, SOS2, TPP1
p70S6K Signaling	GNAI3, KRAS, NOTUM, PDPK1, PIK3R1, PLCD3, RRAS, SOS2, YWHAZ
Leukocyte Extravasation Signaling	ACTB, BCAR1, CRKL, CXCR4, DLC1, GNAI3, MAPK8, NCF2, PIK3R1, PTK2, RHOH, TIMP4
Melanoma Signaling	CCND1, KRAS, MDM2, PIK3R1, RRAS
GM-CSF Signaling	CCND1, ETS1, KRAS, PIK3R1, RRAS, SOS2
ERK5 Signaling	CREBBP, ELK4, KRAS, RPS6KB2, RRAS, YWHAZ
Ephrin B Signaling	CBL, CXCR4, EFNB1, EFNB2, GNAI3, PTK2
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	ACTB, ARPC2, ARPC5, CBL, PIK3R1, PIP5K1A, RPS6KB2
Endocannabinoid Developing Neuron Pathway	ADCY9, CCND1, CREBBP, GNAI3, KRAS, MAPK8, PIK3R1, RRAS
Endothelin-1 Signaling	ADCY9, CASP2, CASP7, EDN1, GNAI3, KRAS, MAPK8, NOTUM, PIK3R1, PLCD3, RRAS
Fc Epsilon RI Signaling	INPP5B, INPPL1, KRAS, MAPK8, PDPK1, PIK3R1, RRAS, SOS2
Angiopoietin Signaling	GRB7, KRAS, PAK4, PIK3R1, PTK2, RRAS
Tec Kinase Signaling	ACTB, GNAI3, MAPK8, PAK4, PIK3R1, PTK2, RHOH, RND3, TNFRSF10B, TNFRSF21
Cholecystokinin/Gastrin-mediated Signaling	BCAR1, KRAS, MAPK8, PTK2, RHOH, RND3, RRAS, SOS2
Renin-Angiotensin Signaling	ADCY9, KRAS, MAPK8, PAK4, PIK3R1, PTK2, RRAS, SOS2
HMGB1 Signaling	IL11, KRAS, MAPK8, PIK3R1, RHOH, RND3, RRAS, SERPINE1, TGFB2, TNFSF9
Aryl Hydrocarbon Receptor Signaling	ALDH9A1, CCNA2, CCND1, CDK6, EP300, MAPK8, MDM2, TGFB2, TGM2
ILK Signaling	ACTB, CCND1, CREBBP, FLNC, LEF1, MAPK8, PDPK1, PIK3R1, PTK2, RHOH, RND3
IL-7 Signaling Pathway	CCND1, MCL1, PDPK1, PIK3R1, PTK2, SOS2
Chemokine Signaling	CXCR4, GNAI3, KRAS, MAPK8, PTK2, RRAS
IL-6 Signaling	IL6R, KRAS, MAPK8, MCL1, PIK3R1, RRAS, SOCS3, SOS2
Adrenomedullin signaling pathway	ADCY9, KRAS, MAPK8, MAX, MYLK, NOTUM, PIK3R1, PLCD3, PTK2, RRAS, SOS2
PPAR Signaling	CREBBP, EP300, KRAS, PDGFRB, PPARGC1A, RRAS, SOS2
IL-2 Signaling	KRAS, MAPK8, PIK3R1, RRAS, SOS2
Acute Phase Response Signaling	APOH, IL6R, KRAS, MAPK8, PDPK1, PIK3R1, RRAS, SERPINE1, SOCS3, SOS2
CDK5 Signaling	ADCY9, CABLES1, CDK5R1, KRAS, LAMC1, MAPK8, RRAS
Pyridoxal 5'-phosphate Salvage Pathway	CDK6, FAM20B, MAPK8, PDXK, PRKAA2
PFKFB4 Signaling Pathway	CREBBP, HK2, PFKFB4, TGFB2
CREB Signaling in Neurons	ADCY9, CREBBP, EP300, GNAI3, GRIN2D, KRAS, NOTUM, PIK3R1, PLCD3, RRAS, SOS2
Huntington's Disease Signaling	ATP5PB, CASP2, CASP7, CDK5R1, CREBBP, EP300, MAPK8, NSF, PDPK1, PIK3R1, SOS2, TGM2
Death Receptor Signaling	ACTB, CASP2, CASP7, MAPK8, TNFRSF10B, TNFRSF21
Ovarian Cancer Signaling	CCND1, EDN1, FZD5, KRAS, LEF1, PIK3R1, RPS6KB2, RRAS

fMLP Signaling in Neutrophils	ARPC2, ARPC5, GNAI3, KRAS, NCF2, PIK3R1, RRAS
TNFR1 Signaling	CASP2, CASP7, MAPK8, PAK4
Small Cell Lung Cancer Signaling	CCND1, CDK6, MAX, PIK3R1, PTK2
UVC-Induced MAPK Signaling	KRAS, MAPK8, RRAS, SMPD1
GNRH Signaling	ADCY9, CREBBP, GNAI3, KRAS, MAPK8, PAK4, PTK2, RRAS, SOS2
Estrogen-Dependent Breast Cancer Signaling	CCND1, CREBBP, KRAS, PIK3R1, RRAS
IL-8 Signaling	CCND1, GNAI3, KRAS, MAPK8, NCF2, PIK3R1, PTK2, RHOH, RND3, RRAS
FcγRIIB Signaling in B Lymphocytes	KRAS, MAPK8, PDPK1, PIK3R1, RRAS
Apelin Cardiomyocyte Signaling Pathway	GNAI3, MAPK8, MYLK, NOTUM, PIK3R1, PLCD3
VEGF Signaling	ACTB, KRAS, PIK3R1, PTK2, RRAS, SOS2
Synaptic Long Term Potentiation	CREBBP, EP300, GRIN2D, KRAS, NOTUM, PLCD3, RRAS
NF-κB Signaling	CREBBP, EP300, KRAS, MAPK8, PDGFRB, PIK3R1, RRAS, TGFBR2, TGFBR3
JAK/Stat Signaling	KRAS, PIK3R1, RRAS, SOCS3, SOS2
Sirtuin Signaling Pathway	ABCA1, ACSS2, ATP5PB, GABARAPL1, GABPA, GABPB1, GADD45B, IDH2, MYCN, PPARGC1A, PRKAA2, SCNN1A, TOMM20
mTOR Signaling	EIF4B, KRAS, PDPK1, PIK3R1, PRKAA2, RHOH, RND3, RPS17, RPS6KB2, RRAS
CNTF Signaling	KRAS, PIK3R1, RPS6KB2, RRAS
PCP pathway	EFNB1, FZD5, LGR4, MAPK8
FGF Signaling	CREBBP, CRKL, MAPK8, PIK3R1, SOS2
VEGF Family Ligand-Receptor Interactions	KRAS, NRP2, PIK3R1, RRAS, SOS2
Wnt/Ca+ pathway	CREBBP, FZD5, NOTUM, PLCD3
PI3K Signaling in B Lymphocytes	CBL, KRAS, NOTUM, PDPK1, PIK3R1, PLCD3, RRAS
Th2 Pathway	CXCR4, NOTCH1, PIK3R1, PSEN1, SOCS3, TGFBR2, TGFBR3
EIF2 Signaling	ACTB, CCND1, KRAS, MYCN, PDPK1, PIK3R1, RPL27A, RPS17, RRAS, SOS2
Type II Diabetes Mellitus Signaling	ACSL4, MAPK8, PDPK1, PIK3R1, PRKAA2, SMPD1, SOCS3
p38 MAPK Signaling	CREBBP, DUSP1, MAX, RPS6KB2, TGFB2, TGFBR2
Phospholipase C Signaling	ADCY9, ARHGEF12, CREBBP, EP300, KRAS, PLCD3, RHOH, RND3, RRAS, SOS2, TGM2
T Cell Exhaustion Signaling Pathway	IL6R, KRAS, MAPK8, PIK3R1, RRAS, SMAD3, TGFBR2, TGFBR3
SPINK1 General Cancer Pathway	IL6R, KRAS, PIK3R1, RRAS
Th1 Pathway	IL6R, IRF1, NOTCH1, PIK3R1, PSEN1, SOCS3
Growth Hormone Signaling	PDPK1, PIK3R1, RPS6KB2, SOCS3
CCR3 Signaling in Eosinophils	GNAI3, KRAS, MYLK, PAK4, PIK3R1, RRAS
Endocannabinoid Neuronal Synapse Pathway	ADCY9, GNAI3, GRIN2D, MAPK8, NOTUM, PLCD3
Systemic Lupus Erythematosus In T Cell Signaling Pathway	CASP2, CASP7, CBL, CREBBP, GNAI3, KRAS, PIK3R1, PTK2, RHOH, RND3, RPS6KB2, RRAS, SOS2
Opioid Signaling Pathway	ADCY9, AP2M1, CREBBP, EP300, GNAI3, GRIN2D, KRAS, RPS6KB2, RRAS, SOS2
IL-3 Signaling	CRKL, KRAS, PIK3R1, RRAS
Cyclins and Cell Cycle Regulation	CCNA2, CCND1, CDK6, TGFB2

LPS-stimulated MAPK Signaling	KRAS, MAPK8, PIK3R1, RRAS
BMP signaling pathway	CREBBP, KRAS, MAPK8, RRAS
Neuroinflammation Signaling Pathway	CREBBP, GRIN2D, IL6R, MAPK8, NCF2, PIK3R1, PSEN1, SLC6A12, TGFB2, TGFBR2, TGFBR3
GP6 Signaling Pathway	LAMC1, LAMC2, PDPK1, PIK3R1, PTK2
Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency	FZD5, KRAS, PIK3R1, RRAS, SOS2
CD28 Signaling in T Helper Cells	ARPC2, ARPC5, MAPK8, PDPK1, PIK3R1
G Beta Gamma Signaling	GNAI3, KRAS, PDPK1, RRAS, SOS2
Gαi Signaling	ADCY9, GNAI3, KRAS, RRAS, SOS2
Salvage Pathways of Pyrimidine Ribonucleotides	CDK6, FAM20B, MAPK8, PRKAA2
Regulation of eIF4 and p70S6K Signaling	KRAS, PDPK1, PIK3R1, RPS17, RRAS, SOS2
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	CREBBP, IRF1, MAPK8, NCF2, PIK3R1, RHOH, RND3
Amyotrophic Lateral Sclerosis Signaling	CASP7, GRIN2D, PIK3R1, RAB5B
Sperm Motility	EPHA2, ERBB4, NOTUM, NPPB, PDE4D, PDGFRB, PLCD3, PTK2
Gα12/13 Signaling	KRAS, MAPK8, PIK3R1, PTK2, RRAS
Dopamine-DARPP32 Feedback in cAMP Signaling	ADCY9, CREBBP, GNAI3, GRIN2D, NOTUM, PLCD3
Neuropathic Pain Signaling In Dorsal Horn Neurons	GRIN2D, NOTUM, PIK3R1, PLCD3
cAMP-mediated signaling	ADCY9, AKAP12, CREBBP, DUSP1, GNAI3, PDE3A, PDE4D, RGS2
PKCθ Signaling in T Lymphocytes	KRAS, MAPK8, PIK3R1, RRAS, SOS2
Cdc42 Signaling	ARPC2, ARPC5, CDC42EP2, MAPK8, MYLK, PAK4
GPCR-Mediated Nutrient Sensing in Enteroendocrine Cells	ADCY9, GNAI3, NOTUM, PLCD3
Dendritic Cell Maturation	CREBBP, MAPK8, NOTUM, PIK3R1, PLCD3
LPS/IL-1 Mediated Inhibition of RXR Function	ABCA1, ACSL4, ALDH9A1, CYP2C8, MAPK8, PPARGC1A
Role of NFAT in Regulation of the Immune Response	GNAI3, KRAS, PIK3R1, RRAS, SOS2
Synaptic Long Term Depression	GNAI3, KRAS, NOTUM, PLCD3, RRAS

Table 18 – HUH7 liver cancer upregulated pathways and associated genes

Pathway Name	**Gene**
Role of CHK Proteins in Cell Cycle Checkpoint Control	BRCA1, CDC25A, CDK1, CDK2, CHEK1, CLSPN, E2F1, E2F2, E2F7, E2F8, MDC1, PCNA, PLK1, PPP2R2B, RAD17, RFC2, RFC3
Cell Cycle: G1/S Checkpoint Regulation	CCND1, CCNE2, CDC25A, CDK2, CDK6, CDKN2C, E2F1, E2F2, E2F7, E2F8, MAX, MDM2, RBL1, TFDP1
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	BRCA1, CCNB1, CDK1, CHEK1, MDM2, PKMYT1, PLK1, TOP2A, YWHAZ
PTEN Signaling	CASP9, CCND1, INPPL1, KRAS, MAGI3, PDGFRB, PDPK1, PTK2, RAC2, RPS6KB2, SOS2, TGFBR3
Sumoylation Pathway	ETS1, MAPK8, MDM2, MYB, PCNA, RAC2, RCC1, RFC2, RFC3
Endocannabinoid Cancer Inhibition Pathway	ADCY9, ATF3, CASP2, CASP9, CCND1, CCNE2, LEF1, PTK2, SMPD1, TCF4
PPAR Signaling	KRAS, NR0B2, PDGFRB, SOS2

AMPK Signaling	CCNA2, CCND1, CHRNA5, PDPK1, PFKP, PHLPP2, PPAT, PPP2R2B
RhoGDI Signaling	ARHGEF12, ARHGEF5, ARPC2, ARPC5, PAK4, PIP4K2C, RAC2
Huntington's Disease Signaling	ATP5PB, CASP2, CASP9, MAPK8, NSF, PDPK1, POLR2D, SOS2
PPARα/RXRα Activation	ADCY9, KRAS, MAPK8, NR0B2, SOS2, TGFBR3

Table 19 - HUH7 liver cancer aberrant pathways and associated genes

Pathway Name	**Gene**
Cell Cycle Control of Chromosomal Replication	CDC45, CDC6, CDK1, CDK2, CDK6, CDT1, DNA2, LIG1, MCM2, MCM3, MCM4, MCM5, MCM6, MCM7, ORC1, PCNA, POLA1, POLA2, POLE, PRIM1, TOP2A
Hereditary Breast Cancer Signaling	BLM, BRCA1, BRCA2, CCNB1, CCND1, CDK1, CDK6, CHEK1, E2F1, FANCD2, FANCE, FANCG, H2AFX, KRAS, MSH2, POLR2D, RAD51, RFC2, RFC3, TUBG1
GADD45 Signaling	BRCA1, CCNB1, CCND1, CCNE2, CDK1, CDK2, PCNA
Mismatch Repair in Eukaryotes	EXO1, FEN1, MSH2, PCNA, RFC2, RFC3
Molecular Mechanisms of Cancer	ADCY9, APH1B, ARHGEF12, ARHGEF5, BRCA1, CASP9, CCND1, CCNE2, CDC25A, CDK1, CDK2, CDK6, CDKN2C, CHEK1, E2F1, E2F2, E2F7, E2F8, FANCD2, KRAS, LEF1, MAPK8, MAX, MDM2, PAK4, PTK2, RAC2, RBL1, SOS2, TCF4, TFDP1
DNA damage-induced 14-3-3σ Signaling	BRCA1, CCNB1, CCNE2, CDK1, CDK2, RAD17
Glioma Signaling	CCND1, CDK6, CDKN2C, E2F1, E2F2, E2F7, E2F8, IDH2, KRAS, MDM2, PDGFRB, RBL1, SOS2, TFDP1
DNA Double-Strand Break Repair by Homologous Recombination	BRCA1, BRCA2, LIG1, POLA1, RAD51
Breast Cancer Regulation by Stathmin1	ADCY9, ARHGEF12, ARHGEF5, CCNE2, CDK1, CDK2, E2F1, E2F2, E2F7, E2F8, KRAS, PPP2R2B, SOS2, STMN1, TUBA1A, TUBA1B, TUBA4A, TUBB4B, TUBG1
Chronic Myeloid Leukemia Signaling	CCND1, CDK6, CRKL, E2F1, E2F2, E2F7, E2F8, KRAS, MDM2, RBL1, SOS2, TFDP1
Prostate Cancer Signaling	CASP9, CCND1, CCNE2, CDK2, E2F1, KRAS, LEF1, MDM2, PDPK1, SOS2, TFDP1
dTMP De Novo Biosynthesis	DHFR, SHMT2, TYMS
BER pathway	FEN1, LIG1, PCNA, POLE
Guanine and Guanosine Salvage I	HPRT1, PNP
Remodeling of Epithelial Adherens Junctions	ARPC2, ARPC5, RAB5B, TUBA1A, TUBA1B, TUBA4A, TUBB4B, TUBG1
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	BRCA1, CCNF, IGF2BP1, NR2F6, NR6A1, SPP1
Acetate Conversion to Acetyl-CoA	ACSS2, ACSS3
Phenylalanine Degradation I (Aerobic)	PCBD1, QDPR
Regulation of Cellular Mechanics by Calpain Protease	CCNA2, CCND1, CDK1, CDK2, CDK6, KRAS, PTK2
Bile Acid Biosynthesis, Neutral Pathway	AKR1C1/AKR1C2, BAAT, SCP2
HER-2 Signaling in Breast Cancer	CASP9, CCND1, CCNE2, CDK6, ITGB8, KRAS, MDM2, SOS2

Ovarian Cancer Signaling	BRCA1, BRCA2, CCND1, E2F1, KRAS, LEF1, MSH2, RAD51, RPS6KB2, TCF4, TFDP1
Folate Polyglutamylation	MTHFD1, SHMT2
Adenine and Adenosine Salvage III	HPRT1, PNP
Granzyme B Signaling	CASP9, LMNB1, LMNB2
Epithelial Adherens Junction Signaling	ARPC2, ARPC5, KRAS, LEF1, TCF4, TGFBR3, TUBA1A, TUBA1B, TUBA4A, TUBB4B, TUBG1
Germ Cell-Sertoli Cell Junction Signaling	KRAS, MAP3K3, MAPK8, PAK4, PDPK1, PTK2, RAC2, TUBA1A, TUBA1B, TUBA4A, TUBB4B, TUBG1
Oxidative Ethanol Degradation III	ACSS2, ACSS3, ALDH9A1
Sphingomyelin Metabolism	SGMS1, SMPD1
Thyroid Cancer Signaling	CCND1, CXCL12, KRAS, LEF1, TCF4
Thio-molybdenum Cofactor Biosynthesis	MOCOS
Xanthine and Xanthosine Salvage	PNP
Folate Transformations I	MTHFD1, SHMT2
Polyamine Regulation in Colon Cancer	KRAS, MAX, TCF4
Factors Promoting Cardiogenesis in Vertebrates	CCNE2, CDC6, CDK2, DKK1, LEF1, TCF4, TGFBR3
Ethanol Degradation IV	ACSS2, ACSS3, ALDH9A1
Glycine Betaine Degradation	BHMT, SHMT2
Role of JAK family kinases in IL-6-type Cytokine Signaling	IL6R, MAPK8, OSMR
Antiproliferative Role of TOB in T Cell Signaling	CCNA2, CCNE2, CDK2
Guanosine Nucleotides Degradation III	NT5E, PNP
Adenine and Adenosine Salvage I	PNP
Glycine Biosynthesis I	SHMT2
L-cysteine Degradation III	MPST
Stearate Biosynthesis I (Animals)	ACOT11, ACOT8, DHCR24, ELOVL2
Acyl-CoA Hydrolysis	ACOT11, ACOT8
Cholesterol Biosynthesis I	DHCR24, LBR
Cholesterol Biosynthesis II (via 24, 25-dihydrolanosterol)	DHCR24, LBR
Cholesterol Biosynthesis III (via Desmosterol)	DHCR24, LBR
Urate Biosynthesis/Inosine 5'-phosphate Degradation	NT5E, PNP
Myc Mediated Apoptosis Signaling	CASP9, KRAS, MAPK8, SOS2, YWHAZ
14-3-3-mediated Signaling	KRAS, MAPK8, TUBA1A, TUBA1B, TUBA4A, TUBB4B, TUBG1, YWHAZ
Androgen Biosynthesis	HSD17B3, SRD5A2
Sonic Hedgehog Signaling	CCNB1, CDK1, DYRK1B
Adenosine Nucleotides Degradation II	NT5E, PNP
Ethanol Degradation II	ACSS2, ACSS3, ALDH9A1
5-aminoimidazole Ribonucleotide Biosynthesis I	PPAT
L-carnitine Biosynthesis	ALDH9A1
Methionine Salvage II (Mammalian)	BHMT
Methylglyoxal Degradation I	GLO1
N-acetylglucosamine Degradation I	GNPDA1
Thiosulfate Disproportionation III (Rhodanese)	MPST
Tyrosine Biosynthesis IV	PCBD1
Parkinson's Signaling	CASP9, MAPK8
DNA Methylation and Transcriptional Repression Signaling	DNMT1, HIST4H4, MTA2

Sertoli Cell-Sertoli Cell Junction Signaling	KRAS, MAP3K3, MAPK8, PRKG2, TGFBR3, TUBA1A, TUBA1B, TUBA4A, TUBB4B, TUBG1
Sphingosine-1-phosphate Signaling	ADCY9, CASP2, CASP9, PDGFRB, PTK2, RAC2, SMPD1
Bladder Cancer Signaling	CCND1, E2F1, FGF19, KRAS, MDM2, TFDP1
UVA-Induced MAPK Signaling	CASP9, KRAS, MAPK8, PARP14, RPS6KB2, SMPD1
1D-myo-inositol Hexakisphosphate Biosynthesis II (Mammalian)	INPPL1, ITPKA
D-myo-inositol (1, 3, 4)-trisphosphate Biosynthesis	INPPL1, ITPKA
Purine Nucleotides Degradation II (Aerobic)	NT5E, PNP
Dopamine Receptor Signaling	ADCY9, PCBD1, PPP2R2B, PRL, QDPR
Arsenate Detoxification I (Glutaredoxin)	PNP
Glutathione Redox Reactions II	GSR
N-acetylglucosamine Degradation II	GNPDA1
PRPP Biosynthesis I	PRPS2
Granzyme A Signaling	HIST1H1E, HMGB2
Phagosome Maturation	CTSK, NSF, RAB5B, TUBA1A, TUBA1B, TUBA4A, TUBB4B, TUBG1
Semaphorin Signaling in Neurons	ARHGEF12, PAK4, PTK2, RAC2
Tetrahydrofolate Salvage from 5, 10-methenyltetrahydrofolate	MTHFD1
PCP pathway	CTHRC1, JUND, LGR4, MAPK8
Endoplasmic Reticulum Stress Pathway	CASP9, MAPK8
TR/RXR Activation	AKR1C1/AKR1C2, MDM2, NRGN, PFKP, TBL1XR1
tRNA Splicing	PDE3A, PDE4D, PLD6
Oncostatin M Signaling	KRAS, OSMR, PLAU
Serotonin Receptor Signaling	ADCY9, PCBD1, QDPR
Superpathway of D-myo-inositol (1, 4, 5)-trisphosphate Metabolism	INPPL1, ITPKA
Glycine Cleavage Complex	OCA2
Zymosterol Biosynthesis	LBR
IL-22 Signaling	IL22RA1, MAPK8
D-myo-inositol (1, 4, 5)-Trisphosphate Biosynthesis	PIP4K2A, PIP4K2C
Purine Ribonucleosides Degradation to Ribose-1-phosphate	PNP
Superpathway of Serine and Glycine Biosynthesis I	SHMT2
Apelin Liver Signaling Pathway	MAPK8, PDGFRB
NAD Salvage Pathway II	NT5E, PXYLP1
GABA Receptor Signaling	ADCY9, ALDH9A1, AP2M1, KCNH2, NSF
FAK Signaling	KRAS, PAK4, PDPK1, PTK2, SOS2
Histidine Degradation III	MTHFD1
Salvage Pathways of Pyrimidine Deoxyribonucleotides	TK1
Superpathway of Cholesterol Biosynthesis	DHCR24, LBR
Axonal Guidance Signaling	ARHGEF12, ARPC2, ARPC5, CRKL, CXCL12, CXCR4, EFNA4, KRAS, PAK4, PLXNA3, PLXNC1, PTK2, RAC2, SEMA4B, SOS2, TUBA1A, TUBA1B, TUBA4A, TUBB4B, TUBG1
Hypoxia Signaling in the Cardiovascular System	MDM2, UBE2C, UBE2L6, UBE2T

Gap Junction Signaling	ADCY9, KRAS, PRKG2, SOS2, TUBA1A, TUBA1B, TUBA4A, TUBB4B, TUBG1
UVC-Induced MAPK Signaling	KRAS, MAPK8, SMPD1
Leucine Degradation I	BCAT2
UDP-N-acetyl-D-galactosamine Biosynthesis II	GNPDA1
CD27 Signaling in Lymphocytes	CASP9, MAP3K3, MAPK8
Role of p14/p19ARF in Tumor Suppression	E2F1, MDM2
Glycolysis I	PFKP
Lipid Antigen Presentation by CD1	AP2M1
Reelin Signaling in Neurons	ARHGEF12, ARHGEF5, CRKL, MAPK8
IL-17A Signaling in Gastric Cells	MAPK8
Tryptophan Degradation X (Mammalian, via Tryptamine)	ALDH9A1
Embryonic Stem Cell Differentiation into Cardiac Lineages	SP4
EGF Signaling	MAPK8, SOS2
Cellular Effects of Sildenafil (Viagra)	ADCY9, KCNH2, MYLK, PDE3A, PDE4D, PRKG2
Glutathione Redox Reactions I	GSR
TCA Cycle II (Eukaryotic)	IDH3A
Tumoricidal Function of Hepatic Natural Killer Cells	CASP9
BMP signaling pathway	FST, KRAS, MAPK8
Lymphotoxin β Receptor Signaling	CASP9, PDPK1
Transcriptional Regulatory Network in Embryonic Stem Cells	HIST4H4, PAX6
HIF1α Signaling	KRAS, MAPK8, MDM2, SLC2A14
FLT3 Signaling in Hematopoietic Progenitor Cells	KRAS, PDPK1, SOS2
PEDF Signaling	ARHGAP22, KRAS, TCF4
Purine Nucleotides De Novo Biosynthesis II	PPAT
Phosphatidylglycerol Biosynthesis II (Non-plastidic)	AGPAT1
JAK/Stat Signaling	KRAS, SOCS2, SOS2
Role of JAK2 in Hormone-like Cytokine Signaling	PRL, SOCS2
Putrescine Degradation III	ALDH9A1
Virus Entry via Endocytic Pathways	AP2M1, ITGB8, KRAS, RAC2
Estrogen Receptor Signaling	KRAS, MED21, NR0B2, POLR2D, SOS2
Assembly of RNA Polymerase I Complex	POLR1E
Cleavage and Polyadenylation of Pre-mRNA	NUDT21
Coagulation System	PLAU, PLAUR
Clathrin-mediated Endocytosis Signaling	AP2M1, ARPC2, ARPC5, FGF19, ITGB8, MDM2, RAB5B
Antioxidant Action of Vitamin C	MAPK8, PLD6, SLC23A2, SLC2A14
IL-4 Signaling	INPPL1, KRAS, RPS6KB2, SOS2
CDP-diacylglycerol Biosynthesis I	AGPAT1
Fatty Acid α-oxidation	ALDH9A1
The Visual Cycle	RDH5
T Cell Receptor Signaling	KRAS, MAPK8, PAG1, SOS2
Induction of Apoptosis by HIV1	CASP9, CXCR4, MAPK8
Interferon Signaling	IFIT3, PSMB8
Erythropoietin Signaling	KRAS, PDPK1, SOS2
GDNF Family Ligand-Receptor Interactions	KRAS, MAPK8, SOS2

Ephrin A Signaling	EFNA4, PTK2
Regulation of the Epithelial-Mesenchymal Transition Pathway	APH1B, ETS1, FGF19, KRAS, LEF1, PDGFRB, SOS2, TCF4
FcγRIIB Signaling in B Lymphocytes	KRAS, MAPK8, PDPK1
IL-2 Signaling	KRAS, MAPK8, SOS2
Assembly of RNA Polymerase III Complex	GTF3C5
NAD Phosphorylation and Dephosphorylation	PXYLP1
Complement System	C1QBP, MBL2
Estrogen-Dependent Breast Cancer Signaling	CCND1, HSD17B3, KRAS
Ceramide Signaling	KRAS, MAPK8, PPP2R2B, SMPD1
Protein Ubiquitination Pathway	BRCA1, CDC20, DNAJB5, MDM2, PSMB8, UBE2C, UBE2L6, UBE2T, USP1, USP39
G-Protein Coupled Receptor Signaling	ADCY9, KRAS, PDE3A, PDE4D, PDPK1, PLD6, RGS10, RGS16, RGS2, SOS2
FAT10 Signaling Pathway	SQSTM1
Methylglyoxal Degradation III	AKR1C1/AKR1C2
Valine Degradation I	BCAT2
Isoleucine Degradation I	BCAT2
Role of PI3K/AKT Signaling in the Pathogenesis of Influenza	CASP9, CRKL, ZNF346
Docosahexaenoic Acid (DHA) Signaling	CASP9, PDPK1
tRNA Charging	FARSA, LARS2
Wnt/β-catenin Signaling	CCND1, DKK1, LEF1, MDM2, PPP2R2B, TCF4, TGFBR3
D-myo-inositol (1, 4, 5)-trisphosphate Degradation	INPPL1
Dermatan Sulfate Degradation (Metazoa)	IDS
Histamine Degradation	ALDH9A1
RAN Signaling	RCC1
Natural Killer Cell Signaling	INPPL1, KRAS, PAK4, RAC2, SOS2
Choline Biosynthesis III	PLD6
IL-15 Production	MST1R, PDGFRB, PTK2, ROR1, TWF1
Mechanisms of Viral Exit from Host Cells	LMNB1, LMNB2
Triacylglycerol Biosynthesis	AGPAT1, ELOVL2
Vitamin-C Transport	SLC23A2
4-1BB Signaling in T Lymphocytes	MAPK8
Activation of IRF by Cytosolic Pattern Recognition Receptors	MAPK8
Adipogenesis pathway	EZH2, TBL1XR1
Agranulocyte Adhesion and Diapedesis	CXCL12, CXCR4, PODXL
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	SPP1
Amyloid Processing	APH1B
Amyotrophic Lateral Sclerosis Signaling	CASP9, NEFH, RAB5B
Androgen Signaling	CCND1, POLR2D
Antigen Presentation Pathway	PSMB8
Antiproliferative Role of Somatostatin Receptor 2	KRAS
Apelin Adipocyte Signaling Pathway	ADCY9, MAPK8
Apelin Cardiomyocyte Signaling Pathway	MAPK8, MYLK
Apelin Pancreas Signaling Pathway	MAPK8
April Mediated Signaling	MAPK8
Assembly of RNA Polymerase II Complex	POLR2D

Atherosclerosis Signaling	CXCL12, CXCR4
Autophagy	CTSK, SQSTM1
B Cell Activating Factor Signaling	MAPK8
BAG2 Signaling Pathway	MDM2
Basal Cell Carcinoma Signaling	LEF1, TCF4
CCR3 Signaling in Eosinophils	KRAS, MYLK, PAK4
CCR5 Signaling in Macrophages	MAPK8
CD40 Signaling	MAPK8
CNTF Signaling	KRAS, RPS6KB2
CREB Signaling in Neurons	ADCY9, KRAS, POLR2D, SOS2
CTLA4 Signaling in Cytotoxic T Lymphocytes	AP2M1, PPP2R2B
Calcium Signaling	CHRNA5, RCAN3
Calcium-induced T Lymphocyte Apoptosis	ORAI1
Cancer Drug Resistance By Drug Efflux	KRAS, MDM2
Caveolar-mediated Endocytosis Signaling	ITGB8, RAB5B
Corticotropin Releasing Hormone Signaling	ADCY9, ARPC5, JUND
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	CASP9
Dendritic Cell Maturation	MAPK8
Dermatan Sulfate Biosynthesis	CHST14
Dermatan Sulfate Biosynthesis (Late Stages)	CHST14
Dopamine Degradation	ALDH9A1
Dopamine-DARPP32 Feedback in cAMP Signaling	ADCY9, PPP2R2B, PRKG2
Endocannabinoid Neuronal Synapse Pathway	ADCY9, MAPK8
Estrogen Biosynthesis	HSD17B3
FXR/RXR Activation	BAAT, FGF19, MAPK8, NR0B2
Fatty Acid β-oxidation I	SCP2
G Beta Gamma Signaling	KRAS, PDPK1, SOS2
GP6 Signaling Pathway	LAMC1, PDPK1, PTK2
GPCR-Mediated Integration of Enteroendocrine Signaling Exemplified by an L Cell	ADCY9
GPCR-Mediated Nutrient Sensing in Enteroendocrine Cells	ADCY9
Glucocorticoid Receptor Signaling	HMGB1, KRAS, KRT23, MAPK8, PBX1, PLAU, POLR2D, PRL, SOS2
Granulocyte Adhesion and Diapedesis	CXCL12, CXCR4
Gustation Pathway	ADCY9, ASIC3, PDE3A, PDE4D, PLD6
Gαi Signaling	ADCY9, KRAS, RGS10, SOS2
Gαq Signaling	PLD6, RAC2, RGS16, RGS2
Gαs Signaling	ADCY9, RGS2
HIPPO signaling	PPP2R2B, YWHAZ
HMGB1 Signaling	HMGB1, KRAS, MAPK8, RAC2
Heparan Sulfate Biosynthesis	PNPLA7
Heparan Sulfate Biosynthesis (Late Stages)	PNPLA7
Hepatic Cholestasis	ADCY9, FGF19, MAPK8, NR0B2
Hepatic Fibrosis / Hepatic Stellate Cell Activation	IL6R, PDGFRB
Human Embryonic Stem Cell Pluripotency	LEF1, PDGFRB, PDPK1, TCF4
IL-1 Signaling	ADCY9, MAPK8
IL-10 Signaling	MAPK8
IL-12 Signaling and Production in Macrophages	MAPK8, MST1R
IL-15 Signaling	KRAS, PTK2

IL-17 Signaling	KRAS, MAPK8
IL-17A Signaling in Airway Cells	MAPK8
IL-3 Signaling	CRKL, KRAS
IL-9 Signaling	SOCS2
Inhibition of Angiogenesis by TSP1	MAPK8
Inhibition of Matrix Metalloproteases	TIMP4
Iron homeostasis signaling pathway	ABCB10, IL6R, PDGFRB
LPS-stimulated MAPK Signaling	KRAS, MAPK8
LPS/IL-1 Mediated Inhibition of RXR Function	ALDH9A1, MAPK8, NR0B2
Leptin Signaling in Obesity	ADCY9, PDE3A
MIF Regulation of Innate Immunity	MAPK8
MSP-RON Signaling Pathway	MST1R
Macropinocytosis Signaling	ITGB8, KRAS
Mitochondrial Dysfunction	APH1B, ATP5PB, CASP9, GSR, MAPK8
NF-κB Activation by Viruses	KRAS
Netrin Signaling	RAC2
Neuropathic Pain Signaling In Dorsal Horn Neurons	KCNH2
Neuroprotective Role of THOP1 in Alzheimer's Disease	TPP1
Nitric Oxide Signaling in the Cardiovascular System	PRKG2
Noradrenaline and Adrenaline Degradation	ALDH9A1
Notch Signaling	APH1B
Nucleotide Excision Repair Pathway	POLR2D
Nur77 Signaling in T Lymphocytes	CASP9, MAP3K3
OX40 Signaling Pathway	MAPK8
Oxidative Phosphorylation	ATP5PB
P2Y Purigenic Receptor Signaling Pathway	ADCY9, KRAS
PD-1, PD-L1 cancer immunotherapy pathway	CDK2, PDCD4
PFKFB4 Signaling Pathway	HK2
PI3K Signaling in B Lymphocytes	ATF3, KRAS, PDPK1
PXR/RXR Activation	NR0B2
Phagosome Formation	MBL2, RAC2
Phospholipases	PLD6
Primary Immunodeficiency Signaling	UNG
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	MAP3K3, MAPK8, PPP2R2B, RAC2
RANK Signaling in Osteoclasts	MAP3K3, MAPK8
RAR Activation	ADCY9, MAPK8, NR2F6, PDPK1, PNRC1, RDH5
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	KRAS, MAPK8, SOS2
Relaxin Signaling	ADCY9, PDE3A, PDE4D, PLD6
Retinoate Biosynthesis I	RDH5
Retinoic acid Mediated Apoptosis Signaling	CASP9, PARP14
Role of IL-17A in Arthritis	MAPK8
Role of JAK1 and JAK3 in γc Cytokine Signaling	KRAS
Role of MAPK Signaling in the Pathogenesis of Influenza	KRAS, MAPK8
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	CCND1, CXCL12, DKK1, IL6R, KRAS, LEF1, TCF4

Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency	KRAS, SOS2
Role of NFAT in Regulation of the Immune Response	KRAS, ORAI1, RCAN3, SOS2
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	CASP9, CTSK, DKK1, LEF1, MAPK8, SPP1, TCF4
Role of PKR in Interferon Induction and Antiviral Response	CASP9
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	MAPK8, MBL2, OAS3
Role of Tissue Factor in Cancer	KRAS, PLAUR
Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza	LEF1, TCF4
Serotonin Degradation	ALDH9A1
Superpathway of Methionine Degradation	BHMT
Synaptic Long Term Depression	KRAS, PPP2R2B, PRKG2
Synaptic Long Term Potentiation	KRAS
Systemic Lupus Erythematosus In T Cell Signaling Pathway	CASP2, CASP9, DNMT1, KRAS, ORAI1, PPP2R2B, PTK2, RAC2, RPS6KB2, SOS2
Systemic Lupus Erythematosus Signaling	IL6R, KRAS, LSM14B, SOS2
T Cell Exhaustion Signaling Pathway	IL6R, KRAS, MAPK8, PPP2R2B, TGFBR3
T Helper Cell Differentiation	IL6R
TGF-β Signaling	KRAS, MAPK8, SOS2
TNFR2 Signaling	MAPK8
TWEAK Signaling	CASP9
Th1 Pathway	APH1B, IL6R
Th1 and Th2 Activation Pathway	APH1B, CXCR4, IL6R, PTGDR2, TGFBR3
Th17 Activation Pathway	IL6R
Th2 Pathway	APH1B, CXCR4, PTGDR2, TGFBR3
Thrombopoietin Signaling	KRAS
Tight Junction Signaling	MYLK, NSF, NUDT21, PPP2R2B, STX4
Toll-like Receptor Signaling	MAPK8
Triacylglycerol Degradation	PNPLA7
Type I Diabetes Mellitus Signaling	CASP9, MAPK8, SOCS2
Type II Diabetes Mellitus Signaling	MAPK8, PDPK1, SMPD1, SOCS2
UVB-Induced MAPK Signaling	MAPK8
Unfolded protein response	MAPK8
VDR/RXR Activation	SPP1
VEGF Family Ligand-Receptor Interactions	KRAS, SOS2
VEGF Signaling	KRAS, PTK2, SOS2
Wnt/Ca+ pathway	ROR1
Xenobiotic Metabolism Signaling	ALDH9A1, KRAS, MAP3K3, MAPK8, PPP2R2B
fMLP Signaling in Neutrophils	ARPC2, ARPC5, KRAS
iCOS-iCOSL Signaling in T Helper Cells	PDPK1
p38 MAPK Signaling	MAX, RPS6KB2
α-Adrenergic Signaling	ADCY9, KRAS

Table 20 - HUH7 liver cancer downregulated pathways and associated genes

Pathway Name	**Gene**
Estrogen-mediated S-phase Entry	CCNA2, CCND1, CCNE2, CDC25A, CDK1, CDK2, E2F1, E2F2, E2F7, E2F8, RBL1, TFDP1
Role of BRCA1 in DNA Damage Response	BLM, BRCA1, BRCA2, BRIP1, CHEK1, E2F1, E2F2, E2F7, E2F8, FANCD2, FANCE, FANCG,

	MDC1, MSH2, PLK1, RAD51, RBL1, RFC2, RFC3
ATM Signaling	BLM, BRCA1, CBX1, CCNB1, CDC25A, CDK1, CDK2, CHEK1, FANCD2, H2AFX, HP1BP3, MAPK8, MDC1, MDM2, PPP2R2B, RAD17, RAD51, RNF168
Cyclins and Cell Cycle Regulation	CCNA2, CCNB1, CCND1, CCNE2, CDC25A, CDK1, CDK2, CDK6, CDKN2C, E2F1, E2F2, E2F7, E2F8, PPP2R2B, TFDP1
NER Pathway	CHAF1A, CHAF1B, COPS3, DNA2, HIST4H4, LIG1, PCNA, POLA1, POLA2, POLE, POLE3, POLR2D, PRIM1, RFC2, RFC3, TOP2A
Mitotic Roles of Polo-Like Kinase	CCNB1, CDC20, CDC25A, CDK1, ESPL1, FBXO5, KIF11, KIF23, PKMYT1, PLK1, PLK4, PPP2R2B
Cell Cycle Regulation by BTG Family Proteins	BTG2, CCND1, CCNE2, CDK2, E2F1, E2F2, E2F7, E2F8, PPP2R2B
Pancreatic Adenocarcinoma Signaling	BRCA2, CASP9, CCND1, CDK2, E2F1, E2F2, E2F7, E2F8, KRAS, MAPK8, MDM2, PLD6, RAD51, TFDP1
Aryl Hydrocarbon Receptor Signaling	ALDH9A1, CCNA2, CCND1, CCNE2, CDK2, CDK6, CHEK1, DHFR, E2F1, MAPK8, MCM7, MDM2, NR0B2, POLA1, RBL1, TFDP1
Small Cell Lung Cancer Signaling	CASP9, CCND1, CCNE2, CDK2, CDK6, E2F1, MAX, PTK2, TFDP1
Agrin Interactions at Neuromuscular Junction	GABPA, KRAS, LAMC1, MAPK8, NRG3, NRG4, PAK4, PTK2, RAC2
Neuregulin Signaling	CRKL, ERBIN, GRB7, KRAS, NRG3, NRG4, PDPK1, RPS6KB2, SOS2, TMEFF2
p53 Signaling	BRCA1, CCND1, CDK2, CHEK1, E2F1, MAPK8, MDM2, PCNA, TP53INP1, TRIM29
Non-Small Cell Lung Cancer Signaling	CASP9, CCND1, CDK6, E2F1, KRAS, PDPK1, SOS2, TFDP1
Glioblastoma Multiforme Signaling	CCND1, CDK2, CDK6, E2F1, E2F2, E2F7, E2F8, KRAS, LEF1, MDM2, PDGFRB, RAC2, SOS2
Pyrimidine Deoxyribonucleotides De Novo Biosynthesis	DUT, RRM1, RRM2, TYMS
IGF-1 Signaling	CASP9, KRAS, MAPK8, PDPK1, PTK2, RPS6KB2, SOCS2, SOS2, YWHAZ
HGF Signaling	CCND1, CDK2, CRKL, ETS1, KRAS, MAP3K3, MAPK8, PTK2, SOS2
Rac Signaling	ABI2, ARPC2, ARPC5, IQGAP3, KRAS, MAPK8, PAK4, PIP4K2C, PTK2
PI3K/AKT Signaling	CCND1, INPPL1, KRAS, MCL1, MDM2, PDPK1, PPP2R2B, RPS6KB2, SOS2, YWHAZ
Integrin Signaling	ARF3, ARPC2, ARPC5, CRKL, GRB7, ITGB8, KRAS, MAPK8, MYLK, MYLK2, PAK4, PTK2, RAC2, SOS2
Endometrial Cancer Signaling	CASP9, CCND1, KRAS, LEF1, PDPK1, SOS2
IL-7 Signaling Pathway	CCND1, CDC25A, CDK2, MCL1, PDPK1, PTK2, SOS2
FAT10 Cancer Signaling Pathway	CXCR4, MAD2L1, PCNA, TCF4, TGFBR3
Actin Cytoskeleton Signaling	ABI2, ARHGEF12, ARPC2, ARPC5, CRKL, FGF19, IQGAP3, KRAS, MYLK, MYLK2, PAK4, PTK2, RAC2, SOS2
Pyridoxal 5'-phosphate Salvage Pathway	CDK1, CDK2, CDK6, FAM20B, MAPK8, PLK1
ErbB2-ErbB3 Signaling	CCND1, KRAS, NRG3, NRG4, PDPK1, SOS2

RhoA Signaling	ANLN, ARHGEF12, ARPC2, ARPC5, LPAR3, MYLK, MYLK2, PIP4K2C, PTK2
ErbB4 Signaling	APH1B, KRAS, NRG3, NRG4, PDPK1, SOS2
Acute Myeloid Leukemia Signaling	CCND1, IDH2, KRAS, LEF1, RPS6KB2, SOS2, TCF4
STAT3 Pathway	CDC25A, IL17RD, IL22RA1, IL6R, KRAS, MAPK8, PDGFRB, SOCS2, TGFBR3
D-myo-inositol-5-phosphate Metabolism	CDC25A, DUSP8, HACD2, MTMR9, NUDT15, PIP4K2A, PIP4K2C, PPFIA3, PPTC7, PXYLP1
Superpathway of Inositol Phosphate Compounds	CDC25A, DUSP8, HACD2, INPPL1, ITPKA, MTMR9, NUDT15, PIP4K2A, PIP4K2C, PPFIA3, PPTC7, PXYLP1
Glioma Invasiveness Signaling	KRAS, PLAU, PLAUR, PTK2, RAC2, TIMP4
ErbB Signaling	KRAS, MAPK8, NRG3, NRG4, PAK4, PDPK1, SOS2
Ephrin Receptor Signaling	ARPC2, ARPC5, CRKL, CXCL12, CXCR4, EFNA4, KRAS, PAK4, PTK2, RAC2, SOS2
PAK Signaling	KRAS, MAPK8, MYLK, PAK4, PDGFRB, PTK2, SOS2
Insulin Receptor Signaling	ASIC3, CRKL, INPPL1, KRAS, MAPK8, PDPK1, RPS6KB2, SOS2, STX4
Apoptosis Signaling	CASP2, CASP9, CDK1, GAS2, KRAS, MAPK8, MCL1
Pyrimidine Ribonucleotides Interconversion	BLM, NUDT15, RAD54L, RECQL4
B Cell Receptor Signaling	ETS1, INPPL1, KRAS, MAP3K3, MAPK8, PAG1, PDPK1, PTK2, RAC2, RPS6KB2, SOS2
Pyrimidine Ribonucleotides De Novo Biosynthesis	BLM, NUDT15, RAD54L, RECQL4
SAPK/JNK Signaling	CRKL, DUSP8, KRAS, MAP3K3, MAPK8, RAC2, SOS2
Telomerase Signaling	E2F1, ETS1, KRAS, PDPK1, PPP2R2B, SOS2, TPP1
PDGF Signaling	CRKL, INPPL1, KRAS, MAPK8, PDGFRB, SOS2
3-phosphoinositide Degradation	CDC25A, DUSP8, HACD2, INPPL1, MTMR9, NUDT15, PPFIA3, PPTC7, PXYLP1
TNFR1 Signaling	CASP2, CASP9, MAPK8, PAK4
Death Receptor Signaling	CASP2, CASP9, GAS2, MAPK8, PARP14, TNFRSF21
SPINK1 General Cancer Pathway	IL6R, KRAS, MT1F, MT1M, MT1X
Melanoma Signaling	CCND1, E2F1, KRAS, MDM2
Actin Nucleation by ARP-WASP Complex	ARPC2, ARPC5, KRAS, RAC2, SOS2
NGF Signaling	KRAS, MAP3K3, MAPK8, PDPK1, RPS6KB2, SMPD1, SOS2
Regulation of Actin-based Motility by Rho	ARPC2, ARPC5, MYLK, PAK4, PIP4K2C, RAC2
Endocannabinoid Developing Neuron Pathway	ADCY9, BRCA1, CCND1, KRAS, MAPK8, PAX6, RAC2
D-myo-inositol (1, 4, 5, 6)-Tetrakisphosphate Biosynthesis	CDC25A, DUSP8, HACD2, MTMR9, NUDT15, PPFIA3, PPTC7, PXYLP1
D-myo-inositol (3, 4, 5, 6)-tetrakisphosphate Biosynthesis	CDC25A, DUSP8, HACD2, MTMR9, NUDT15, PPFIA3, PPTC7, PXYLP1
Salvage Pathways of Pyrimidine Ribonucleotides	CDK1, CDK2, CDK6, FAM20B, MAPK8, PLK1
Angiopoietin Signaling	CASP9, GRB7, KRAS, PAK4, PTK2
3-phosphoinositide Biosynthesis	CDC25A, DUSP8, HACD2, MTMR9, NUDT15, PIP4K2C, PPFIA3, PPTC7, PXYLP1

CXCR4 Signaling	ADCY9, CXCL12, CXCR4, ELMO2, KRAS, MAPK8, PAK4, PTK2, RAC2
ERK/MAPK Signaling	CRKL, ETS1, KRAS, MYCN, PAK4, PPP2R2B, PTK2, RAC2, SOS2, YWHAZ
Chemokine Signaling	CXCL12, CXCR4, KRAS, MAPK8, PTK2
Adrenomedullin signaling pathway	ADCY9, KCNH2, KRAS, MAPK8, MAX, MYLK, MYLK2, PRKG2, PTK2, SOS2
Prolactin Signaling	KRAS, PDPK1, PRL, SOCS2, SOS2
Acute Phase Response Signaling	IL6R, KRAS, MAPK8, MBL2, OSMR, PDPK1, SOCS2, SOS2, TCF4
Colorectal Cancer Metastasis Signaling	ADCY9, CASP9, CCND1, GRK3, IL6R, KRAS, LEF1, MAPK8, MSH2, RAC2, SOS2, TCF4
Paxillin Signaling	ITGB8, KRAS, MAPK8, PAK4, PTK2, SOS2
Fc Epsilon RI Signaling	INPPL1, KRAS, MAPK8, PDPK1, RAC2, SOS2
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	ARPC2, ARPC5, PLD6, RAC2, RPS6KB2
Signaling by Rho Family GTPases	ARHGEF12, ARHGEF5, ARPC2, ARPC5, MAPK8, MYLK, PAK4, PIP4K2C, PTK2, RAC2, STMN1
GM-CSF Signaling	CCND1, ETS1, KRAS, SOS2
Renin-Angiotensin Signaling	ADCY9, KRAS, MAPK8, PAK4, PTK2, SOS2
ERK5 Signaling	KRAS, MAP3K3, RPS6KB2, YWHAZ
Ephrin B Signaling	CXCL12, CXCR4, PTK2, RAC2
Growth Hormone Signaling	PDPK1, PRL, RPS6KB2, SOCS2
Neurotrophin/TRK Signaling	KRAS, MAPK8, PDPK1, SOS2
Synaptogenesis Signaling Pathway	ADCY9, AP2M1, ARPC2, ARPC5, CADM1, CRKL, EFNA4, KRAS, NSF, RAB5B, RPS6KB2, SOS2, THBS3
Renal Cell Carcinoma Signaling	ETS1, KRAS, PAK4, SOS2
mTOR Signaling	EIF4B, KRAS, PDPK1, PLD6, PPP2R2B, RAC2, RPS17, RPS21, RPS6KB2
Sirtuin Signaling Pathway	ACSS2, ATP5PB, E2F1, GABPA, HIST1H1E, IDH2, MYCN, POLR1E, TOMM20, TUBA1A, TUBA1B, TUBA4A
CDK5 Signaling	ADCY9, KRAS, LAMC1, MAPK8, PPP2R2B
Leukocyte Extravasation Signaling	CRKL, CXCL12, CXCR4, MAPK8, PTK2, RAC2, TIMP4
Cdc42 Signaling	ARPC2, ARPC5, IQGAP3, MAPK8, MYLK, PAK4
FGF Signaling	CRKL, FGF19, MAPK8, SOS2
ILK Signaling	CCND1, ITGB8, LEF1, MAPK8, PDPK1, PPP2R2B, PTK2, RAC2
Opioid Signaling Pathway	ADCY9, AP2M1, GRK3, KRAS, RAC2, RGS10, RGS16, RPS6KB2, SOS2
NRF2-mediated Oxidative Stress Response	DNAJB5, GSR, HERPUD1, JUND, KRAS, MAPK8, SQSTM1
Cardiac β-adrenergic Signaling	ADCY9, GRK3, PDE3A, PDE4D, PLD6, PPP2R2B
Mouse Embryonic Stem Cell Pluripotency	KRAS, LEF1, SOS2, TCF4
eNOS Signaling	ADCY9, CASP9, CCNA2, CHRNA5, LPAR3, PDPK1
Aldosterone Signaling in Epithelial Cells	ASIC3, DNAJB5, KRAS, PDPK1, PIP4K2C, SOS2
p70S6K Signaling	KRAS, PDPK1, PPP2R2B, SOS2, YWHAZ
Regulation of eIF4 and p70S6K Signaling	KRAS, PDPK1, PPP2R2B, RPS17, RPS21, SOS2

EIF2 Signaling	ATF3, CCND1, KRAS, MYCN, PDPK1, RPL27A, RPS17, RPS21, SOS2
GNRH Signaling	ADCY9, KRAS, MAP3K3, MAPK8, PAK4, PTK2, SOS2
Cholecystokinin/Gastrin-mediated Signaling	KRAS, MAPK8, PTK2, RAC2, SOS2
IL-6 Signaling	IL6R, KRAS, MAPK8, MCL1, SOS2
Thrombin Signaling	ADCY9, ARHGEF12, ARHGEF5, KRAS, MYLK, PDPK1, PTK2, RAC2
Protein Kinase A Signaling	ADCY9, CDC25A, DUSP8, HIST1H1E, LEF1, MYLK, MYLK2, PDE3A, PDE4D, PLD6, PTK2, PTPN3, PTPN9, TCF4, YWHAZ
Melanocyte Development and Pigmentation Signaling	ADCY9, KRAS, RPS6KB2, SOS2
Apelin Endothelial Signaling Pathway	ADCY9, KRAS, MAPK8, RPS6KB2
CD28 Signaling in T Helper Cells	ARPC2, ARPC5, MAPK8, PDPK1
Cardiac Hypertrophy Signaling	ADCY9, IL6R, KRAS, MAP3K3, MAPK8, RAC2
Cardiac Hypertrophy Signaling (Enhanced)	ADCY9, FGF19, IL17RD, IL22RA1, IL6R, KRAS, MAP3K3, MAPK8, PDE3A, PDE4D, PLD6, PTK2, RPS6KB2, TGFBR3
Endothelin-1 Signaling	ADCY9, CASP2, CASP9, KRAS, MAPK8, PLD6
Gα12/13 Signaling	KRAS, LPAR3, MAPK8, PTK2
IL-8 Signaling	CCND1, KRAS, MAPK8, PLD6, PTK2, RAC2
NF-κB Signaling	KRAS, MAP3K3, MAPK8, PDGFRB, TGFBR3
Neuroinflammation Signaling Pathway	APH1B, CXCL12, HMGB1, IL6R, MAPK8, TGFBR3
Osteoarthritis Pathway	CASP2, CASP9, DKK1, HMGB1, LEF1, SPP1, TCF4
PKCθ Signaling in T Lymphocytes	KRAS, MAP3K3, MAPK8, RAC2, SOS2
Phospholipase C Signaling	ADCY9, ARHGEF12, ARHGEF5, KRAS, PLD6, RAC2, SOS2
Role of NFAT in Cardiac Hypertrophy	ADCY9, KRAS, MAPK8, RCAN3, SOS2
Sperm Motility	MST1R, PDE4D, PDGFRB, PRKG2, PTK2, ROR1, TWF1
Tec Kinase Signaling	MAPK8, PAK4, PTK2, RAC2, TNFRSF21
cAMP-mediated signaling	ADCY9, PDE3A, PDE4D, PLD6, RGS10, RGS2

Example 2 - RNA-sequencing, differential gene expression, and pathway analysis after treatment of different cancer cell lines with miRNA-193a

miRNA-193a was tested in different cancer cell lines (see Table 2.1). The cells were treated with miRNA-193a as described for example 1 at different concentrations (1, 3, 10 nM). Controls (mock, untreated, and scrambled) were measured for all cell types. Assays were performed after 24h, 48h and 72h. Table 2.1 shows results at 10nM concentration at indicated time points. The results were quantified and normalized to the mock control. 10nM was a suitable concentration, because the cells showed no signs of a toxic effect at that concentration.

Table 2.1 – effect of miRN-193a on various tumours

Cancer type	Cell line	Viability (96h)	Apoptosis (48/72h)	Cell cycle arrest (72h)	Motility (18 to 24h)
Liver	HEP3B	< *50%*	< *2x*	G2/M	> *50%*
	HUH7	< *50%*	< *2x*	-	n.a.
Lung	A549	< *50%*	> 2x	SubG1	> *50%*
	H460	< *50%*	> 2x	SubG1	n.a

miRNA-193a treatment in the cancer cell lines decreased cell viability over time as measured by either an MTS assay or by cell count. Apoptosis induction was enhanced over time as measured by a caspase 3/7 apoptosis assay. Cell cycle arrest profiles were measured performing either nuclei imaging or flow cytometry. miRNA-193a treatment induced either a G2/M or a SubG1 cell cycle arrest profile in a manner depending on the cell line. While in HUH7 no obvious cell cycle arrest profile was observed following the indicated methods, an increased apoptosis was observed indicated by Caspase 3/7 activation and enhanced cleaved-parp protein on western blot (data not shown) following miRNA-193a treatment in this cell line. This result indicates that miRNA-193a treatment affects the viability of the cells. Cell motility of two cell lines was significantly decreased after treatment as assessed via a Boyden chamber assay.

Conclusion

miRNA-193a treatment decreased cell viability partly by inducing apoptosis and by an increase in the cell cycle arrest profile. miRNA-193a treatment also decreases cell motility of cancer cells, indicating its role in the inhibition of cancer cell migration.

Example 3 – further study of the PTEN pathway activation

Example 1 shows that the IPA analysis identified the tumor suppressive PTEN pathway as the most enriched canonical pathway which was activated by miRNA-193a. Here regulation of selected miRNA-193a targets is analysed at the protein level by western blotting, including: FAK (PTK2), P70S6 (RPS6KB2), PI3KR1, TGFBRIII and other important signaling molecules including P-AKT, AKT, p-ERK1/2, ERK1/2, p-c-RAF and c-RAF, all factors in the PTEN pathway.

Materials and methods

Cell preparation

Human cancer cell lines were cultured in appropriate media (see table below) and seeded into 6-well plates before transfection with 10 nM miRNA-193a-3p mimic as described in example 1, 10 nM scrambled random control, or mock using Lipofectamine RNAiMAX (Thermofisher). Media was aspirated 72h after transfection and plates were stored at -80°C.

3. 1. Cell lines details

Cell line	Cancer type	Medium
A549	Lung (NSCLC)	F-12K + 10% FBS + P/S
BT549	Breast (TNBC)	RPMI-1640 + 10% FBS + P/S + 0.023 IU/mL insulin
H460	Lung (NSCLC)	RPMI-1640 + 10% FBS + P/S
HEP3B	Liver (HCC)	EMEM + 10% FBS + P/S
HUH7	Liver (HCC)	DMEM low glucose+ 10% FBS + P/S + L-glutamine
PANC-1	Pancreas	DMEM + 10% FBS + P/S
SNU449	Liver (HCC)	RPMI-1640 + 10% FBS + P/S

FBS: fetal bovine serum, P/S: penicillin streptomycin

Protein isolation and quantification

RIPA buffer (50 mM Tris-HCl pH 8, 150 mM NaCl, 1% NP40, 0.5% sodium deoxycholate, 0.1% SDS, 0.5 mM EDTA), supplemented with protease and phosphatase inhibitor cocktails, was added to harvested cells. Lysates were centrifugated at 15,000 g for 1h at 4°C and clarified by removing the cell debris pellet. Protein concentration was determined using the Pierce BCA Protein Assay Kit (Thermo Fisher).

Electrophoresis and immunoblotting

Samples were separated at 120 V by SDS-PAGE on Mini-PROTEAN TGX Stain-Free precast gels (Bio-Rad). Proteins were transferred at 200 mA for 2 h to PVDF membranes in transfer buffer (25 mM Tris, 192 mM glycine, 20% methanol). The membranes were blocked using 5% milk or 5% BSA in Tris-buffered saline with Tween (20 mM Tris pH 7.6, 137 mM NaCl, 0.1% Tween). Blots were probed with primary and horseradish peroxidase-conjugated secondary antibodies. Proteins were detected using ECL reagents. Membranes were stripped in stripping buffer (62.5 mM Tris pH 6.8, 2% SDS, 100 mM 2-mercaptoethanol) for 30 min at 50°C and reprobed as appropriate.

Results

Lysates from cells transfected with 10 nM scrambled control or 10 nM miRNA-193a-3p mimic as described in example 1 were immunoblotted to assess the protein level of selected predicted miR-193a-3p target genes as well as phosphorylation status of key signalling proteins in the PTEN pathway. In all tested cell lines (A549, HUH7, SNU449, BT549, H460, A2058, HEP3B and PANC-1) downregulation of FAK, also called PTK2, was observed in the miRNA-193a sample compared to mock and scrambled control (Figure 4). TGFBRIII was also downregulated by miRNA-193a in cell lines where a constitutive expression level could be observed (A549, HUH7, SNU449, BT549 and H460). Protein level of PIK3R1, the regulatory subunit of PI3K, was decreased in all cell lines except SNU449. P70S6, also called RPS6KB2, was downregulated in H460, A2058 and HEP3B. Vinculin and tubulin were used as loading controls. In A549 and H460, tubulin was affected by miRNA-193a, whereas vinculin was stable, indicating that miRNA-193a does not reduce general protein levels. Additionally, we observed downregulation of AKT phosphorylation by miRNA-193a in most cell lines (A549, A2058, SNU449, HUH7, H460 and HEP3B (Figure 5). Interestingly, miRNA-193a increased phosphorylation of ERK in at least two cell lines (A549 and A2058). In SNU449, both ERK phosphorylation and ERK total protein level were upregulated. Phosphorylation of c-RAF was only downregulated in PANC-1.

Conclusion

These results are in line with the RNA-sequencing data obtained previously. miRNA-193a-3p mimic miRNA-193a decreased protein expression of FAK, P70S6K, PIK3R1 and TGFBRIII in multiple human tumor cell lines. In addition, treatment of cells with miRNA-193a-3p mimic miRNA-193a lead to reduced phosphorylation of AKT, which could be due to downregulation of upstream signaling proteins such as PIK3R1 and FAK. Furthermore, we observed increased phosphorylation of ERK, which could be a consequence of decreased AKT activity via effects on RAF, although phosphorylation of c-RAF was decreased in only one cell line (PANC-1). Increased phosphorylation of ERK may also be the result of other upstream events, including decreased phosphatase activity or increased activity of upstream kinases.

Example 4 – miRNA-193a is an Immunogenic Cell Death (ICD) inducer

Introduction: The concept of Immunogenic Cell Death (ICD) has been defined as a unique class of regulated cell death capable of eliciting antigen-specific adaptive immune responses through the emission of a spatiotemporally defined set of danger signals known as damage associated molecular patterns (DAMPs) (Krysko *et al.*, *Nat. Rev. Cancer*, 2012; Casares *et al.*, *J. Exp. Med.*, 2005; Kroemer *et al.*, *Annu. Rev. Immunol.*, 2013). The most notable DAMPs are: release of HGMB1, release of ATP and surface expression of calreticulin (CRT), as a sign of ER stress. Induction of ICD by some (specific) anticancer agents upon induction of cancer cell death leads to release of DAMPs into the tumor microenvironment (TME), which operate on receptors expressed by dendritic cells, and in turn stimulate presentation of tumor-associated antigens to T cells, leading to T cell activation and proliferation eventually culminating in enhanced cytotoxicity against the tumor cells, and formation of an immunological memory against the tumor antigens.

Materials and methods

Transfection: A2058 melanoma and HEP3B hepatocyte tumor cells were transfected with different concentrations of miRNA-193a as described in example 1, or a mock ("fake transfection") control. In brief, $5x10^5$ A2058 or HEP3B cells were seeded in 1.5mL complete media in 6-well cell culture plates. Both cell lines were transfected 4 h later. A 500 µL transfection mix containing 7.5 µL Lipofectamine RNAiMAX (Thermo Fisher) and the appropriate concentration miRNA-193a-3p was added to each well. Transfection conditions included were 0.1, 1, 3 or 10 nM miRNA-193a and the mock-transfected negative control. Both cell lines were passaged into 24-well plates 16 h after transfection by aspirating and retaining media in 5-mL tubes, washing 1x with TrypLE (Gibco), and incubating for 10 to 12 min until detached. Cells were collected with 1 mL fresh media and added to the retained media. Tubes were centrifuged for 5 min at 1,500 RPM and supernatant removed. Cells were resuspended in 500 µL fresh media and counted using a 1:1 dilution with trypan blue using the Luna-II cell counter (Westburg). $5x10^4$ cells in 1 mL fresh media were seeded per well.

Flow cytometry: For flow cytometric analysis at mentioned time post transfection, cells were harvested after washing 1x with TrypLE (Gibco), and incubating for 10 to 12 min until detached. For each condition, 200 µL of single cell suspensions containing $5x10^4$ cells were prepared in 4-mL polypropylene tubes. Cells were stained with fluorescently labeled antibodies in a 1:200 dilution. The expression of CRT was

measured using a DyLight™ 488 conjugate anti-human Calreticulin (CRT) antibody (Clone FMC 75, Enzo Life science). Also, DAPI (BioLegend) was added at a final concentration of 2 µM, to detect live/dead cells, and dead cells were excluded from further analyses. Flow cytometry was performed using a FACSCanto II cytometer (BD Biosciences), data was analyzed with FlowJo software (Tree Star inc.).

Co-culture with CFSE labeled PBMCs: PBMCs were isolated from fresh blood buffy coat (Sanquin), using SepMate™-50 tubes (STEMCELL), following manufacturer's protocol. Ficoll® Paque Plus (SigmaAldrich) was used as the density gradient medium. PBMCs were then labeled with CFSE using CFSE Cell Division Tracker Kit (BioLegend), following the manufacturer's protocol. A2058 cells were transfected and 16 h after transfection, cells were passaged to a 24 well plate as explained before. $3x10^4$ A2058 cells were seeded in 0.5 mL of fresh medium into each well. Also, 0.5 mL of CFSE labeled PBMC suspensions containing $1.2x10^5$ PBMCs was added into each well. Same amount of PBMCs, without any A2058 cells, was cultured as "PBMC only" control condition. The co-culture was incubated at 37° C for mentioned time. For detection of T cells, cells were stained with Brilliant Violet 510™ anti-human CD3 Antibody (Clone UCHT1, BioLegend) in a 1:200 dilution.

Results

To investigate the effect of miRNA-193a on tumor cells, the expression of CRT on the surface of miRNA-193a transfected tumor cells was assessed by flow cytometry. As shown in Figure 6A and 6B, miRNA-193a induced expression of the CRT marker on the cell surface in A2058 cells (up to 46% after 72h) and to a lesser extent in Hep3B cells (up to 8% after 72h), compared with mock transfected cells containing only 5% and 4% surface-CRT^+ cells, respectively. Moreover, via targeting two major ectonucleotidases CD39 and CD73, miRNA-193a can prevent the conversion of extracellular ATP to ADP, AMP and adenosine, and thereby retains the ATP content of the TME.

Next, we addressed the effect of miRNA-193a on proliferation of T cells in co-culture with miRNA-193a transfected tumor cells. PBMCs were labeled with CFSE, a fluorescent non-toxic marker that can be retained within the cells and gets diluted with each cell division. Levels of CFSE measured by flow cytometry were compared between three conditions: 1) PBMCs in culture alone, 2) PBMCs in culture with mock transfected A2058 cells, and 3) PBMCs in culture with miRNA-193a 1nM transfected A2058 cells. The results show that keeping PBMCs in co-culture with miRNA-193a-transfected A2058 cells enhanced the proliferation of T cells.

Furthermore, miRNA-193a increased the vulnerability of tumor cells to PBMC-mediated cytotoxicity, as showed by fixation, staining and colorimetric quantification of survived tumor cells following co-culture with PBMCs. Interestingly, in vivo experiments in a syngeneic murine 4T1 orthotopic breast cancer model confirmed the formation of a long-term T cell mediated anti-tumor immunity in miRNA-193a treated animals, or in naïve mice that had received an adoptive T cell transfer from miRNA-193a treated mice.

Taken together, these results strongly suggest that miRNA-193a is a bona fide ICD inducer which kills the tumor cells in a way that not only stimulates PBMC-mediated cytotoxicity to enhance overall anti-tumor efficacy, but also activates the formation of an adaptive anti-tumor immunity.

Example 5 Effect of miRNA-193a on human PBMC-mediated tumor cell killing following transfection in human tumor cells

One of the most recent developments in the understanding of cancer biology is the field of immuno-oncology (IO). Often tumors present the ability to evade cancer immunosurveillance, which represents one of the hallmarks of cancer (Hanahan et al., 2011) Accordingly, the main goals of cancer immunotherapy are to strengthen the patient's immune response to the tumor by improving its capacity for tumor recognition and the disruption of immunosuppressive mechanisms (Chen et al., 2017). As part of the induction mechanisms supporting pronounced immune suppression of the tumors, adenosine levels in the tumor microenvironment (TME) have recently attracted significant attention to develop novel therapeutic intervention in oncology. Adenosine in the tumor microenvironment (TME) is generated mainly by ectonucleotidases CD39 (ENTPD1; which converts extracellular adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and then to adenosine monophosphate (AMP)) and CD73 (NT5E; which is responsible for the generation of adenosine from AMP) (Stagg et al., 2010). NT5E can act as inhibitory immune checkpoint molecule, since free adenosine generated by NT5E inhibits cellular immune responses, thereby promoting immune escape of tumor cells. Indeed, adenosine is a potent immunosuppressive metabolite that is generated in response to pro-inflammatory stimuli, such as cellular stress initiated by hypoxia or ischemia. Landmark studies by Ohta and colleagues have highlighted the importance of adenosine for tumor immune escape (Ohta et al., 2006). Extracellular adenosine concentrations in solid tumors are reported to be higher than under normal physiological conditions (Blay et al., 1997).

Our transcriptome analysis identified a pool of immune related genes among the genes whose expression was affected by a mimic of miR-193a-3p as described in example 1. Among them were modifiers of TME, such as CD73. Moreover, our in vivo studies in murine models strongly suggested that miR-193a-3p, on top of its other effects, modifies the interaction between tumor cells and the immune system in a way that immune cells become more active in killing tumor cells. To assess the IO related effect of miR-193a-3p in human cells, and also to investigate the mechanism of the miR-193a-3p mediated IO effect, we established an in vitro assay in which, tumor cells were co-cultured together with human peripheral blood mononuclear cells (hPBMCs) isolated from healthy donor's peripheral blood, and the cytotoxic effect of hPBMCs on tumor cells was assessed with or without transfection with miR-193a-3p (see example 4).

As a first step and to establish the technical validity of such a cell-based assay, human anti CD3/CD28 T cell activator antibodies (positive control) was added to the tumor cells and PBMCs co-culture. The used activator comprises a soluble tetrameric antibody complex that binds CD3 and CD28 immune cell surface ligands. This binding results in cross-linking of CD3 and CD28, thereby providing the required primary and co-stimulatory signals for an effective T cell activation (Riddell et al., 1990; Bashour et al., 2014). As illustrated in Figure 8, although unstimulated human PBMCs showed limited effect on tumor cell survival (co-culture), addition of anti CD3/CD28 antibodies in the co-culture led to a pronounced decrease in tumor cell survival, most likely consequent to an efficient T cell activation and subsequent T cell-mediated tumor cell killing. Interestingly, in similar study performed with primary human dermal fibroblasts, no effect of anti CD3/CD28 on fibroblast viability was observed (data not shown), strongly suggesting that experimental T cell activation does not lead to T cell-mediated normal fibroblast killing.

Next, human melanoma A2058 and NSCLC A549 tumor cells were transfected with increasing concentrations of miR-193a-3p after which they were co-cultured with human PBMCs (at different PBMCs:Tumor cells ratio) for different times. Human PBMCs from independent donors were able to induce time-dependent marked tumor cell killing upon transfection of tumor cells with miRNA-193a as described in example 1, but not the (negative) miRNA control (scramble), validating sequence-specificity of miRNA-193a activity (Figure 9).

Taken together, our results demonstrate that transfection of tumor cells with miR-193a-3p clearly increases the vulnerability of tumor cells (e.g., A2058 and A549 tumor cells) to human PBMC cytotoxicity, by sensitizing tumor cells to PBMCs, and/or by releasing signals from transfected tumor cells to activate T cell-containing PBMCs.

Claims

1. A miRNA-193a or a source thereof, for use in treating a condition associated with PTEN-deficiency.

2. The miRNA-193a or a source thereof for use according to claim 1, wherein the miRNA-193a is a PTEN agonist.

3. The miRNA-193a or a source thereof for use according to claim 1 or 2, wherein the miRNA-193a is a miRNA-193a molecule, an isomiR, or a mimic thereof, wherein it is preferably an oligonucleotide with a seed sequence comprising at least 6 of the 7 nucleotides of the seed sequence represented by SEQ ID NO: 22.

4. The miRNA-193a or a source thereof for use according to any one of claims 1-3, wherein a source of a miRNA is a precursor of a miRNA and is a nucleic acid of at least 50 nucleotides in length.

5. The miRNA-193a or a source thereof for use according to any one of claims 1-4,
wherein said miRNA shares at least 70% sequence identity with any one of SEQ ID NOs: 56, 121, or 122,
and/or wherein said miRNA is from 15-30 nucleotides in length,
and/or wherein said source of a miRNA is a precursor of said miRNA and shares at least 70% sequence identity with any one of SEQ ID NOs: 5 or 13.

6. The miRNA-193a or a source thereof for use according to any one of claims 1-5, wherein the condition associated with PTEN deficiency is a PTEN-deficient cancer.

7. The miRNA-193a or a source thereof for use according to any one of claims 1-6, wherein the PTEN-deficient cancer is a PTEN-deficient sarcoma, brain cancer, head and neck cancer, breast cancer, lung cancer, kidney cancer, liver cancer, colon cancer, ovarian cancer, melanoma, pancreatic cancer, thyroid cancer, hamartoma, tumour of the haematopoietic and lymphoid malignancy, or prostate cancer.

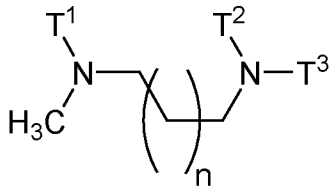
8. The miRNA-193a or a source thereof for use according to any one of claims 1-7, wherein the miRNA-193a modulates expression of a gene selected from the group consisting of RPS6KB2, KRAS, PDGFRB, SOS2, TGFBR3, CASP9, INPPL1, PIK3R1, PTK2, CBL, PDPK1, CCND1, BCAR1, MAGI3, MDM2, YWHAZ, and MCL1, preferably from the group consisting of RPS6KB2, KRAS, PDGFRB, CASP9, INPPL1, PIK3R1, PTK2, CBL, PDPK1, CCND1, BCAR1, MAGI3, MDM2, YWHAZ, MCL1, more preferably selected from PDPK1 or INPPL1.

9. A composition comprising a miRNA-193a or a source thereof as defined in any one of claims 1-8, for use as defined in any one of claims 1-8.

10. The composition for use according to claim 9, further comprising a further miRNA or precursor thereof, wherein the further miRNA is selected from the group consisting of miRNA-323, miRNA-342, miRNA-520f, miRNA-520f-i3, miRNA-3157, and miRNA-7, or an isomiR thereof, or a mimic thereof.

11. The composition for use according to claim 9 or 10, further comprising an additional pharmaceutically active compound, preferably selected from the group consisting of a PP2A methylating agent, an inhibitor of hepatocyte growth factor (HGF), an antibody, a PI3K inhibitor, an Akt inhibitor, an mTOR inhibitor, a binder of a T cell co-stimulatory molecule such as a binder of OX40, and a chemotherapeutic agent.

12. A nanoparticle composition, for use as defined in any one of claims 1-8, the nanoparticle comprising a diamino lipid and a miRNA-193a or a source thereof as defined in any one of claims 1-8, wherein the diamino lipid is of general formula (I)



(I)

wherein

n is 0, 1, or 2, and

T^1, **T^2**, and **T^3** are each independently a C_{10}-C_{18} chain with optional unsaturations and with zero, one, two, three, or four substitutions, wherein the substitutions are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkenyl, and C_1-C_4 alkoxy.

13. The nanoparticle composition for use according to claim 12, wherein the nanoparticles comprise:

i) 20-60 mol% of diamino lipid, and

ii) 0-40 mol% of a phospholipid, and

iii) 30-70 mol% of a sterol, and

iv) 0-10 mol% of a conjugate of a water soluble polymer and a lipophilic anchor.

14. An in vivo, in vitro, or ex vivo method for agonising PTEN, the method comprising the step of contacting a cell with a miRNA as defined in any one of claims 1-8, or with a composition as defined in any one of claims 9-13.

15. A method for treating a PTEN-deficient cancer, the method comprising the step of administering to a subject a miRNA-193a as defined in any one of claims 1-8, or a composition as defined in any one of claims 9-13.

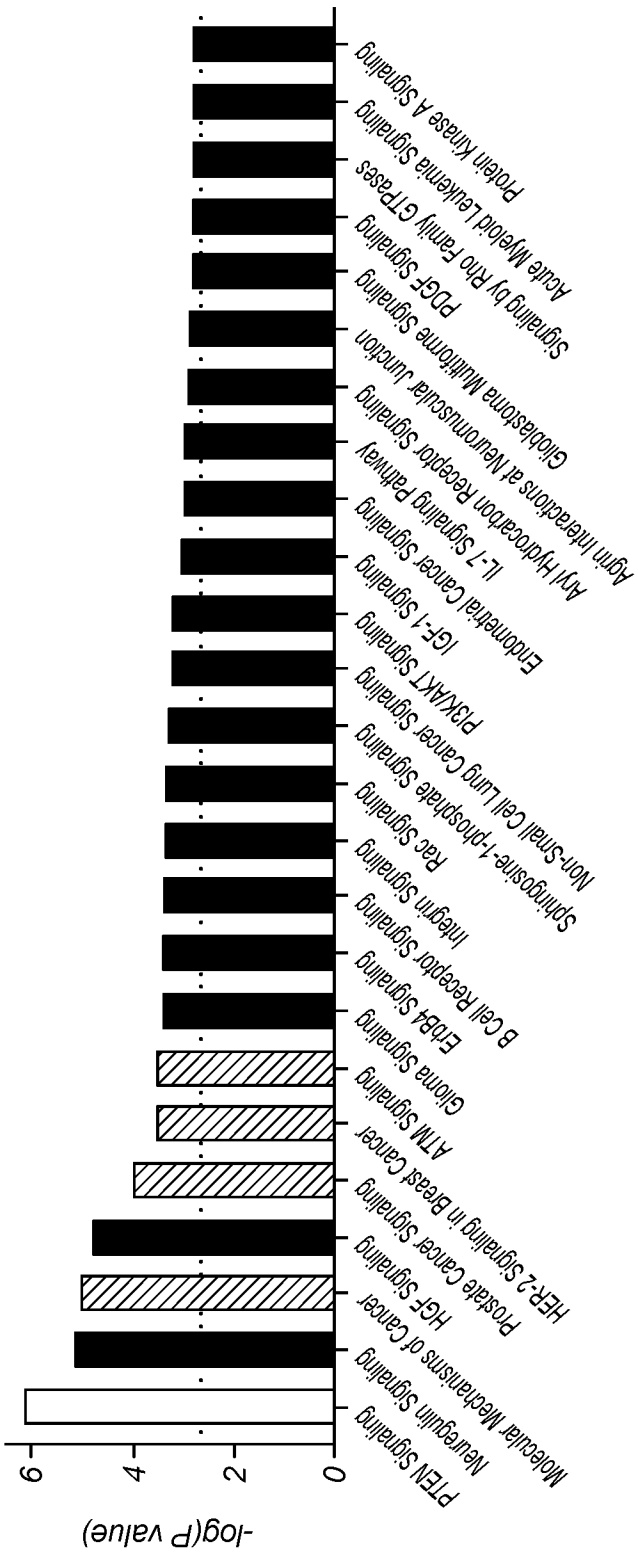

PTEN Signaling
Neuregulin Signaling
Molecular Mechanisms of Cancer
HGF Signaling
Prostate Cancer Signaling
HER-2 Signaling in Breast Cancer
ATM Signaling
Glioma Signaling
ErbB4 Signaling
B Cell Receptor Signaling
Integrin Signaling
Rac Signaling
Sphingosine-1-phosphate Signaling
Non-Small Cell Lung Cancer Signaling
PI3K/AKT Signaling
IGF-1 Signaling
Endometrial Cancer Signaling
IL-7 Signaling Pathway
Aryl Hydrocarbon Receptor Signaling
Agrin Interactions at Neuromuscular Junction
Glioblastoma Multiforme Signaling
PDGF Signaling
Signaling by Rho Family GTPases
Acute Myeloid Leukemia Signaling
Protein Kinase A Signaling
0
2
4
6
-log(P value)

Fig. 1A

Fig. 1B

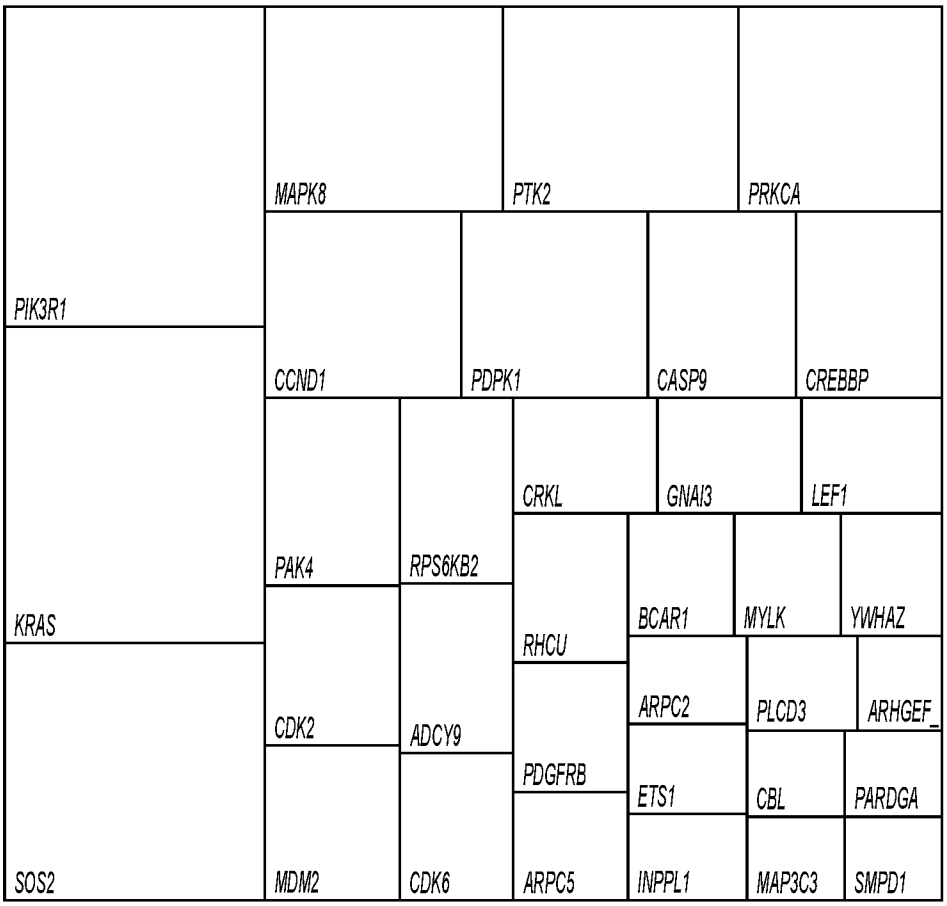

MAPK8
PTK2
PRKCA
PIK3R1
CCND1
PDPK1
CASP9
CREBBP
CRKL
GNAI3
LEF1
PAK4
RPS6KB2
RHCU
BCAR1
MYLK
YWHAZ
KRAS
CDK2
ADCY9
ARPC2
PLCD3
ARHGEF_
PDGFRB
ETS1
CBL
PARDGA
SOS2
MDM2
CDK6
ARPC5
INPPL1
MAP3C3
SMPD1

Fig. 2

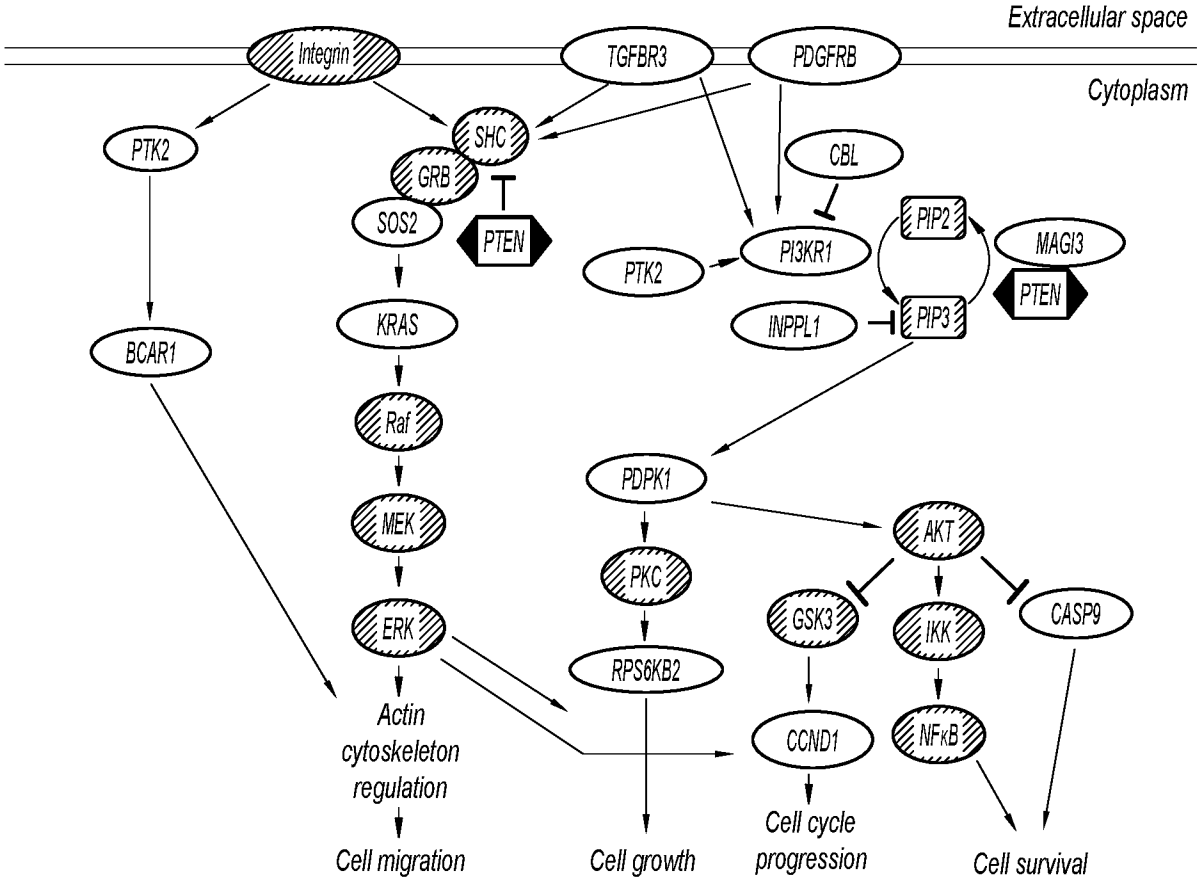

Extracellular space
Cytoplasm
Integrin
TGFBR3
PDGFRB
PTK2
SHC
GRB
SOS2
PTEN
CBL
PI3KR1
PTK2
PIP2
MAGI3
PTEN
INPPL1
PIP3
BCAR1
KRAS
Raf
MEK
ERK
PDPK1
PKC
RPS6KB2
AKT
GSK3
IKK
CASP9
NFκB
CCND1
Actin cytoskeleton regulation
Cell migration
Cell growth
Cell cycle progression
Cell survival

Fig. 3

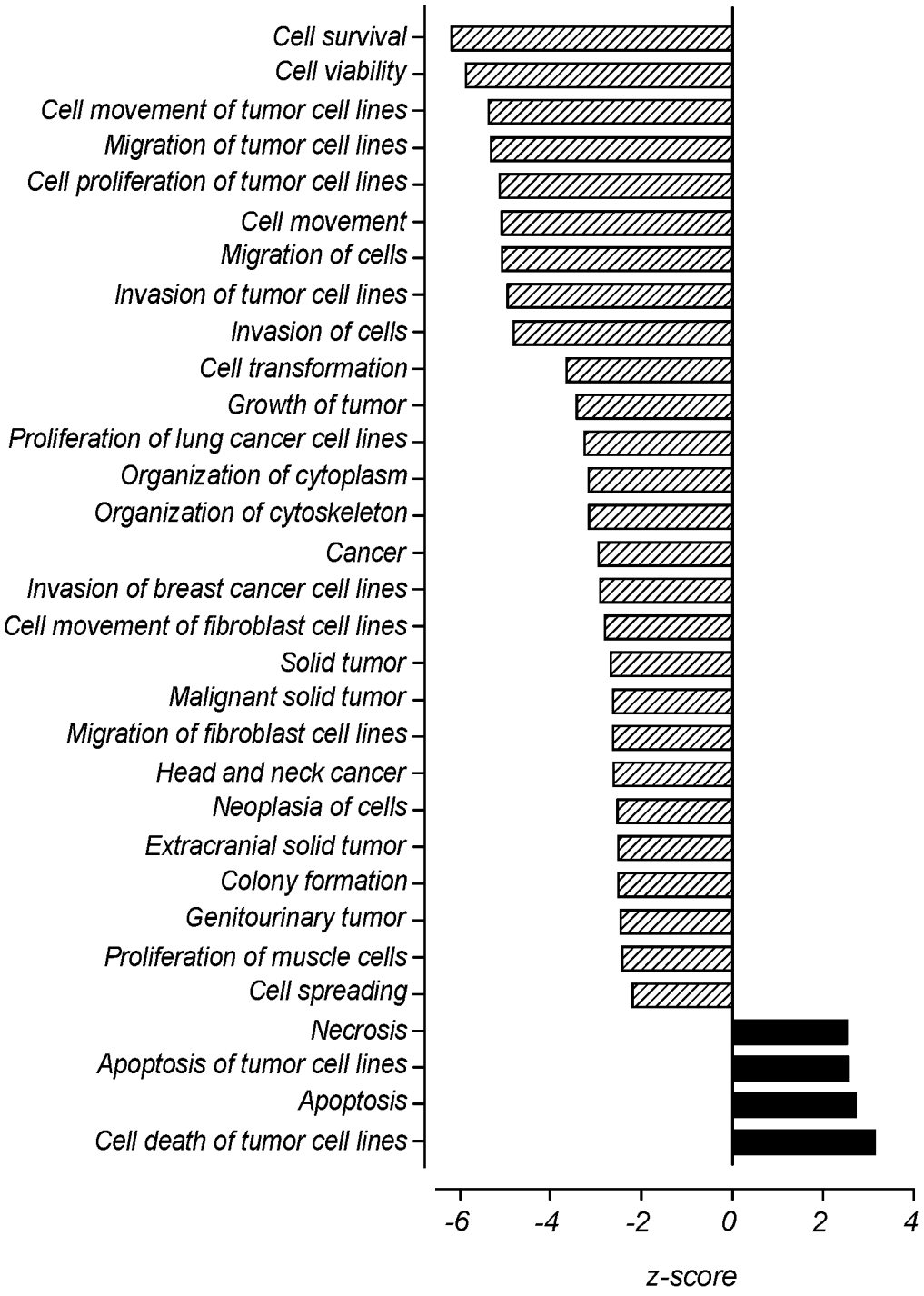

Cell survival
Cell viability
Cell movement of tumor cell lines
Migration of tumor cell lines
Cell proliferation of tumor cell lines
Cell movement
Migration of cells
Invasion of tumor cell lines
Invasion of cells
Cell transformation
Growth of tumor
Proliferation of lung cancer cell lines
Organization of cytoplasm
Organization of cytoskeleton
Cancer
Invasion of breast cancer cell lines
Cell movement of fibroblast cell lines
Solid tumor
Malignant solid tumor
Migration of fibroblast cell lines
Head and neck cancer
Neoplasia of cells
Extracranial solid tumor
Colony formation
Genitourinary tumor
Proliferation of muscle cells
Cell spreading
Necrosis
Apoptosis of tumor cell lines
Apoptosis
Cell death of tumor cell lines
-6
-4
-2
0
2
4
z-score

Fig. 4

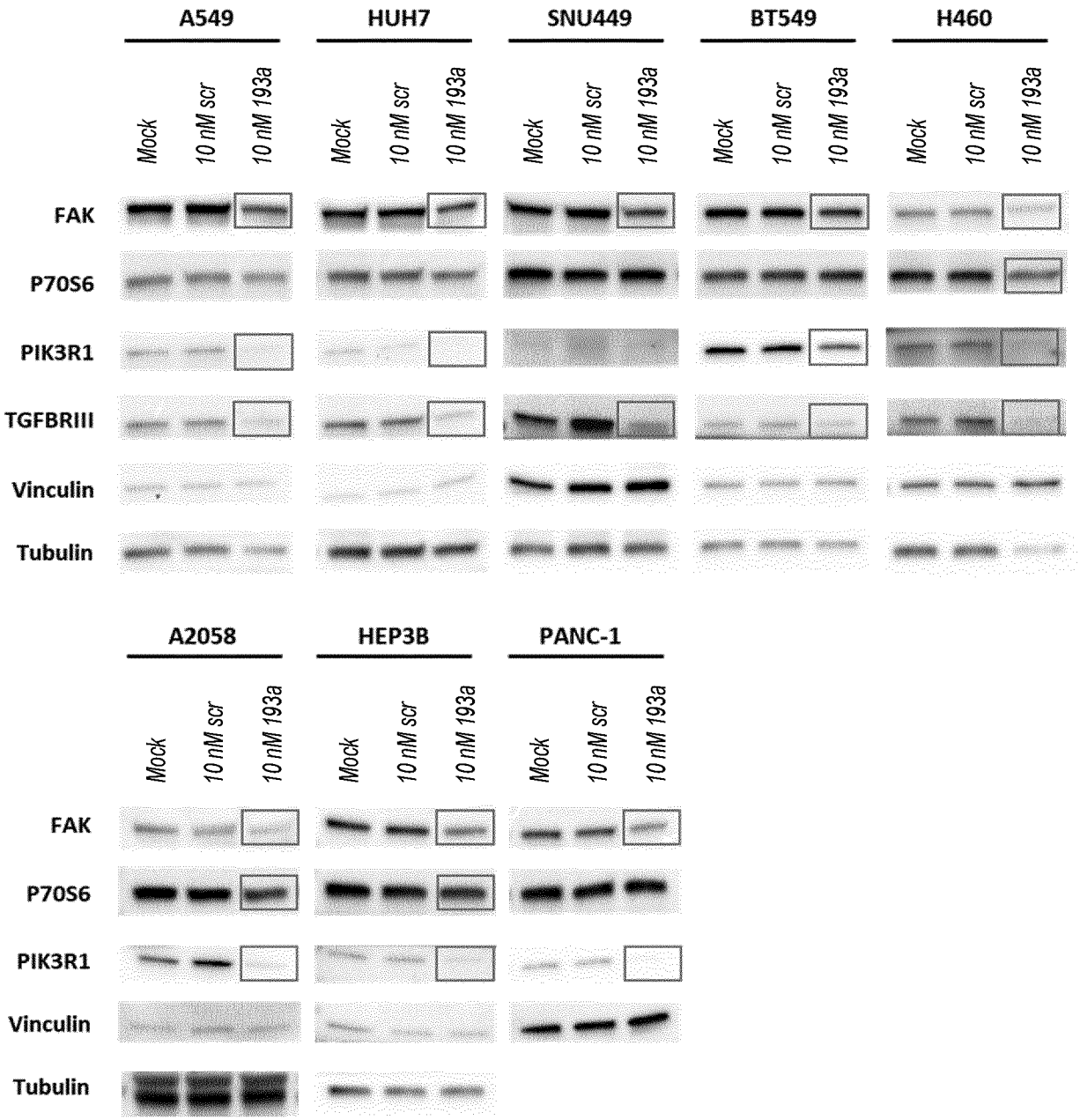

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SNU449
BT549
H460
Mock
10 nM scr
10 nM 193a
FAK
P70S6
PIK3R1
TGFBRIII
Vinculin
Tubulin
A2058
HEP3B
PANC-1

Fig. 5

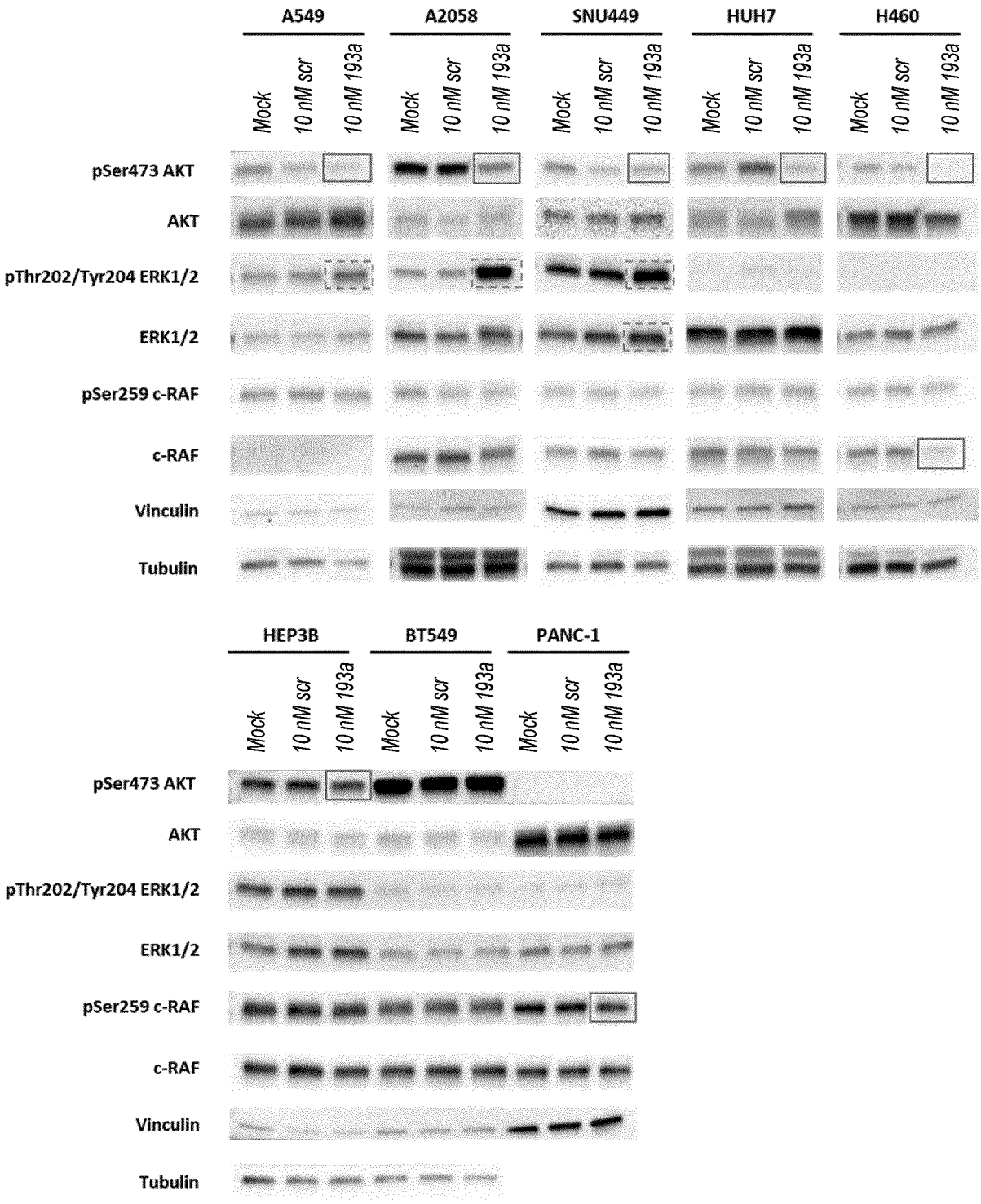
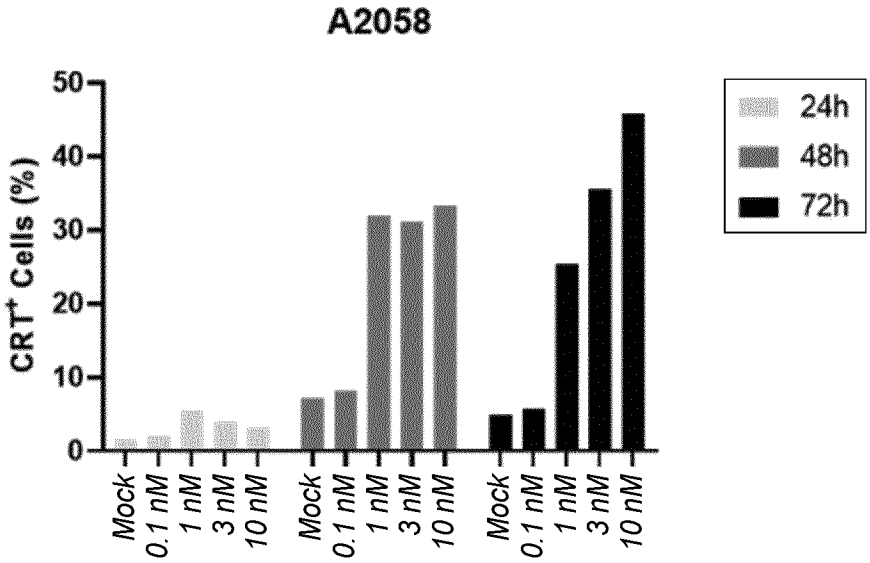

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A2058
SNU449
HUH7
H460
Mock
10 nM scr
10 nM 193a
pSer473 AKT
AKT
pThr202/Tyr204 ERK1/2
ERK1/2
pSer259 c-RAF
c-RAF
Vinculin
Tubulin
HEP3B
BT549
PANC-1
Mock
10 nM scr
10 nM 193a
pSer473 AKT
AKT
pThr202/Tyr204 ERK1/2
ERK1/2
pSer259 c-RAF
c-RAF
Vinculin
Tubulin

Fig. 6

A


A2058
CRT+ Cells (%)
0
10
20
30
40
50
Mock
0.1 nM
1 nM
3 nM
10 nM
24h
48h
72h

B

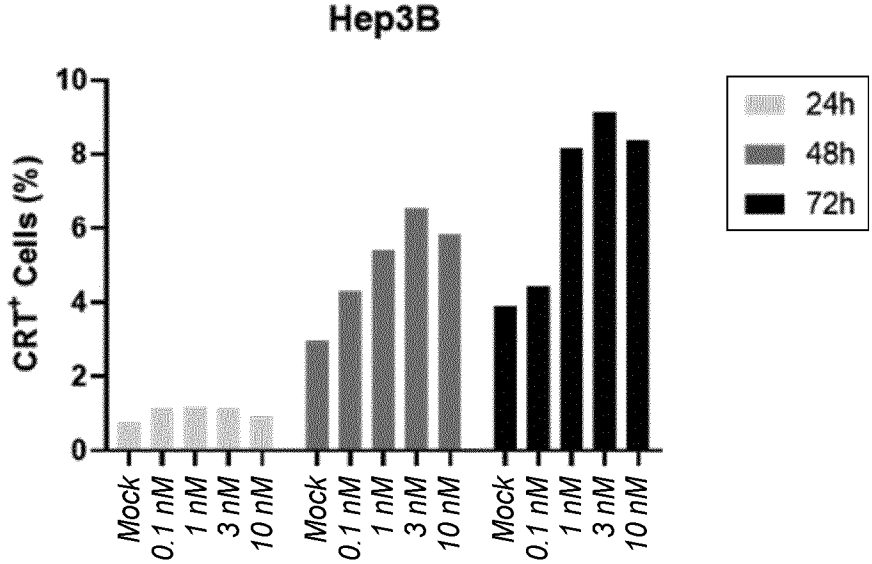

Hep3B
CRT+ Cells (%)
0
2
4
6
8
10
Mock
0.1 nM
1 nM
3 nM
10 nM
24h
48h
72h

Fig. 6

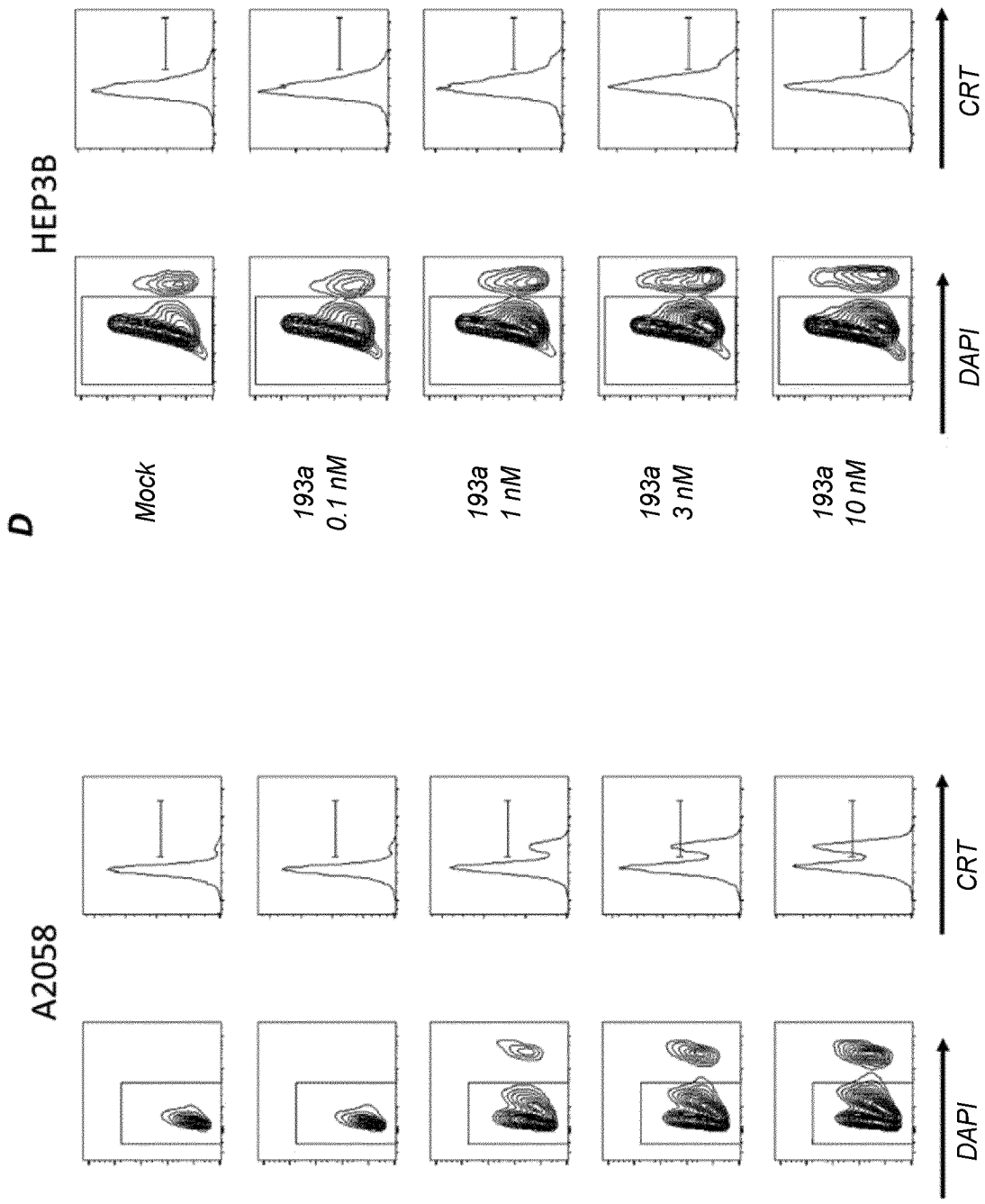

c
A2058
Mock
193a 0.1 nM
193a 1 nM
193a 3 nM
193a 10 nM
DAPI
CRT
D
HEP3B
Mock
193a 0.1 nM
193a 1 nM
193a 3 nM
193a 10 nM
DAPI
CRT

Fig. 7

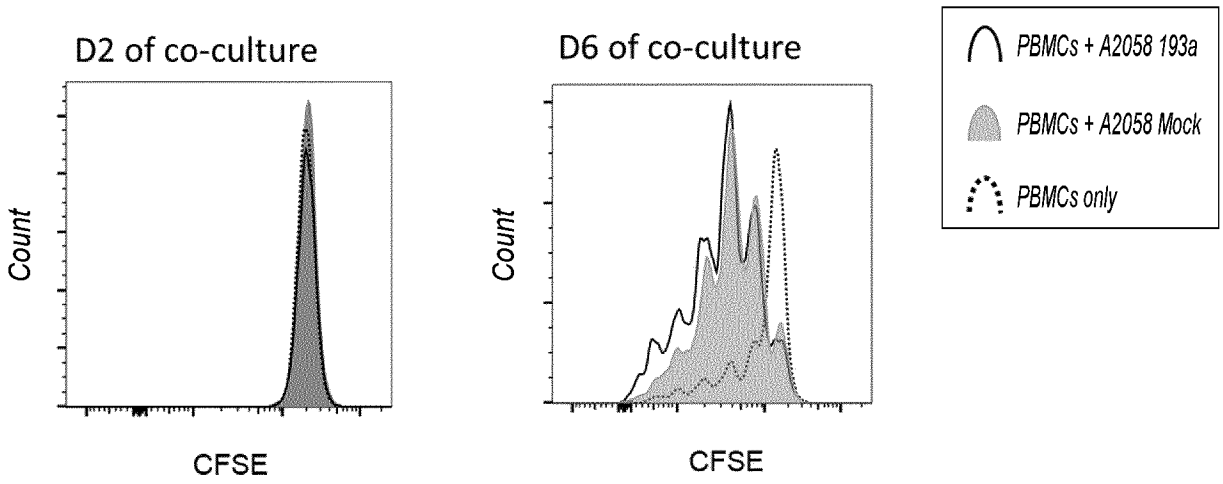


Fig. 8

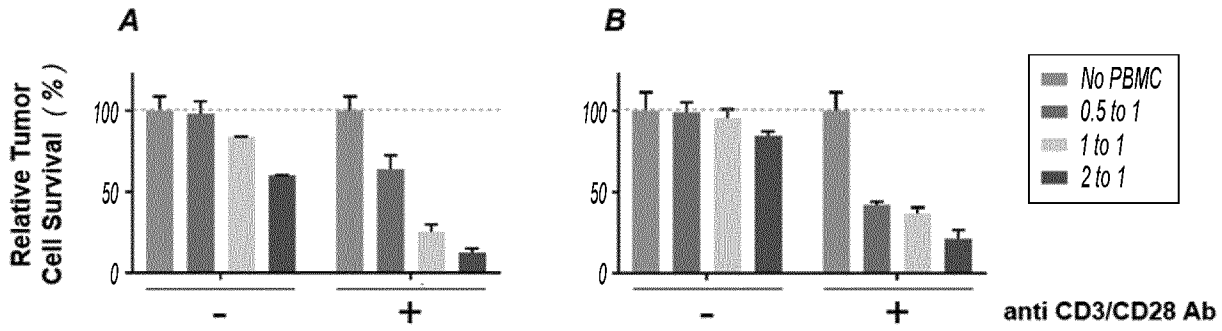
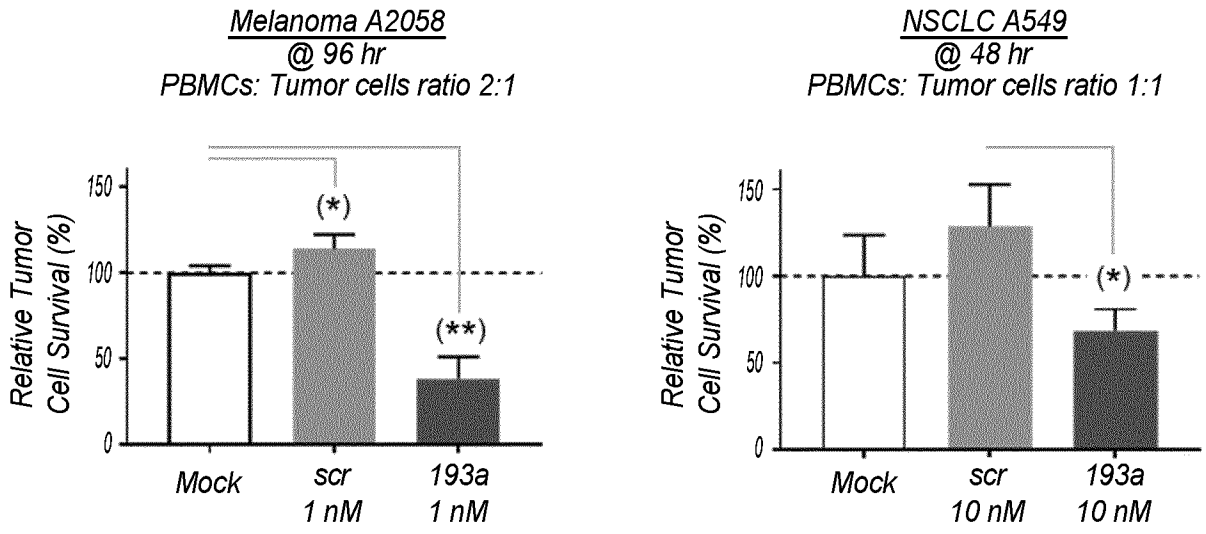


Fig. 9



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