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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 May 2023 (19.05.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/086552 A2

(51) International Patent Classification:
C12N 15/11 (2006.01) *A61K 48/00* (2006.01)

(21) International Application Number:
PCT/US2022/049676

(22) International Filing Date:
11 November 2022 (11.11.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/278,950 12 November 2021 (12.11.2021) US

(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, 12th Floor, Oakland, California 94607 (US).

(72) Inventors: **ORTIZ URDA, Susana**; 1111 Franklin Street, 12th Floor, Oakland, California 94607 (US). **FEICHTENSCHLAGER, Valentin**; 1111 Franklin Street, 12th Floor, Oakland, California 94607 (US). **VUJIC, Igor**; 1111 Franklin Street, 12th Floor, Oakland, California 94607 (US). **SANLORENZO, Martina**; 1111 Franklin Street, 12th Floor, Oakland, California 94607 (US). **CHEN, Emily**; 1111 Franklin Street, 12th Floor, Oakland, California 94607 (US). **COPPE, Jean-Philippe**; 1111 Franklin Street, 12th Floor, Oakland, California 94607 (US).

(74) Agent: **HINSCH, Matthew** et al.; KILPATRICK TOWNSEND AND STOCKTON LLP, Mail Stop: IP Docketing - 22, 1100 Peachtree Street NE, Suite 2800, Atlanta, Georgia 30309-4528 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS,

(54) Title: LNCRNA TRANSCRIPTS IN MELANOMAGENESIS

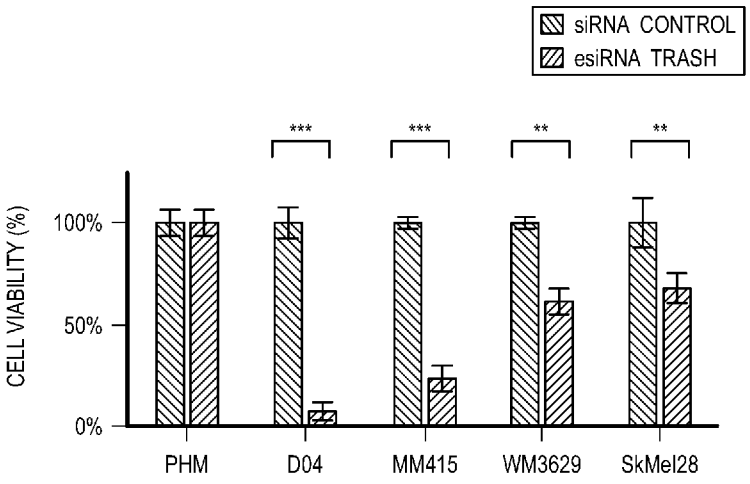

FIG. 1D

(57) Abstract: The invention provides compositions and methods for treatment of melanoma and other cancers. In particular, the invention provides a single or double-stranded nucleic acid that inhibits a certain group of long non-coding RNAs (lncRNAs) that have been discovered to be associated with melanoma. Inhibition of these lncRNAs in melanoma cells and xenograft mouse models leads to inhibition of cell proliferation, induction of apoptosis, and reduced cancer cell growth. The invention also relates to a method of inhibiting cancer cell growth with specific kinase inhibitors that have been found to show similar inhibition effects as the nucleic acids targeting the lncRNAs. The single or double-stranded nucleic acid and the specific kinase inhibitors constitute a novel therapeutic strategy in the treatment of melanoma and other cancers.

WO 2023/086552 A2

[Continued on next page]

RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

LNCRNA TRANSCRIPTS IN MELANOMAGENESIS

BACKGROUND OF THE INVENTION

[0001] The present patent application claims benefit of priority to U.S. Provisional Patent Application No. 63/278,950, filed November 12, 2021, which is incorporate by reference for all purposes.

BACKGROUND OF THE INVENTION

[0002] Melanoma is the deadliest form of skin cancer and its incidence is rising [Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Populations - Total U.S. (1969-2019) <Katrina/Rita Adjustment> - Linked To County Attributes - Total U.S., 1969-2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released December 2020]. Most solid tumors, including melanoma, harbor oncogene mutations which activate MAPK pathways. These important HNRNPA2signaling cascades turn extracellular stimulation into intracellular reactions and regulate cell proliferation, survival, and apoptosis. Targeting essential components of the MAPK pathway such as the BRAF and MEK kinases tremendously increased melanoma therapy progress during the last two decades.[Yuan, et al.,. *The MAPK and AMPK signalings: interplay and implication in targeted cancer therapy.* J Hematol Oncol **13**, 113 (2020).; Santarpia, et al.,. *Targeting the MAPK–RAS–RAF signaling pathway in cancer therapy. Expert Opinion on Therapeutic Targets* 16, 103–119 (2012).; Attwood, M. et al, *Trends in kinase drug discovery: targets, indications and inhibitor design. Nat Rev Drug Discov* (2021) doi:10.1038/s41573-021-00252-y].The antitumor effect of BRAF/MEK inhibitors and other agents relies on the stimulation of apoptosis activating pathways.[Niessner, H. et al. *BRAF Inhibitors Amplify the Proapoptotic Activity of MEK Inhibitors by Inducing ER Stress in NRAS-Mutant Melanoma.* Clin Cancer Res 23, 6203–6214 (2017)]. Apoptosis is a caspase dependent dissolution of cell components such as proteins and DNA. Effector caspases, like caspase 3 and 7 mediate apoptosis. The mechanisms of apoptosis involve a complex machinery of interlocking processes that can be cancer specific and negatively or positively regulated on many levels.[Carneiro, B. A. & El-Deiry, W. S. *Targeting apoptosis in cancer therapy.* Nat Rev Clin Oncol 17, 395–417

(2020).]. An example for an apoptosis inhibiting oncogene is hnRNPA2/B1. It is overexpressed in many types of cancer.[Gupta, A. et al. *The HNRNPA2B1–MST1R–Akt axis contributes to epithelial-to-mesenchymal transition in head and neck cancer.* Lab Invest (2020) doi:10.1038/s41374-020-0466-8.; Barceló, C. et al. *Ribonucleoprotein HNRNPA2B1 Interacts With and Regulates Oncogenic KRAS in Pancreatic Ductal Adenocarcinoma Cells.* Gastroenterology 147, 882-892.e8 (2014); Liu, et al; *Identification of anti-tumoral feedback loop between VHLα and hnRNPA2B1 in renal cancer.* Cell Death Dis 11, 688 (2020).; Klinge, et al; *HNRNPA2/B1 is upregulated in endocrine-resistant LCC9 breast cancer cells and alters the miRNA transcriptome when overexpressed in MCF-7 cells.* Sci Rep 9, 9430 (2019)]. In melanoma hnRNPA2/B1 inhibits apoptosis and could serve as potent biomarker.[Li, et al; *Increased expression of YTHDF1 and HNRNPA2B1 as potent biomarkers for melanoma: a systematic analysis.* Cancer Cell Int **20**, 239 (2020).; Chu, et al., *Requirement of splicing factor hnRNP A2B1 for tumorigenesis of melanoma stem cells.* Stem Cell Res Ther 12, 90 (2021)] hnRNPA2/B1 affects apoptosis through modulating the AKT pathway and regulating caspase activity.[Barceló, C. et al. *Ribonucleoprotein HNRNPA2B1 Interacts With and Regulates Oncogenic KRAS in Pancreatic Ductal Adenocarcinoma Cells.* Gastroenterology 147, 882-892.e8 (2014).; Yin, et al., *Effect of hnRNPA2/B1 on the proliferation and apoptosis of glioma U251 cells via the regulation of AKT and STAT3 pathways.* Bioscience Reports **40**, BSR20190318 (2020).; Yin, et al., *Effect of hnRNPA2/B1 on the proliferation and apoptosis of glioma U251 cells via the regulation of AKT and STAT3 pathways.* Bioscience Reports **40**, BSR20190318 (2020).; Chen, Z.-Y. et al. *Fyn requires HnRNPA2B1 and Sam68 to synergistically regulate apoptosis in pancreatic cancer.* Carcinogenesis **32**, 1419–1426 (2011); Jiang, F. et al. *HNRNPA2B1 promotes multiple myeloma progression by increasing AKT3 expression via m6A-dependent stabilization of ILF3 mRNA.* J Hematol Oncol **14**, 54 (2021). Deng, J. et al. *Effects of hnRNP A2/B1 Knockdown on Inhibition of Glioblastoma Cell Invasion, Growth and Survival.* Mol Neurobiol **53**, 1132–1144 (2016).; Yang, Y. et al. *Loss of hnRNPA2B1 inhibits malignant capability and promotes apoptosis via down-regulating Lin28B expression in ovarian cancer.* Cancer Letters **475**, 43–52 (2020).; Peng, W. et al. *hnRNPA2B1 regulates the alternative splicing of BIRC5 to promote gastric cancer progression.* Cancer Cell Int **21**, 281 (2021).; Chen, Z. et al. *Integrative Analysis of NSCLC Identifies LINC01234 as an Oncogenic lncRNA that Interacts with HNRNPA2B1 and Regulates miR-106b Biogenesis.* Molecular Therapy **28**, 1479–1493 (2020).] One of the main goals of clinical oncology is the development of therapeutic agents that eradicate cancer cells by promoting apoptosis. [Carneiro, et al.,

Targeting apoptosis in cancer therapy. Nat Rev Clin Oncol **17**, 395–417 (2020)] However, patients with initial or acquired treatment resistance point toward the limitations of existing cancer therapy. To overcome these limitations, an increased armament of anticancer therapeutics is urgently needed.[Luke, et al., *Targeted agents and immunotherapies: optimizing outcomes in melanoma*. Nat Rev Clin Oncol 14, 463–482 (2017)].

[0003] The majority of the human transcriptome does not get translated to proteins. A large fraction of these untranslated transcripts are long non-coding RNAs (lncRNAs), defined as non-coding complexes longer than 200 nucleotides.[Cabili, M. N. et al. *Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses.* Genes & Development 25, 1915–1927 (2011)]

[0004] lncRNAs can play role in oncogenesis through several mechanisms. They can regulate cancer specific gene expression as splicing factors or through epigenetic histone modification. [Amodio, N. et al. *MALAT1: a druggable long non-coding RNA for targeted anti-cancer approaches*. J Hematol Oncol 11, 63 (2018)] They can also promote malignant processes through activating or stabilizing protein binding partners.[Wang, S. et al. *JAK2-binding long noncoding RNA promotes breast cancer brain metastasis. Journal of Clinical Investigation* 127, 4498–4515 (2017).; Lin, A. et al. *The LINK-A lncRNA interacts with PtdIns(3,4,5)P3 to hyperactivate AKT and confer resistance to AKT inhibitors.* Nat Cell Biol 19, 238–251 (2017).] Recent research has identified and characterized novel cancer specific lncRNA transcripts.[Huarte, M. *The emerging role of lncRNAs in cancer.* Nat Med 21, 1253–1261 (2015).; Ding, L. et al. *Role of noncoding RNA in drug resistance of prostate cancer.* Cell Death Dis 12, 590 (2021).]

[0005] In recent years, an increasing number of RNA-targeting therapeutics such as Antisense Oligonucleotides (ASOs) have been brought to clinical trials and obtained FDA approval.[Bedikian, et al., *Dacarbazine with or without oblimersen (a Bcl-2 antisense oligonucleotide) in chemotherapy-naive patients with advanced melanoma and low–normal serum lactate dehydrogenase: 'The AGENDA trial'.* Melanoma Research **24**, 237–243 (2014).; Beer, T. M. et al. *Custirsen (OGX-011) combined with cabazitaxel and prednisone versus cabazitaxel and prednisone alone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (AFFINITY): a randomised, open-label, international, phase 3 trial.* The Lancet Oncology **18**, 1532–1542 (2017).] In particular, lncRNA-targeted gene silencing shows promising emerging results. [Winkle, et al.,

Noncoding RNA therapeutics — challenges and potential solutions. Nat Rev Drug Discov **20**, 629–651 (2021).]

BRIEF SUMMARY OF THE INVENTION

[0006] Aspects of the invention as described herein. In some aspects, the disclosure provides a single or double-stranded nucleic acid of 12-50 nucleotides in length comprising at least 12 nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12, wherein introduction of the single or double-stranded nucleic acid into a cell expressing long non-coding RNA (lncRNA) BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201 inhibits expression of the lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201.

[0007] In some embodiments, the single or double-stranded nucleic acid comprises at least 12 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12.

[0008] In some embodiments, the single or double-stranded nucleic acid is a single-stranded nucleic acid that is an antisense polynucleotide or a ribozyme that targets lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. In some embodiments, the single-stranded nucleic acid comprises the sequence of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO:41 or SEQ ID NO:47.

[0009] In some embodiments, the single or double-stranded nucleic acid is a double-stranded nucleic acid that is a small interfering RNA (siRNA) or a short hairpin RNA (shRNA) that targets lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. In some embodiments, the double-

stranded nucleic acid comprises a sense strand and an antisense strand, wherein the sense strand and the antisense comprise the sequence of SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 42 and SEQ ID NO: 50; SEQ ID NO: 43 and SEQ ID NO: 51; SEQ ID NO: 44 and SEQ ID NO: 52; SEQ ID NO: 45 and SEQ ID NO: 53; or SEQ ID NO: 46 and SEQ ID NO: 54.

[0010] In some embodiments, the single or double-stranded nucleic acid is a single-stranded nucleic acid that is a guide RNA (gRNA) that targets a polynucleotide encoding lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201.

[0011] In some embodiments, comprises at least one modified nucleotide. In some embodiments, the modified nucleotide comprises a modification selected from the group consisting of a sugar modification, a nucleic acid base modification, and a phosphate backbone modification. In some embodiments, the 2'-sugar modification is selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA, and locked nucleic acid (LNA) modification. In some embodiments, the phosphate backbone modification is a 5' phosphorylation.

[0012] In some embodiments, the double-stranded nucleic acid and comprises one or two 1-6 nucleotide (e.g., 3') overhang.

[0013] In some aspects, the disclosure provides a vector comprising the single or double-stranded nucleic acid as described above r elsewhere herein. In some embodiments, the vector is a viral vector. In some embodiments, the viral vector is a retroviral, a lentiviral, or an adeno-associated viral (AAV) vector.

[0014] In some aspects, the disclosure provides a pharmaceutical composition comprising the single or double-stranded nucleic acid as described above or elsewhere herein or the vector as described above or elsewhere herein and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition further comprises a specific inhibitor of one or more kinases selected from the group consisting of MEK, PLK1, TAF, AURKA,

HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, and RAF. In some embodiments, the specific inhibitor is selected from the group consisting of trametinib, volasertib, tozasertib, alisertib, Bay-299, and CeMMEC1.

[0015] In some embodiments, the pharmaceutically acceptable carrier comprises a copolymer, a lipid, or a nanoparticle. In some embodiments, the nanoparticle is a liposomal nanoparticle.

[0016] In some aspects, the disclosure provides methods of inhibiting cancer cell. In some embodiments, the cancer cell is dependent on MAPK pathway hyperactivation. In some embodiments, the method comprises contacting the single or double-stranded nucleic acid as described above or elsewhere herein, the vector as described above or elsewhere herein, or the pharmaceutical composition as described above or elsewhere herein with the cancer cell such that expression of lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201 is inhibited.

[0017] In some embodiments, the cancer cell is a neuroblastoma ras sarcoma viral oncogene homolog (NRAS)-mutated cancer cell. In some embodiments, the cancer cell is a BRAF-mutated cancer cell.

[0018] In some embodiments, the cancer cell is in a human and the method comprises administering a therapeutically-effective amount of the single or double-stranded nucleic acid to the human.

[0019] In some embodiments, the method further comprises contacting the cancer cell with a specific inhibitor of one or more kinases selected from the group consisting of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, and RAF. In some embodiments, the specific inhibitor is selected from the group consisting of trametinib, volasertib, tozasertib, alisertib, Bay-299, CeMMEC1.

[0020] In some embodiments, the method comprising contacting the cancer cell with a specific inhibitor of one or more kinases selected from the group consisting of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, and RAF in an amount to inhibit the cancer cell growth. In some embodiments, the cancer cell is a neuroblastoma ras sarcoma viral oncogene homolog (NRAS)-mutated cancer cell. In some embodiments, the cancer cell is a BRAF-mutated cancer cell. In some embodiments, the

specific inhibitor is selected from the group consisting of trametinib, volasertib, tozasertib, alisertib, Bay-299, and CeMMEC1.

[0021] In some embodiments, the cancer cell is in a human. In some embodiments, the cancer cell is a melanoma cell. In some embodiments, the cancer cell is a metastatic melanoma cancer cell. In some embodiments, the cancer cell is a MEK-therapy resistant cancer cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] **Figure 1A-E. The lncRNA TRASH (AC004540.4) is responsive to MAPK-activation and essential for melanoma cell survival A)** Schematic draft of Pipeline steps to identify MAPK responsive lncRNAs that are essential for melanoma cell survival. NRAS mutant melanocytic and melanoma cell lines were compared to wild type melanocytic cell lines and differential expressed (DE) genes were filtered for lncRNAs, high occurrence (<90%) in TCGA patient samples and essentialness in melanoma cell lines **B)** Venn diagram showing the transcriptome intersect of DE genes of the three comparisons PHM^{Q61}/ PHM^{E}, D04/PHM^{E} and MM415/PHM^{E}. Expression change >2-fold was considered DE and 237 DE genes were filtered out. **C)** Scatter chart showing the percentage of expression in a TCGA patient dataset of NRAS mutant melanoma for the 119 lncRNAs derived from the list of 237 DE genes. LncRNA genes were ranked from 1 (lowest) to 119 (highest) average FPKM expression values. FPKM values >0.2 were considered as expressed. Only lncRNA genes that were expressed in >90% of patients were kept for further analysis. The red dot, highlighted with a red arrow represents TRASH. **D)** esiRNA respectively **E)** siRNA mediated silencing of TRASH affects cell viability of melanoma cell lines, but not of melanocytic cell lines. Cell viability was compared to incubation with non-targeting pooled siRNA, cells were incubated in 50nM oligonucleotide concentration for 72 hours (n=3). ATP quantitation was used as marker for metabolically active cells. Error bars represent standard deviation, Significance shown as p-values calculated by students t-test. *=p<0.05, **=p<0.01, ***=p<0.001.

[0023] **Figure 2A-F. Biological Characterization of TRASH. A)** Subcellular enrichment of lncRNAs TRASH, in D04 cells (n=3). Data was normalized to NEAT1 expression. MALAT1 (nuclear enriched) and H19 (cytoplasmic enriched) served as control. **B)** Relative Enrichment comparison of 4 different regions of the TRASH using primer pairs that target Exon 1 (1), Intron 1 (2), Intron1/Exon2 transition region (3) and Exon 2 (4) of the Isoform ENST00000451264.1 in D04 cells. Fold enrichment was calculated using the $2^{-\Delta\Delta Ct}$ method,

normalized to primer pair 4 (n=3). **C)** Gene expression of TRASH and hnRNPA2/B1 is significantly upregulated in TCGA melanoma samples (n=469) when compared to GTEx patient samples of non-cancerous skin biopsies (n=394). Significance shown as p-values calculated by students t-test. *=p<0.05, **=p<0.01, ***=p<0.001. **D)** GapmeR Antisense Oligonucleotide (ASO) mediated TRASH inhibition (TRASHi) leads to significant lower TRASH expression, without significant impact on hnRNPA2/B1 expression. Gene expression fold change was measured by qRT-PCR from RNA extract of D04 cells after 24 hours of 50nM ASO incubation (n=3) and is presented relation to Non-targeting GapmeR ASO incubation. Fold-change cut off for significant expression inhibition was considered as 0.5 (blue bar). **E)** Immunoblotting showing downregulation of hnRNPA2/B1 upon 1- and 2-day long ASO mediated TRASHi (100nM) in D04 cells. Beta Actin served as loading control. Cell lysate of D04 cells incubated in non-targeting ASOs served as control. **F)** Left: qRT–qPCR after RIP shows >65-fold enrichment of TRASH in hnRNPA2/B1 pulldown when compared to Rabbit IgG negative control pulldown (n=3). Right: Immunoblotting showing enrichment of hnRNPA2/B1 in hnRNPA2/B1 pulldown samples compared to Rabbit IgG negative control pulldown samples. Error bars represent standard deviation.

[0024] Figure 3A-D. Anti-apoptotic TRASH is essential for melanoma cell survival. A) Cell viability decrease upon TRASHi in the D04, MM415, WM1366, VMM39, Sk-Mel-2, WM3629, Sk-Mel-28, WM3211 standard melanoma cell lines and the Hs852.T and AV5 primary derived melanoma cell lines. Cell viability is relative to incubation with non-targeting ASOs. Incubation time was 5 days (n=3). **B)** Left: Colony count in the D04, MM415 and Sk-Mel-28 melanoma cell lines upon TRASHi compared to incubation with non-targeting ASOs (n=3). Right: Formed colonies in 10cm dishes after TRASHi and incubation with non-targeting control ASOs in the D04 melanoma cell line. Incubation time was 7 days. **C)** Cell viability decrease upon GapmeR ASO mediated hnRNPA2/B1 (SEQ ID NO: 48) knockdown in the D04 cell line. Cell viability is relative to incubation with non-targeting ASOs. Incubation time was 5 days (n=3). **D)** Activity levels of the apoptosis markers Caspase 3+7 upon TRASHi and GapmeR ASO mediated hnRNPA2/B1 knockdown in the D04 cell line. Incubation time was 1 day (n=3). ASO concentration for A-D was 50nM and in A+C ATP quantitation was used as marker for metabolically active cells. Significance is shown as p-values calculated by students t-test. *=p<0.05, **=p<0.01, ***=p<0.001. Error bars represent standard deviation.

[0025] Figure 4A-E. TRASHi presents features of clinical value. A) Cell viability is significantly decreased upon TRASHi in the trametinib resistant melanoma cell lines D04RM, MM415RM, WM3629RM and Sk-Mel-2RM. Cell viability is relative to incubation with non-targeting ASOs. Incubation time was 5 days (n=3). Incubation concentration was 50nM. ATP quantitation was used as marker for metabolically active cells. **B)** Multi drug applications of TRASHi (25 and 50nM) and trametinib (100-0.2nM) present combination Index (CI) values that show synergistic effects on cell viability decrease (n=2). Incubation time was 3 days. **C)** Tumor growth of mice that harbor xenograft (D04, AV5) and PDX (TM01341) melanoma tumors and received either systemic TRASHi or non-targeting control ASO treatment. Weight change during treatment is presented below the tumor growth curves. **D)** Systemic in vivo TRASHi leads to significant lower TRASH expression. Gene expression fold change was measured by qRT-PCR from RNA extracts of PDX (TM01341) tumors after 21 days of treatment (n=2) and is presented in relation to RNA levels of tumors that received non-targeting GapmeR ASO treatment. Fold-change cut off for significant expression inhibition was considered as 0.5 (blue bar). **E)** Left: Immunohistochemical staining for the expression of the apoptosis marker cleaved caspase 3 in D04 tumors after 21 days of systemic in vivo TRASHi (top) and non-targeting control ASO treatment (bottom). Right: Hematoxylin-eosin staining of liver tissue after 21 days of systemic in vivo TRASHi (top) and non-targeting control ASO treatment (bottom). Significance is shown as p-values calculated by students t-test. *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$. Error bars represent standard deviation.

Figure 5: **A)** Images of DAPI-, hnRNPA2/B1-, and TRASH-derived fluorescence in untreated D04 melanoma cells. Fluorescence labelling serves as visual confirmation for strong nuclear enrichment of hnRNPA2/B1 and TRASH in melanoma cells. **B)** Trametinib treatment causes dose dependent upregulation of hnRNPA2/B1 and TRASH expression in the D04 and MM415 cell line. **C)** TRASH-ASO treatment has a global effect on gene expression. Scatter plot diagram showing differential gene expression after TRASH-ASO treatment compared to Control-ASO treatment. (cut-off for significance was adjusted p-value < 0.05). Data was obtained from RNA-Seq of D04 melanoma cells, treatment period was three days. **D)** In contrast to MEKi, TRASH-ASO treatment does not lead to drug resistance. D04 Cells that survived initial TRASH-ASO (50nM) or MEKi (15nM) treatment subsequently recovered in drug free media. Repetition of the preceding drug treatment in the surviving cell-subpopulation (same conditions) led to significantly increased (p=0.004) cell-growth

reduction for TRASH-ASO treatment and significantly decreased ($p<0.001$) cell-growth reduction for MEKi treatment. Cell-growth is relative to incubation with Control-ASOs (TRASH) or drug free media (MEKi). Drug-incubation time was five days (n=3). ATP quantitation was used as marker for metabolically active cells. **E)** Annexin V and Propidium Iodide staining od D04 cells after 24 hours of ASO mediated TRASH inhibition confirms induction of apoptosis followed by TRASH-ASO treatment.). Significant differences of expression correlations are shown as p-values calculated by students t-test. *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$. Error bars represent standard deviation.

Figure 6. Mapping the phospho-catalytic signatures of TRASH-dependent cells identifies inhibition of anti-apoptotic kinases upon TRASH-ASO treatment. A) Peptide-associated phosphorylation profiles of melanoma cell-lines treated with Control-ASOs or TRASH-ASOs for one day (50nM). Unsupervised clustering was applied (uncentered correlation and average linkage for both peptides/horizontal and samples/vertical). The profile of each sample is the average of two independent assay repeats. **B)** Kinase activity signatures of melanoma cell-lines treated with Control-ASOs, or TRASH-ASOs for one day (50nM). Kinases signatures are derived from results shown in panel A). Kinases for which ≥3 biological peptides are available, are shown. Unsupervised clustering was applied as in panel a). **C)** Kinase activity profiles of a subset of kinases known to promote cell-survival by preventing apoptosis. Kinase activities are normalized to Control-ASO treatment per cell-line. The effect of TRASH-ASOs on these kinases is compared side-by-side to MALAT1-ASO treatment. **D)** MALAT1-ASO treatment inhibits cell-growth and induces apoptosis. Left: Cell-growth is significantly ($p<0.001$) decreased upon MALAT1-ASO treatment (50nM) in the D04 cell-line. Cell-growth is relative to Control-ASO treatment (50nM). Incubation time was five days (n=3). ATP quantitation was used as marker for metabolically active cells. Right: Activity levels of the apoptosis markers Caspase-3 & -7 are significantly ($p=0.003$) upregulated upon MALAT1-ASO treatment (50nM) in the D04 cell-line. Caspase activity was normalized to treatment with Control-ASOs (50nM). Incubation time was one day (n=4). and significance is shown as p-values calculated by Students t-test. *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$. Error bars represent standard deviation. **E)** The specificity of the effects of TRASH-ASO treatment on the kinase activity signatures of melanoma cells is assessed in comparison to MALAT1-ASO treatment using Pearson correlation. **F)** Schematic summarizing the molecular impact of TRASH-ASO treatment. Expression of the lncRNA

TRASH is an essential dependency that promotes the survival of melanoma cells, and that can be effectively targeted with ASOs.

[0026] Figure 7A-D. Generating NRAS mutant melanocytic cell lines. A) Sanger Sequencing of Pooled primary human melanocytic cell lines (PHM) were equipped with an $NRAS^{Q61}$ mutation(PHM^{Q61}), respectively an empty vector (PHM^{E}) using the Gateways entry vector pENTR/D-topo, identifies a missense mutation in codon 61 (182A>G) in NRAS in PHM^{Q61} but not in PHM^{E} B) Left: Standard microscopic imaging of PHM^{Q61} and PHM^{E} cells carrying transduction efficacy reporter vectors that co-express green fluorescent protein, right: Fluorescence microscopic imaging of same cells. Microscopic images are inn 20x magnification. C) Immunoblotting showing upregulation of NRAS an the NRAS downstream signalling effectors AKT, p-AKT, ERK, p-ERK and NRAS in PHM^{E} compared to PHM^{Q61} . GAPDH served as loading control. D) PHM^{E} and PHM^{Q61} show no significant differences in cell proliferation. ATP quantitation was used as marker for metabolically active cells and measured 5 days after seeding equal number of cells (n=3). Significant differences of expression correlations are shown as p-values calculated by students t-test. *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$. Error bars represent standard deviation.

[0027] Figure 8. TRASH and hnRNPA2/B1 RNA expression in melanoma and healthy skin. Expression correlation of TRASH and hnRNPA2/B1 opposed to average expression correlation of TRASH (a+c), respectively hnRNPA2/B1 (b+d) compared to 10 sets of 200 random genes in melanoma patient biopsies of the TCGA SKCM dataset (n=469, a-b) and non-cancerous skin samples from the GTEx dataset (n=394, c-d). The red line represents Spearman rank-order correlation coefficient for expression correlation in TCGA-SKCM ($\rho=0.41$, a-b) and in GTEx skin samples ($\rho=0.24$, c-d). Significant differences of expression correlations are shown as p-values calculated by students t-test. *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$. Error bars represent standard deviation.

DEFINITIONS

[0028] As used herein, the term "nucleic acid" and "polynucleotide" are used interchangeably and refer to a polymer of nucleotides, including deoxyribonucleic acids (DNA), ribonucleic acids (RNA), or any combination and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing modified nucleotides.

[0029] A "nucleotide", as used herein, consists of a nucleobase, a sugar, and one or more phosphate groups. They are monomeric units of a nucleic acid sequence. In RNA, the sugar is a ribose, and in DNA a deoxyribose, i.e. a sugar lacking a hydroxyl group that is present in ribose. The nitrogenous base is a derivative of purine or pyrimidine. The purines are adenine (A) and guanine (G), and the pyrimidines are cytosine (C) and thymine (T) (or in the context of RNA, uracil (U)). Nucleotides are usually mono, di- or triphosphates. A "nucleoside" is structurally similar to a nucleotide, but does not include the phosphate moieties.

[0030] The term "modified nucleotide", as used herein refers to a nucleotide whose core structure is the same as, or closely resembles that of a nucleotide, but which has a modification, such as a sugar modification, a nucleic acid base modification and/or a phosphate backbone modification, including any known analog or derivative. A modified nucleotide may be a naturally occurring nucleotide or a non-natural nucleotide. The term "modification", as used herein, refers to any chemical or physical modification, including substitutions and additions of chemical moieties.

[0031] As used herein, the term "complementary" or "complementarity" refer to specific base pairing between nucleotides or nucleic acids. In some embodiments, for example, and not to be limiting, base pairing between an antisense oligonucleotide and a target nucleic acid sequence in a long non-coding RNA (lncRNA) is described. Complementary nucleotides are, generally, adenine (A) and thymine (T) (or A and uracil (U)), and guanine (G) and cytosine (C). It will be understood that term "complementary" or "complementarity" also encompasses base paring between modified nucleotides, or between non-modified and modified nucleotides. In the absence of a "%" term value, complementary means fully complementary or 100% complementary. The term "% complementary" as used herein, refers to the number of nucleotides in percent of a nucleotide region or sequence in a nucleic acid (e.g. an antisense polynucleotide) which, at a given position, are complementary to (i.e. form Watson Crick base pairs with) a nucleotide sequence, at a given position of a separate nucleic acid (e.g. a lncRNA).

[0032] The term "long non-coding RNA" or "lncRNA", as used herein refers to a non-protein coding RNA transcript that is longer than about 200 nucleotides and therefore can be distinguished from small regulatory RNAs such as microRNAs (miRNAs), small interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), and

other short RNAs. In some embodiments, the lncRNA is 200 nucleotides in length. In some embodiments, the lncRNA is no longer than 200 nucleotides in length.

[0033] The term "BX470102.3", as used herein, refers to the gene with accession number ENSG00000238279.1 in the Ensembl database. The gene is transcribed as a single isoform (or splice variant) referred herein as "BX470102.3-008" (ENST00000420695.1, SEQ ID NO: 1) with a length of 531 bp.

[0034] The term "AC004540.4", as used herein, refers to the gene with accession number ENSG00000225792 in the Ensembl database. The gene has two isoforms referred herein as "AC004540.4-001" (ENST00000451368; SEQ ID NO: 2) with a length of 611 bp, and "AC004540.4-002" (ENST00000451264; SEQ ID NO: 3) with a length of 508 bp.

[0035] The term "RP11-7011.3", as used herein, refers to the gene with accession number ENSG00000237950.1 in the Ensembl database. The gene has three isoforms referred herein as "RP11-7011.3-001" (ENST00000446167.1; SEQ ID NO: 4) with a length of 486 bp, "RP11-7011.3-003" (ENST00000445226.1; SEQ ID NO: 5) with a length of 294 bp, and "RP11-7011.3-002" (ENST00000412378.1; SEQ ID NO: 6) with a length of 494 bp.

[0036] The term "RN7SL1", as used herein, refers to the gene with accession number ENSG00000258486.1 in the Ensembl database. The gene has two isoforms referred herein as "RN7SL1-202" (ENST00000635274.1; SEQ ID NO: 7) with a length of 300 bp, and "RN7SL1-201" (ENST00000618786.1; SEQ ID NO: 8) with a length of 299 bp.

[0037] The term "ARF-AS1", as used herein, refers to the gene with accession number ENSG00000272146 in the Ensembl database. The gene has three isoforms referred herein as "ARF-AS1-201" (ENST00000606192.5; SEQ ID NO: 9) with a length of 327 bp, "ARF-AS1-202" (ENST00000607297.1; SEQ ID NO: 10) with a length of 437 bp, and "ARF-AS1-203" (ENST ENST00000607782.1; SEQ ID NO: 11) with a length of 552 bp.

[0038] The term "AL157871.4", as used herein, refers to the gene with accession number ENSG00000258666 in the Ensembl database. The gene is transcribed as a single isoform referred herein as "AL157871.4-201" (ENST00000557226.1; SEQ ID NO: 12) with a length of 385 bp.

[0039] As used herein, the term "inhibition", or any grammatical variation thereof (*e.g.*, inhibit, inhibiting, etc.) as referred to herein, relates to the retardation, restraining or reduction of the lncRNA levels, expression and/or activity by the nucleic acids of the invention and the

specific kinase inhibitors by at least 5%, at least 10%, at least 20%, at least 30%, at least, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100%, or any percentage in between.

[0040] As used herein, an "antisense polynucleotide", "antisense oligonucleotide" or "ASO" is a single-stranded nucleic acid sequence (DNA, RNA, or a nucleotide analog) capable of hybridizing to a target RNA sequence (e.g., a lncRNA). Upon binding to their target RNA, ASOs can inhibit gene expression and/or initiate the degradation of the target RNA through various mechanisms, for example by inducing cleavage of the target RNA through endoribonuclease (RNase) recruitment.

[0041] As used herein "ribozymes" are catalytic RNA oligonucleotides that can bind to a target RNA and cleave the target RNA through various cleavage mechanisms. Generally, ribozymes comprise a catalytic region and one or more binding regions. The binding regions hybridize to a complementary sequence of the target RNA, and the catalytic region cleaves the target RNA.

[0042] The term "hybridizes" or any grammatical variation thereof (e.g., hybridizing, hybridization, etc.) and “bind” or any grammatical variation thereof (e.g., binding, etc.) are used interchangeably and refer to the annealing of two nucleic acids strands. In particular, two nucleic acid strands form hydrogen bonds between base pairs of the two strands, thereby forming a duplex. In certain embodiments, an antisense oligonucleotide, an siRNA, or a shRNA may hybridize with a target nucleic acid sequence contained in a lncRNA.

[0043] As used herein "target sequence" or “target nucleic acid sequence” refers to a particular nucleotide sequence of the target nucleic acid to which a complementary nucleic acid binds to. In certain embodiments, the target sequence may be contained in the lncRNAs or a polynucleotide encoding one of the lncRNAs as described herein.

[0044] The term "target" or any grammatical variation thereof (e.g., targeting etc.) refers to the capability of a nucleic acid to bind to or hybridize with a target sequence on a complementary nucleic acid strand and inhibit its expression, reduce its levels and/or activity.

[0045] As used herein, the term "small interfering RNA (siRNA)" refers to a double-stranded RNA (or RNA analog) that is capable of directing or mediating RNA interference. In some embodiments, the siRNA is 10-50 nucleotides (or nucleotide analogs), e.g., 12-30 nucleotides in length, e.g., 15-25 nucleotides in length, e.g., 19-23 nucleotides in length, e.g., 21-23

nucleotides in length. Therefore, exemplary siRNA molecules are 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 28 or 29 nucleotides in length. In certain embodiments, the siRNA is a 21-mer comprising 21 nucleotides.

[0046] The term "short hairpin RNA", "small hairpin RNA", and "shRNA" are used interchangeably and refer to a double-stranded interfering RNA (e.g., siRNA) where the two strands are connected to form a hairpin or loop region.

[0047] The term "antisense strand" refers to the strand of the siRNA or shRNA that contains some degree of complementarity to the target sequence. As used herein, the term “sense strand” refers to the strand of the siRNA or shRNA that contains complementarity to the antisense strand.

[0048] As used herein, the term "overhang" refers to a single-stranded portion of a double-stranded nucleic acid that extends beyond the terminus of the complementary strand of the double-stranded nucleic acid.

[0049] The term "guide RNA" or "gRNA", as used herein refers to a nucleic acid that binds to a Cas protein and aids in targeting the Cas protein to a specific target sequence within DNA. A gRNA may comprise a crisp RNA (crRNA) and a transactivating crisp RNA (tracrRNA).

[0050] The term "vector", as used herein, refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a “viral vector” comprising virus derived sequences used to deliver a nucleic acid (e.g. an antisense oligonucleotide, an siRNA or shRNA, a ribozyme, or a gRNA) to a cell.

[0051] The term "specific inhibitor", as used herein refers to a compound that interacts with a certain kinase or a certain group of kinases and inhibits the enzymatic activity of that specific kinase or that specific group of kinases, but does not significantly interact with and inhibit the enzymatic activity of other kinases.

[0052] "Pharmaceutically acceptable carrier" and "pharmaceutically acceptable excipient" are used interchangeably and refer to a substance or compound that aids or facilitates preparation, storage, administration, delivery, effectiveness, absorption by a subject, or any other feature of the composition for its intended use or purpose. Such pharmaceutically acceptable carrier is not biologically or otherwise undesirable and can be included in the compositions of the present invention without causing a significant adverse toxicological

effect on the subject or interacting in a deleterious manner with the other components of the pharmaceutical composition.

[0053] As used herein, the term "administering", "administration", or "administer" means delivering the pharmaceutical composition as described herein to a target cell or a subject (e.g., a human). The pharmaceutical compositions described herein are designed for delivery to subjects in need thereof by any suitable route or a combination of different routes. In particular embodiments, pharmaceutical compositions are administered by intratumoral injection.

[0054] The term "neuroblastoma ras sarcoma viral oncogene homolog (NRAS)-mutated cancer cell" or "neuroblastoma ras sarcoma viral oncogene homolog (NRAS)-mutated cancer", as used herein, refers to a cancer cell or cancer that comprises a NRAS mutation. A "NRAS mutation", as used herein, refers to a mutation that occurs on a gene located in humans on chromosome 1 and which encodes the small GTPase Ras family protein neuroblastoma ras sarcoma viral oncogene homolog (NRAS).

[0055] The term "v-Raf murine sarcoma viral oncogene homolog B1 (BRAF)-mutated cancer cell" or "v-Raf murine sarcoma viral oncogene homolog B1 (BRAF)-mutated cancer", as used herein, refers to a cancer cell or cancer that comprises a BRAF mutation. A "BRAF mutation", as used herein, refers to a mutation that occurs on a gene located in humans on chromosome 7 and which encodes the B-Raf protein.

[0056] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals, including leukemia, carcinomas and sarcomas.

[0057] "Tumor," as used herein, refers to all neoplastic cell growth and proliferation and cancerous cells and tissues.

[0058] As used herein, the term "melanoma" refers to a form of skin cancer that may affect the skin only or may spread (metastasize) through the blood or lymph systems to organs and bones. Melanoma can develop in an existing mole or other mark on the skin or on unmarked skin. As used herein, the term "metastatic melanoma" refers to melanoma that has spread to other tissues or organs.

[0059] "MEK-therapy resistant cancer cell", as used herein, refers to a cancer cell that does not respond to a MEK therapy (such as a therapy including a MEK inhibitor). The cancer cell

may be intrinsically resistant to a MEK therapy or may have acquired resistance to a MEK therapy.

[0060] "MAPK-therapy resistant cancer cell", as used herein, refers to a cancer cell that does not respond to a MAPK therapy (such as a therapy including a MAPK inhibitor). The cancer cell may be intrinsically resistant to a MAPK therapy or may have acquired resistance to a MAPK therapy.

[0061] "BRAF-therapy resistant cancer cell", as used herein, refers to a cancer cell that does not respond to a BRAF therapy (such as a therapy including a BRAF inhibitor). The cancer cell may be intrinsically resistant to a BRAF therapy or may have acquired resistance to a BRAF therapy.

DETAILED DESCRIPTION OF THE INVENTION

1. Introduction

[0062] Recently, genomic studies have identified a class of non-protein-coding RNAs lacking protein-coding capacity, defined as long non-coding RNAs (lncRNAs). They have been shown to be involved in a variety of transcriptional and post-transcriptional gene regulatory processes through multiple mechanisms. The inventors have developed compositions and methods for treatment of melanoma and other NRAS-mutated cancers, *inter alia*, by delivering nucleic acids that inhibit the expression of a certain group of lncRNAs newly associated with cancer. In particular, the inventors have discovered that inhibiting lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201 reduces the oncogenic phenotype of melanoma, exemplified as reduced in vitro proliferation, increased apoptosis, as well as reduced tumor growth in a xenograft mouse model of melanoma. Further, the inventors discovered a certain group of kinases that is downregulated as a result of lncRNA inhibition. Specifically, the inventors discovered that inhibiting these specific kinases mimics the inhibition effects of the lnRNAs and leads to significant reduction in cell viability. Moreover, the inventors demonstrate improved effects when combining specific kinase inhibitors with antisense oligonucleotides (ASOs) that target the lncRNAs. Finally, lncRNA knockdown experiments in other cancer cell lines indicate targeting these lncRNAs are effective in treating other cancer types as well.

[0063] Accordingly, the disclosure provides a single or double-stranded nucleic acid that inhibits expression of the lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. As described herein, a series of novel antisense oligonucleotides (ASOs) and small interfering RNA (siRNAs) have been developed that target the specific lncRNAs.

[0064] In some approaches, the disclosure provides a method of inhibiting a cancer cell. In some embodiments, the cancer cell is a neuroblastoma ras sarcoma viral oncogene homolog (NRAS)-mutated cancer cell. In some embodiments, the cancer cell is a v-Raf murine sarcoma viral oncogene homolog B1 (BRAF)-mutated cancer cell. In some aspects, the method involves contacting the single or double-stranded nucleic acid with the cancer cell such that expression of lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201 is inhibited. In one approach, the method involves administering a therapeutically-effective amount of the single or double-stranded nucleic acid to a human. In some embodiments, the human is in need of treatment. In some aspects, the human has cancer. In one embodiment, the human has skin cancer, such as melanoma. In some embodiments, the cancer is an astrocytoma, a glioblastoma, a neuroblastoma, multiple myeloma, a small cell lung cancer, a large cell carcinoma, optionally from lung, a non-small cell lung cancer, a colon adenocarcinoma or an osteosarcoma.

[0065] In some embodiments, the method further comprises contacting the cancer cell with a specific inhibitor of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, or RAF kinase.

[0066] Aspects of the disclosure further relate to a method of inhibiting a cancer cell (e.g., a NRAS-mutated cancer cell or a BRAF-mutated cancer cell), where the method involves contacting the cancer cell with a specific inhibitor of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, or RAF kinase in an amount to inhibit the cancer cell growth. In one approach, the cancer cell is in a human, and the human is in need of treatment. In some aspects, the human has cancer. In one embodiment the human has skin cancer, such as melanoma. In some embodiments, the cancer is an astrocytoma, a glioblastoma, a neuroblastoma, multiple myeloma, a small cell lung

cancer, a large cell carcinoma, optionally from lung, a non-small cell lung cancer, a colon adenocarcinoma or an osteosarcoma.

2. Inhibiting expression of lncRNAs

[0067] In some aspects, the invention provides a single or double-stranded nucleic acid that inhibits expression of the lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. In some embodiment, the single or double-stranded nucleic comprises a sequence complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the single or double-stranded nucleic acid is 8-100, e.g., 12-50, e.g., 16-30 nucleotides in length. In some aspects, the single or double-stranded nucleic acid comprises at least 8, at least 9, at least 10, at least, 11, at least, 12, at least 13, at least 14, at least 15, or at least 16 nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some aspects, the single or double-stranded nucleic acid comprises at least 8, at least 9, at least 10, at least, 11, at least, 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some aspects, the single or double-stranded nucleic acid comprises 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12.

[0068] The complementarity between a nucleic acid and its corresponding target sequence may be 100%. In some embodiments, the complementarity between a nucleic acid and its corresponding target sequence is less than 100%, although 100% complementarity is desired to avoid off-target effects. In some embodiments, the complementarity between a nucleic acid and its corresponding target sequence is at least 95%, at least 90%, at least 85%, or at least 80%.

[0069] Introduction of the single or double-stranded nucleic acid into a cell expressing lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201 inhibits expression of the lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-xxx, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. In some embodiments, the inhibition of expression is at least 5% compared to the normal expression level in a cell expressing lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. Normal expression levels can be assessed in a control without the introduction of the single or double-stranded nucleic acid, e.g., as described herein. In some embodiments, the inhibition of expression is at least 5%, at least 10%, at least 20%, at least 30%, at least, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100%, or any percentage in between. Ideally, the inhibition of expression is between 95% and 100%.

[0070] The single or double-stranded nucleic acid can act at the DNA level or at the RNA level to inhibit the expression of the lncRNAs. Any suitable method may be used to achieve such inhibition. For example, inhibition at the RNA level may involve the use of antisense oligonucleotides (ASOs), ribozymes, or gene silencing methods in the form of RNA interference (RNAi). Inhibition at the DNA level may be performed through CRISPR/Cas systems using guide RNAs (gRNA). These and other compounds will be further detailed herein below.

2.1 Antisense oligonucleotides

[0071] In some aspects, the single or double-stranded nucleic acid is a single-stranded nucleic acid that is an antisense polynucleotide that targets and binds to lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. The antisense polynucleotide or antisense oligonucleotide (ASO) specifically hybridizes with the lncRNA and reduces levels of lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-xxx, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. In some embodiment, the antisense polynucleotide comprises a sequence complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID

NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the antisense polynucleotide is 8-100, e.g., 12-50, e.g., 16-30 nucleotides in length. In some embodiments, the antisense polynucleotide is 16 nucleotides in length. In some embodiments, the antisense polynucleotide comprises at least 12 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the antisense polynucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the antisense polynucleotide comprises the sequences of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO:41 or SEQ ID NO:47.

[0072] In some embodiments, an antisense polynucleotide comprising SEQ ID NO: 48 is provided, wherein introduction of the antisense polynucleotide into a cell expressing HNRNPA2/B1 inhibits expression of HNRNPA2/B1. In some embodiments, the antisense polynucleotide is 8-100, e.g., 12-50, e.g., 16-30 nucleotides in length. In some embodiments, the antisense polynucleotide is 16 nucleotides in length.

[0073] In some embodiments, an antisense polynucleotide comprising SEQ ID NO: 49, wherein introduction of the antisense polynucleotide into a cell expressing SNX10 inhibits expression of SNX10. In some embodiments, the antisense polynucleotide is 8-100, e.g., 12-50, e.g., 16-30 nucleotides in length. In some embodiments, the antisense polynucleotide is 16 nucleotides in length.

[0074] The complementarity between an antisense polynucleotide and its corresponding target sequence may be 100%. In some embodiments, the complementarity between the antisense polynucleotide and its corresponding target sequence is less than 100%, although 100% complementarity is desired to avoid off-target effects. In some embodiments, the complementarity between the antisense polynucleotide and its corresponding target sequence is at least 95%, at least 90%, at least 85%, or at least 80%.

[0075] In some embodiments, the antisense oligonucleotide comprises one or more modified nucleotides. In some embodiments, the modified nucleotide comprises a sugar modification, a nucleic acid base modification, and/or a phosphate backbone modification. Exemplary modifications are described further below. In one particular embodiment, the antisense polynucleotide is designed as a gapmer comprising a central stretch (gap) of nucleotides capable of inducing RNase H cleavage, and two flanking regions containing one or more modified nucleosides. Gapmer structures are well characterized and may be designed using known methods in the art, see, e.g., Monia et al. (1993), "Evaluation of 2 "-modified oligonucleotides containing 2-"deoxy gaps as antisense inhibitors of gene expression", J. Biol. Chem.; 268:14514–14522; Deleavey et al. (2012), "Designing chemically modified oligonucleotides for targeted gene silencing", Chem. Biol.; 19:937–954; and Stanley T. Crooke (2008), "Antisense Drug Technology- Principles, Strategies, and Applications", 2nd Edition, CRC press. Accordingly, in some aspects, the antisense polynucleotide is a gapmer. In some embodiments, the antisense polynucleotide is a locked nucleic acid (LNA) gapmer, where the modified nucleotides in the flanking regions are LNA nucleotides. In some embodiments, the antisense polynucleotide is a mixmer comprising alternating stretches of LNA and unmodified nucleotides, see e.g. U.S. Pat. Nos. 5,013,830; 5,149,797; 5, 220,007; 5,256,775, each of which is herein incorporated by reference. In one embodiment, the antisense polynucleotide is a headmer comprising only a flanking region at the 5' terminus. In another embodiment, the antisense polynucleotide is a tailmer comprising only a flanking region at the 3' terminus.

[0076] In some embodiments, the antisense polynucleotide comprises 1-8, e.g., 2-6 LNA nucleotides. In some embodiments, the antisense polynucleotide comprises 1, 2, 3, 4, 5, 6, 7, or 8 LNA nucleotides.

2.2 Ribozymes

[0077] In some embodiments, the single or double-stranded nucleic acid is a single-stranded nucleic acid that is a ribozyme that targets and binds to lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. Ribozymes are catalytic RNA oligonucleotides with enzyme-like cleavage properties that bind and cleave target RNAs. Ribozyme structures useful for targeting the lncRNAs as described herein include hammerhead ribozymes and hairpin ribozymes, and are

characterized, for example, in Citti and Rainaldi (2005), "Synthetic hammerhead ribozymes as therapeutic tools to control disease genes", Curr Gene Ther.; 5(1):11–24; Hean & Weinberg (2008), "The Hammerhead Ribozyme Revisited: New Biological Insights for the Development of Therapeutic Agents and for Reverse Genomics Applications", In Morris KL (ed.). RNA and the Regulation of Gene Expression: A Hidden Layer of Complexity. Norfolk, England: Caister Academic Press; Usman and McSwiggen, "Ch. 30 - Catalytic RNA (Ribozymes) as Drugs," Annual Reports in Medicinal Chemistry 30:285-294 (1995). In general, a ribozyme comprises a target binding portion that hybridizes to a target sequence of RNA and an enzymatic portion that acts to cleave the target RNA.

[0078] Accordingly, in some embodiment, the ribozyme comprises a sequence complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the ribozyme polynucleotide is 8-100, e.g., 12-50 nucleotides in length. In some embodiments, the ribozyme comprises at least 12 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the ribozyme comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12.

[0079] The complementarity between a target binding portion of a ribozyme and its corresponding target sequence may be 100%. In some embodiments, the complementarity between target binding portion of a ribozyme and its corresponding target sequence is less than 100%, although 100% complementarity is desired to avoid off-target effects. In some embodiments, the complementarity between the target binding portion of a ribozyme and its corresponding target sequence is at least 95%, at least 90%, at least 85%, or at least 80%.

[0080] In some embodiments, the ribozyme comprises one or more modified nucleotides. Such modified nucleotides may comprise a sugar modification, a nucleic acid base modification, and/or a phosphate backbone modification. Exemplary modifications include those described for antisense oligonucleotides (see above) or those described in §2.5, below.

2.3 RNA interference

[0081] In some embodiments, the single or double-stranded nucleic acid is a double-stranded nucleic acid that is a small interfering RNA (siRNA) or a small hairpin RNA (shRNA) that targets lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. siRNA and shRNA are involved in the RNA interference (RNAi) pathway where they can induce degradation of a target RNA. Methods for constructing siRNAs useful for inhibiting target RNAs are known to those of skill in the art, see e.g., Fire et al. (1998), "Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans", Nature, 391:806–811; Elbashir et al. (2001), "Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells", Nature, 411:494–498; Brummelkamp (2002), "A System for Stable Expression of Short Interfering RNAs in Mammalian Cells", Science, 296:550–553; Wittrup and Lieberman (2015), "Knocking down disease: a progress report on siRNA therapeutics", Nature Rev Genet.,16:543–552; Vickers et al. (2003), "Efficient Reduction of Target RNAs by Small Interfering RNA and RNase H-dependent Antisense Agents", J. Biol. Chem., 278:7108–7118. siRNAs comprise a sense strand and a complementary antisense strand annealed together by standard Watson Crick base pairing interactions. The sense strand may comprise a nucleic acid sequence that is identical to a target sequence contained within a target RNA, and the antisense strand may comprise a nucleic acid sequence that is complementary to a target sequence contained within the target RNA. In the case of the shRNA, the sense and antisense strand are covalently linked by a single-stranded loop region, and the shRNA is converted into a siRNA by a cleavage event mediated by the enzyme Dicer. The loop region may be between 2 and 12 nucleotides in length. In some cases, the loop region is from 4 to 10 nucleotides in length. Details on the structure of shRNAs can be found, for example, in Paddison et al. (2002), "Short hairpin RNAs (shRNAs) induce sequence-specific silencing in mammalian cells", Genes Dev., 16(8):948–958; Brummelkamp (2002), Science, 296:550–553; and Yu et al. (2002), "RNA interference by expression of short-interfering RNAs and hairpin RNAs in mammalian cells", Proc Natl Acad Sci USA, 99:6047–6052). siRNAs associate with an endonuclease-containing complex, known as RNA-induced silencing complex (RISC). RISC specifically recognizes and cleaves the target RNA that contains a nucleic acid sequence complementary to the antisense strand.

[0082] Accordingly, in some embodiments, the siRNA or shRNA that targets and binds to the lncRNA as described herein comprises a sequence complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the siRNA or shRNA is 8-100, e.g., 12-50, e.g., 16-30, e.g., 19-25 nucleotides in length. In some embodiments, the siRNA or shRNA is 21 nucleotides in length. In some embodiments, the siRNA or shRNA comprises at least 12 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the siRNA or shRNA comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least, 17, at least, 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12.

[0083] In some aspects, the siRNA or shRNA comprises a sense strand and an antisense strand, where the sense strand and the antisense comprise the sequence of SEQ ID NO: 23 and SEQ ID NO: 24, respectively; SEQ ID NO: 25 and SEQ ID NO: 26, respectively; SEQ ID NO: 27 and SEQ ID NO: 28, respectively; SEQ ID NO: 29 and SEQ ID NO: 30, respectively; SEQ ID NO: 31 and SEQ ID NO: 32, respectively; SEQ ID NO: 33 and SEQ ID NO: 34, respectively; SEQ ID NO: 35 and SEQ ID NO: 36, respectively; SEQ ID NO: 37 and SEQ ID NO: 38, respectively; SEQ ID NO: 39 and SEQ ID NO: 40, respectively; SEQ ID NO: 42 and SEQ ID NO: 50, respectively; SEQ ID NO: 43 and SEQ ID NO: 51, respectively; SEQ ID NO: 44 and SEQ ID NO: 52, respectively; SEQ ID NO: 45 and SEQ ID NO: 53, respectively; or SEQ ID NO: 46 and SEQ ID NO: 54, respectively.

[0084] The complementarity between an siRNA or shRNA and its corresponding target sequence may be 100%. In some embodiments, the complementarity between the siRNA or shRNA and its corresponding target sequence is less than 100%, although 100% complementarity is desired to avoid off-target effects. In some embodiments, the complementarity between the siRNA or shRNA and its corresponding target sequence is at least 95%, at least 90%, at least 85%, or at least 80%.

[0085] In some embodiments, the siRNA or shRNA comprises one or more modified nucleotides. In some embodiments, the modified nucleotide of the siRNA or shRNA comprises a sugar modification, a nucleic acid base modification, and/or a phosphate backbone modification. Exemplary modifications are described further below. In one particular embodiment, the siRNA or shRNA includes one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. See e.g., Elmen et al. (2005), Nucleic Acids Research 33(1):439-447; Mook et al. (2007), Mol Canc Ther 6(3):833-843; Grunweller et al. (2003), Nucleic Acids Research 31(12):3185-3193).

[0086] In some embodiments, the siRNA or shRNA comprises an overhang on either the sense strand or the antisense strand or both (e.g., on each 3' end of both strands). In some embodiments, siRNA or shRNA includes an overhang on both the sense and the antisense strand. The overhang may be at either the 5' end or the 3' end of the strand. In some embodiments, both the 5' end and the 3' end comprise an overhang. The overhang can have any nucleotide sequence and may be 1-10 nucleotides in length. In some embodiments, the overhang is 2-6 nucleotides in length. In some embodiments, the overhang is 2-4 nucleotides in length. In some cases, the overhang comprises modified nucleotides. For example, the overhang may include locked nucleic acids (LNAs).

2.4 CRISPR/Cas systems

[0087] In some approaches, CRISPR technology is used to inhibit expression of lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. The CRISPR technology is a gene-editing method that makes use of the CRISPR/CAS system. The "CRISPR/Cas" system refers to a widespread class of bacterial systems for defense against foreign nucleic acid. CRISPR/Cas systems include type I, II, and III sub-types. Wild-type type II CRISPR/Cas systems use the RNA-mediated nuclease, for example, Cas9, in complex with guide and activating RNA to recognize and cleave foreign nucleic acid. In nature, many CRISPR systems include transactivating crisp RNA (tracrRNA), which binds the Cas endonuclease, and crisp RNA (crRNA), which binds to the DNA target sequence. Some CRISPR systems (*e.g.*, CRISPR Cas12a/Cpf1) require only crRNA. In research and biomedical applications it is more typical to use a chimeric single guide RNA ("sgRNA"), which is a crRNA-tracrRNA fusion that binds both the Cas endonuclease and the DNA target sequence. It will be understood that, except where apparent

from context, reference to a "gRNA" includes any suitable guide RNA with appropriate binding specificity (*e.g.*, a sgRNA, crRNA, or other RNA that binds to any of the genes encoding the lncRNAs of interest). The most commonly used sgRNA's comprise a nucleic acid sequence approximately 20 nucleotides in length which is complementary to a target sequence, and which is located at or near the 5' end of the sgRNA. Methods for designing sgRNAs that target a specified target sequence are well known in the art. See e.g., Doench et al. (2016), Optimized sgRNA design to maximize activity and minimize off-target effects of CRISPR-Cas9", Nat. Biotechnol. 34:184-191; Horlbeck et al. (2016), "Compact and highly active next-generation libraries for CRISPR-mediated gene repression and activation, eLife. 5, e19760 (2016); Cui et al., "Review of CRISPR/Cas9 sgRNA Design Tools. Interdiscip. Sci. 2018, 10:455–465; and Kiani et al. (2015), "Cas9 gRNA engineering for genome editing, activation and repression", Nat Methods 2015;12:1051–4.

[0088] Aspects of the invention relate to a single-stranded nucleic acids that is a guide RNA (gRNA) that targets a polynucleotide encoding lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. In some embodiments, the polynucleotide is BX470102.3, AC004540.4, RP11-7011.3, RN7SL1, ARF-AS1, or AL157871.4.

[0089] In some aspects, introduction of the gRNA in a cell expressing lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201 inhibits expression of the lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201. In some embodiments, the gRNA is of 20 nucleotides in length. In some embodiments, the gRNA comprises at least 12, at least 15, or at least 20 nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the gRNA comprises at least 12 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some cases, the guide RNA is an sgRNA. In some embodiments, the gRNA comprises at least 8, at least 9, at least 10, at least 11, at least 12, at

least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some cases, the guide RNA is an sgRNA.

[0090] The complementarity between a gRNA and its corresponding target sequence may be 100%. In some embodiments, the complementarity between the gRNA and its corresponding target sequence is less than 100%, although 100% complementarity is desired to avoid off-target effects. In some embodiments, the complementarity between the gRNA and its corresponding target sequence is at least 95%, at least 90%, at least 85%, or at least 80%.

[0091] In some embodiments, the gRNA comprises one or more modified nucleotides. In some embodiments, the modified nucleotide comprises a sugar modification, a nucleic acid base modification, and/or a phosphate backbone modification. gRNAs comprising modified nucleotides are described, for example in WO2018107028. See also e.g., Filippova et al. (2019), "Guide RNA modification as a way to improve CRISPR/Cas9-based genome-editing systems", Biochimie., 167:49–60; Ryan et al. (2018), "Improving CRISPR–Cas specificity with chemical modifications in single-guide RNAs", Nucleic Acids Res. 46, 792–803; and Hendel et al. (2015), "Chemically modified guide RNAs enhance CRISPR-Cas genome editing in human primary cells". Nat. Biotechnol. 2015;33:985–989. Additional modifications that may be used are described further below.

[0092] In some aspects, the invention relates to a CRISPR/Cas system, where the system comprises a Cas protein and a guide RNA (e.g., an sgRNA) as described above. The sgRNA and Cas can be expressed from the same or different vectors of the system. Cas proteins and their amino acid sequence are well known in the art. Non-limiting examples of Cas proteins include Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9 (also known as Csn1 and Csx12), Cas10, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, Csf4, homologs thereof, or modified versions thereof. An exemplary Cas9 protein is the *Streptococcus pyogenes* Cas9 protein. The amino acid sequence of S. pyogenes Cas9 protein may be found in the SwissProt database under accession number Q99ZW2. Additional Cas9 proteins and homologs thereof

are described in, *e.g.,* Chylinksi, *et al.*, RNA Biol. 2013 May 1; 10(5): 726–737; Nat. Rev. Microbiol. 2011 June; 9(6): 467-477; Hou, *et al.*, Proc Natl Acad Sci U S A. 2013 Sep 24;110(39):15644-9; Sampson *et al.*, Nature. 2013 May 9;497(7448):254-7; and Jinek, *et al.*, Science. 2012 Aug 17;337(6096):816-21. In some embodiments, the Cas (such as Cas9) lacks nuclease activity (*e.g.*, dCas9). In some cases, the CRISPR/Cas system comprises a Cas fursion protein including a Cas DNA binding domain and a transcription repressor. In some cases, the Cas is a nuclease deficient dCas (such as dCas9). Other RNA-mediated nucleases that can also be used in a CRISPR/Cas system to inhibit the expression of the lncRNAs include, for example, Cas 12a and Cascade/Cas3 (see e.g., Pickar-Oliver and Gersbach (2019), "The next generation of CRISPR-Cas technologies and applications", Nat. Rev. Mol. Cell Biol., 20: 490–507).

[0093] In some cases, the gRNA binds to a target sequence that is contiguous with a protospacer adjacent motif (PAM) recognized by the Cas protein. For example, Cas9 generally requires the PAM motif NGG for activity. Thus, in some systems, certain target sequences will be preferred based on the proximity of the target sequence to a PAM. However, some Cas proteins, including variants of Cas9, have flexible PAM requirements (see Karvekis et al., 2019, "PAM recognition by miniature CRISPR-Cas14 triggers programmable double-stranded DNA cleavage." bioRxiv.; Legut et al., 2020, "High-Throughput Screens of PAM-Flexible Cas9", Cell Reports 30:2859–2868; Gleditzsch et al., 2019, PAM identification by CRISPR-Cas effector complexes: diversified mechanisms and structures. RNA Biol. 2019 Apr; 16(4): 504–517) and other Cas proteins are PAM-independent (*e.g.*, Cas14a1). Exemplary PAMs are described, e.g., in Zhao et al. (2017), CRISPR-offinder: a CRISPR guide RNA design and off-target searching tool for user-defined protospacer adjacent motif. Int J Biol Sci; 13(12):1470-1478.

2.5 Modifications to the nucleic acids

[0094] In some aspects, the single or double-stranded nucleic acid of the present disclosure may include one or more modified nucleotides to improve certain properties of the nucleic acids, such as binding affinity, stability, and/or nuclease resistance. Accordingly, in some embodiments, the single or double-stranded nucleic acid of the present disclosure comprises at least one nucleotide that is modified. In some embodiments, the antisense oligonucleotide comprises at least one modified nucleotide. In some embodiments, the ribozyme comprises at least one modified nucleotide. In some embodiments, the siRNA or shRNA comprises at least

one modified nucleotide. In some embodiments, the gRNA comprises at least one modified nucleotide. In some aspects, the modified nucleotide comprises a sugar modification, a nucleic acid base modification, and/or a phosphate backbone modification. Modifications that are useful for optimizing the single or double-stranded nucleic of the present disclosure are described, e.g., in Freier & Altmann (1997), Nucl. Acid Res., 25, 4429-4443; Uhlmann (2000), Curr. Opinion in Drug Development, 3(2), 293-213; and Deleavey and Damha (2012), Chemistry and Biology, 19: 937-954, and U.S. Pat. Nos. 5,684,143, 5,858,988 and 6,291,438. Below are some exemplary modifications that may be incorporated.

[0095] Sugar modifications include alternations of the substituent groups on the ribose ring to groups other than hydrogen, or the 2'-OH group naturally found in DNA and RNA nucleosides. Substituents may, for example be introduced at the 2', 3', 4' or 5' positions. In some embodiments, the single or double-stranded nucleic acid of the present disclosure comprises at least one 2' sugar modification. A 2' sugar modification comprises any modification made at the 2' position of the sugar, where the nucleotide comprises a substituent other than H or --OH at the 2' position of the sugar. For example, the 2' modified sugar may provide enhanced binding affinity and/or increased nuclease resistance to the oligonucleotide. In some embodiments, the 2' sugar modification is a 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA, and locked nucleic acid (LNA) modification.

[0096] Sugar modifications may also include those where the ribose ring structure is modified, e.g. by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradicle bridge between the C2 and C4 carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a bond between the C2 and C3 carbons (e.g. UNA). In some embodiments, modifications comprise an ethylene-bridged nucleic acid (ENA) modification (see e.g., Koizumi (2006), "ENA oligonucleotides as therapeutics". Current Opinion in Molecular Therapeutics. 8 (2): 144–149). Other sugar modified nucleosides include, for example, bicyclohexose nucleic acids (see e.g., WO2011/017521) or tricyclic nucleic acids (see e.g., WO2013/154798). Sugar modification also include those where the sugar moiety is replaced with a non-sugar moiety, for example in the case of peptide nucleic acids (PNA), or morpholino nucleic acids.

[0097] In some embodiments, the single or double-stranded nucleic acid of the present disclosure comprise one or more phosphate backbone modifications. In some embodiments,

the phosphate backbone modification is a 5' phosphorylation. Additional phosphate backbone modifications include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkyl phosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates. Representative U.S. patents that teach the preparation of the above phosphorus-containing backbones include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195.

[0098] Phosphate backbone modifications may also include those that do not include a phosphorus atom, therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar modification); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; and amide backbones. See e.g., U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141. In some embodiments, the single or double-stranded nucleic acid of the present disclosure have a morpholino backbone structure.

[0099] In some embodiments, the single or double-stranded nucleic acid of the present disclosure comprises one or more nucleic acid base modifications. Nucleic acid base modifications include, for example, the addition or substitution of a chemical group or a substitution of the nitrogen atom of the ring. Exemplary nucleic acid base modifications include but are not limited to 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleic acid base

modifications include those disclosed in "Modified Nucleosides in Biochemistry", Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008. Some nucleic acid base modifications may be particularly useful for increasing the binding affinity of the the single or double-stranded nucleic acid of the present disclosure. These may include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine.

3. Delivery vehicles and pharmaceutical compositions

3.1 Vectors

[0100] In some aspects, the single or double-stranded nucleic acid of the present disclosure can be delivered to a target cell by a suitable vector. Accordingly, the disclosure provides a vector comprising the single or double-stranded nucleic acid as described above. For example, the vector may comprise an antisense oligonucleotide, a ribozyme, an siRNA or shRNA, or a gRNA that target lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 AL157871.4-201, HNRNPA2/B1 or SNX10.

[0101] Vectors and methods useful for the delivery of the single or double-stranded nucleic acid are well known in the art. Generally, DNA encoding the ASO, the ribozyme, the siRNA or shRNA, or the gRNA is cloned into a vector downstream of a promoter for expression. In some embodiments, the vector is a viral vector. Exemplary viral vectors include retroviral, lentiviral, adeno-associated viral (AAV) vectors. Retroviral vectors for the delivery of nucleic acids are described e.g., in Miller et al. (1993), "Use of retroviral vectors for gene transfer and expression", Methods Enzymol 217:581–599; Salmons and Gunzberg, (1993), Human Gene Therapy 4:129-141; and Grossman and Wilson, (1993) Curr. Opin. in Genetics and Devel. 3:110-114. Lentiviral vectors contemplated for use are described e.g., in U.S. Pat. Nos. 6,143,520; 5,665,557; and 5,981,276, which are herein incorporated by reference. Suitable AAV vectors are described e.g., in Aponte-Ubillus et al., 2018, "Molecular Design For Recombinant Adeno-Associated Virus (Raav) Vector Production" Applied microbiology and biotechnology 102.3:1045-1054; Naso et al., 2017, "Adeno-Associated Virus (Aav) As A Vector For Gene Therapy" BioDrugs 31:317; Penaud-Budloo et al., 2018., "Pharmacology of Recombinant Adeno- Associated Virus Production" Molecular Therapy: Methods & Clinical Development 8:166-180; Walsh et al., (1993) Proc. Soc. Exp. Biol. Med. 204:289-300; Samulski et al. (1987), J. Virol. 61: 3096-3101; Fisher et al. (1996), J. Virol, 70: 520-532;

Samulski et al. (1989), J. Virol. 63: 3822-3826; and U.S. Pat. No. 5,436,146; 5,252,479; 5,139,941. Other viral vectors that may be used include, but are not limited to, adenoviruses (AV), pox viruses, alphaviruses, herpes viruses, bovine papilloma virus (BPV-I), and Epstein-Barr virus (pHEBo, pREP-derived and p205). A suitable AV vector and a method for delivering the vector into target cells, is described, for example, in Xia et al. (2002), Nat. Biotech. 20: 1006-1010.

[0102] Any suitable promoter that can direct transcription initiation of the sequences encoded by the nucleic acids may be used. The promoter may be an inducible promoters, organism specific promoters, tissue specific promoters, or a cell type specific promoter. Examples of promoters include, but are not limited to, simian virus 40 (SV40) early promoter, a mouse mammary tumour virus promoter, a human immunodeficiency virus long terminal repeat promoter, a Moloney virus promoter, an avian leukaemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus (RSV) promoter, a human actin promoter, a human myosin promoter, a human haemoglobin promoter, cytomegalovirus (CMV) promoter and a human muscle creatine promoter, a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter (tet-on or tet-off), a HER-2 promoter, and PSA associated promoter. In some embodiments, the promoter is a U6 or H1 promoter.

[0103] The gene encoding the ASO, the ribozyme, the siRNA or shRNA, or the gRNA of the present disclosure may also be under the control of other regulatory elements such as enhancer or activator sequences, leader or signal sequences, ribosomal binding sites, transcription start and termination sequences, and polyadenylation sequence. Enhancers that may be used in approaches of the invention include but are not limited to: an SV40 enhancer, a cytomegalovirus (CMV) enhancer, an elongation factor 1 (EF1) enhancer, yeast enhancers, viral gene enhancers, and the like. Termination control region may comprise or be derived from a synthetic sequence, synthetic polyadenylation signal, an SV40 late polyadenylation signal, an SV40 polyadenylation signal, a bovine growth hormone (BGH) polyadenylation signal, viral terminator sequences, or the like. Such regulatory elements are described e.g., in Molecular Cell Biology Editors: H. Lodish et al., 8th edition 2016.

[0104] The vectors described herein may also be used to deliver CRISPR elements, including the gRNAs (e.g., sgRNAs or other gRNAs), Cas proteins (with or without nuclease activity), and Cas-transcriptional activator fusion proteins (see e.g., Byrne et al. (2014),

"Genome editing in human stem cells", Methods in Enzymology. 2014;546:119–138; Dunbar et al., 2018, "Gene Therapy Comes Of Age" Science 359:6372; and Cong et al., Science (80). 339, 819-823).

[0105] The vectors described herein may be generated and isolated using methods known in the art. See, e.g., U.S. Pat. Nos. 7,790,449, U.S. Pat. No. 7,588,772, and Zolotukin et al., "Production And Purification Of Serotype 1, 2, And 5 Recombinant Adeno-Associated Viral Vectors." Methods 28:158-167 (2002), Penaud-Budloo et al., 2018; Gonçalves, M.A. "Adeno-associated virus: from defective virus to effective vector." *Virol J* 2: 43 (2005); Li, et al "Engineering adeno-associated virus vectors for gene therapy." *Nat Rev Genet* 21: 255–272 (2020); all incorporated by reference and cited above. For general methods on genetic and recombinant engineering, recombinant engineering, and transfection techniques see e.g., Sambrook et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, N.Y.; Graham et al., Virol., 52:456 (1973); Davis et al., Basic Methods in Molecular Biology, Elsevier, (1986); and Chu et al., Gene 13:197 (1981).

[0106] Non-viral vectors or methods can also be used to deliver the nucleic acids of the present disclosure. In one approach, virus-like particles (VLP's) are used to deliver the ASO, siRNA or shRNA, the ribozyme, or the gRNA. The VLP comprises an engineered version of a viral vector, where nucleic acid cargo are packaged into VLPs through alternative mechanisms (*e.g.*, mRNA recruitment, protein fusions, protein-protein binding). See Itaka and Kataoka, 2009, "Recent development of nonviral gene delivery systems with virus-like structures and mechanisms," Eur J Pharma and Biopharma 71:475-483; and Keeler et al., 2017, "Gene Therapy 2017: Progress and Future Directions" *Clin. Transl. Sci.* (2017) 10, 242–248, incorporated by reference.

3.2 Pharmaceutical compositions

[0107] Another aspect of the invention pertains to pharmaceutical compositions the single or double-stranded nucleic acid or the vector as described herein. In some embodiments, the pharmaceutical composition comprises an effective amount of the single or double-stranded nucleic acid or the vector comprising the same and a pharmaceutically acceptable carrier.

[0108] In some embodiments, the pharmaceutical composition further comprising a specific inhibitor of one or more kinases selected from the group consisting of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, and RAF. Specific inhibitors of these kinases are well known in the art and include, but are not

limited to trametinib, volasertib, tozasertib, alisertib, Bay-299, CeMMEC1. For example, the pharmaceutical composition may comprise an antisense oligonucleotide or a ribozyme and a specific kinase inhibitor, such as trametinib, volasertib, tozasertib, alisertib, Bay-299, and/or CeMMEC1. In another example, the pharmaceutical composition may comprise an siRNA or shRNA and a specific kinase inhibitor, such as trametinib, volasertib, tozasertib, alisertib, Bay-299, and/or CeMMEC1. In yet another example, the pharmaceutical composition may comprise a gRNA and a specific kinase inhibitor, such as trametinib, volasertib, tozasertib, alisertib, Bay-299, and/or CeMMEC1. In some embodiments, the pharmaceutical composition comprises an effective amount of the single or double-stranded nucleic acid or the vector comprising the same, an effective amount of a specific kinase inhibitor, and a pharmaceutically acceptable carrier.

[0109] A suitable pharmaceutically acceptable carrier may be buffered saline or other buffers, e.g., HEPES, to maintain pH at appropriate physiological levels, stabilizing agents, adjuvants, diluents, or surfactants. Exemplary pharmaceutically acceptable carriers include sterile, pyrogen-free water and sterile, pyrogen-free, phosphate buffered saline (PBS), sodium and potassium salts. A variety of such known carriers are provided in U.S. Patent Publication No. 7,629,322 and PCT Publication No. WO 2007/031091, incorporated herein by reference. In some embodiments, the pharmaceutically acceptable carrier is PBS. The carrier may be, for example an isotonic sodium chloride solution, or a balanced salt solution.

[0110] In some approaches, sterile injectable solutions can be prepared with the nucleic acids or the vectors in the required amount and pharmaceutically acceptable carrier or an additive suitable for injection into a human. For injection, the carrier or excipient will typically be a liquid.

[0111] In some embodiments, the pharmaceutically acceptable carrier comprises a copolymer, a lipid, or a nanoparticle. In some embodiments, the nanoparticle is a liposomal nanoparticle. Suitable pharmaceutically acceptable carrier include, for example, the cationic lipid Genzyme Lipid 67 (GL67), polyethylene glycol (PEG) liposomes, cationic liposomes, chitosan nanoparticles and cationic cell penetrating peptides (CPPs). Additional exemplary carriers and encapsulation methods that can be used are described e.g., in Ozcan et al. (2015), "Preclinical and clinical development of siRNA-based therapeutics", Adv. Drug Deliv. Rev., 87, 108–119 and Juliano (2016), "The delivery of therapeutic oligonucleotides", Nucleic Acids Research, 2016, Vol. 44, No. 14. In some embodiments, the nucleic acids described

herein are encapsulated in liposomes. In some embodiments, the nucleic acids described herein are encapsulated in gold nanoparticles.

[0112] Antisense compounds may be covalently linked to one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the resulting antisense oligonucleotides. Typical conjugate groups include cholesterol moieties and lipid moieties. Additional conjugate groups include carbohydrates, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.

[0113] In some embodiments, the disclosure provides the use of the single or double-stranded nucleic, the vector, or the pharmaceutical composition described herein for the preparation of a medicament for treating cancer. In some embodiments, the disclosure relates to the single or double-stranded nucleic, the vector, or the pharmaceutical composition as described herein for the preparation of a medicament for treating cancer.

4. Administration and Dosage

4.1 Administration

[0114] Aspects of the invention include methods of administering a therapeutically-effective amount of the single or double-stranded nucleic acid and/or specific kinase inhibitor to a subject. In one embodiment, the subject is a human. Administration is not limited to a particular site or method. Any suitable route of administration or combination of different routes can be used, including topical (such as, to the skin) or enteral (such as, orally or through the gastrointestinal tract) or systemic administration (*e.g.*, intravenous, intravascular, intraarterial), or local injection (intratumoral, intraocular, intramuscular, subcutaneous, intradermal injection, transdermal, intracranial, intracerebral, intracerebroventricular, or intrathecal injection). In some embodiments, the nucleic acids, specific kinase inhibitors, or pharmaceutical compositions are administered through subcutaneous intratumoral injections.

[0115] Administration can be performed by use of an osmotic pump, by electroporation, or by other means. In some approaches, administration of the nucleic acid, specific kinase inhibitor, or pharmaceutical compositions can be performed before, after, or simultaneously with surgical tumor removal or biopsy.

4.2 Dosage and effective amounts

[0116] Dosage values may depend on the nature of the product and the severity of the condition. It is to be understood that for any particular subject, specific dosage regimens can be adjusted over time and in course of the treatment according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Accordingly, dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

[0117] The amount of the nucleic acids and/or specific kinase inhibitors administered will be an "effective amount" or a "therapeutically effective amount," *i.e.*, an amount that is effective, at dosages and for periods of time necessary, to achieve a desired result. A desired result would include inhibition of expression of lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 AL157871.4-201 , HNRNPA2/B1 or SNX10, inhibition of a cancer cell (e.g., a NRAS-mutated cancer cell or a BRAF-mutated cancer cell), reduction in tumor size and/or tumor growth, prolonged survival or a detectable improvement in a symptom associated with cancer that improves patient quality of life. Alternatively, if the pharmaceutical composition is used prophylactically, a desired result would include a demonstrable prevention of one or more symptoms of cancer. A therapeutically effective amount of such a composition may vary according to factors such as the disease state, molecular tumor profile (e.g. tumor mutation types), age, sex, and weight of the individual, or the ability of the nucleic acid and/or kinase inhibitor to elicit a desired response in the individual. Dosage regimens may be adjusted to provide the optimum response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the nucleic acid and/or kinase inhibitor are outweighed by the therapeutically beneficial effects.

[0118] Generally, nucleic acids of the present invention, such as an antisense oligonucleotide, siRNA or shRNA, ribozyme, or gRNA may be administered less than 75 mg per kg of body weight, such as for example less than 70, 60, 50, 40, 30, 20, 10, 5, 2, 1, 0.5, 0.1, 0.05, 0.01, 0.005, 0.001, or 0.0005 mg per kg of body weight. Exemplary dosage ranges for kinase inhibitors may be 5-100mg/kg/week, depending on the inhibitor. As non-limiting examples, in some embodiments, trametinib is administered at 2mg/kg/day and/or volasertib is administered at 50mg/kg/week (both oral gavage). This refers to oral gavage, other routes may require other forms of dosage and application frequency. The particular amounts may be

determined by conventional tests which are well known to the person skilled in the art. Suitable tests are, for example, described in Tamhane and Logan (2002), "Multiple Test Procedures for Identifying the Minimum Effective and Maximum Safe Doses of a Drug", Journal of the American statistical association, 97(457):1-9. If a vector is used as a delivery system, quantification of genome copies (GC), vector genomes (VG), virus particles (VP), or infectious viral titer may be used as a measure of the dose contained in a formulation or suspension. Any method known in the art can be used to determine the GC, VG, VP or infectious viral titer as described in, e.g. in Dobkin et al., "Accurate Quantification and Characterization of Adeno-Associated Viral Vectors." Front Microbiol 10: 1570-1583 (2019); Lock et al., "Absolute determination of single-stranded and self-complementary adeno-associated viral vector genome titers by droplet digital PCR." Hum Gene Ther Methods 25: 115–125 (2014); and Grimm, et al. "Titration of AAV-2 particles via a novel capsid ELISA: packaging of genomes can limit production of recombinant AAV-2." Gene Ther 6: 1322–1330 (1999); which are incorporated herein by reference. An exemplary human dosage range in vector genomes per kilogram bodyweight (vg/kg) may be 10e6 vg/kg - 10e15/kg vg per injection in a volume of 1-100,000 µl.

[0119] In one approach, the nucleic acid and/or specific kinase inhibitor, or pharmaceutical composition is administered in a single dosage. In another embodiment, the method involves administering the compositions in two or more dosages (e.g., split dosages). In another embodiment, the composition is administered at different locations. In another embodiment, a second administration is performed at a later time point. Such time point may be weeks, months or years following the first administration. In some embodiments, multiple treatments may be required in any given subject over a lifetime.

4.3 Combination therapies

[0120] In some approaches, the nucleic acids and/or kinase inhibitors of the present disclosure are used in combination with one or more additional anti-cancer agents and/or therapies, including any known, or as yet unknown, anti-cancer agent or therapy which helps preventing development of, slowing progression of, reversing, or ameliorating the symptoms of cancer. The one or more additional anti-cancer agents and/or therapies may be administered and/or performed before, concurrent with, or after administration of the nucleic acids described herein. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation. In some embodiments, the

nucleic acids of the present disclosure are used in combination with one or more anticancer therapies, such as chemotherapy, radiation therapy, immunotherapy, and surgical treatment.

[0121] In one embodiment, the nucleic acids and/or kinase inhibitors are used in combination with other kinase inhibitors. Exemplary kinase inhibitors include, but are not limited to trametinib or volasertib or both.

[0122] Other chemotherapeutic agents that may be used in combination with the nucleic acids and/or kinase inhibitors include temozolomide (TMZ), cyclophosphamide, docetaxel, hydroxydaunorubicin, adriamycin, doxorubicin, vincristine, and prednisolone.

[0123] In some approaches, the nucleic acid and/or kinase inhibitors of the present disclosure are used in combination with immunotherapy, for example a checkpoint inhibitor, such as ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab.

[0124] Examples of other anti-cancer agents that can be combined with the nucleic acids and or kinase inhibitors includes, without limitation any one or more of a co-stimulation molecule blocker, an adhesion molecule blocker, an antiangiogenic agent (e.g., bevacizumab), an anti-cytokine antibody or functional fragment thereof, a corticosteroid, a non-steroidal anti-inflammatory agent, a nitrogen mustard, an aziridine, an alkyl sulfonate, a nitrosourea (e.g., carmustine, semustine, lomustine, nimustine, or fotemustine), a non-classical alkylating agent, a folate analog, a purine analog, an adenosine analog, a pyrimidine analog, a substituted urea, an antitumor antibiotic, an epipodophyllotoxin, a microtubule agent, a camptothecin analog, a cytokine, a monoclonal antibody, a recombinant toxin, an immunotoxin, a cancer gene therapy, a cancer cell therapy, an oncolytic viral therapy, or a cancer vaccine.

5. Method of treating cancer

[0125] In some aspects, the present disclosure provides a method of inhibiting a cancer cell. The method comprises contacting the single or double-stranded (e.g., the ASO, the ribozyme, the siRNA or shRNA, or the gRNA), the vector, or the pharmaceutical composition comprising the same with the cancer cell such that expression of lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 AL157871.4-201, HNRNPA2/B1 or SNX10 is inhibited.

[0126] In some aspects, the method further comprises contacting the cancer cell with a specific inhibitor of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, or RAF. In some embodiments, the specific inhibitor is trametinib, volasertib, tozasertib, alisertib, Bay-299, CeMMEC1. In some approaches, the cancer cell may be contacted with two or more specific inhibitor of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, or RAF.

[0127] The cancer cell may be contacted with s specific kinase inhibitor only. In some approaches, a cancer cell may be inhibited by contacting the cancer cell with a specific inhibitor alone without using any of the nucleic acids described above. Accordingly, in some aspects, the present disclosure provides a method of inhibiting a cancer cell, where the cancer cell is contacted with a specific inhibitor of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, or RAF in an amount to inhibit the cancer cell growth. In some embodiments, the specific inhibitor is trametinib, volasertib, tozasertib, alisertib, Bay-299, CeMMEC1. In some approaches, the cancer cell may be contacted with two or more specific inhibitors of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, or RAF.

[0128] In some embodiments, the cancer cell is a NRAS-mutated cancer cell. In some aspects, the NRAS-mutated cancer cell comprises a NRAS G12A, NRAS G12C, NRAS G12D, NRAS G12R, NRAS G12S, NRAS G12V, NRAS G13D, NRAS G12S2, NRAS G13A, NRAS G13S, NRAS G13V, NRAS G13R, NRAS G13C, NRAS Q61H, NRAS Q61L, NRAS Q61R, NRAS A146T, or a NRAS A146V mutation. $

456=$ In some embodiments, the cancer cell is a BRAF-mutated cancer cell. In one aspect, the BRAF-mutated cancer cell comprises a BRAF V600E mutation. In some aspects, the BRAF-mutated cancer cell comprises a BRAF R461I, BRAF I462S, BRAF G463E, BRAF G463V, BRAF G465A, BRAF G465E, BRAF G465V, BRAF G468A, BRAF G468E, BRAF N580S, BRAF E585K, BRAF D593V, BRAF F594L, BRAF G595R, BRAF L596V, BRAF T598I, BRAF V599D, BRAF V599E, BRAF V599K, BRAF V599R, BRAF V600K, or a BRAF A727V mutation. Other BRAF mutations are described e.g., in Davies at al. (2002), "Mutations of the BRAF gene in human cancer", Nature, 27;417(6892):949-54; and Dankner et al. (2018), Classifying BRAF alterations in cancer: new rational therapeutic strategies for actionable mutations. Oncogene, 37(24):3183–3199.

5.1 Patients

[0130] In some embodiments, the cancer cell that is contacted with the nucleic acid of the present disclosure and/or with a specific kinase inhibitor is in a mammal, such as a human, a non-human primate, a mouse, a dog, a cat, a horse, a rabbit, a cow, a pig, or a sheep. In some embodiments, the cancer cell that is contacted with the nucleic acid of the present disclosure and/or with a specific kinase inhibitor is in a human. In some embodiments, the human is receiving a treatment and the treatment involves contacting the human cell with the nucleic acid of the present disclosure and/or with a specific kinase inhibitor. Humans who are candidates for treatment with the nucleic acid and/or with a specific kinase inhibitor include "patients" or "subjects" experiencing or having experienced one or more signs, symptoms, or other indicators of cancer.

[0131] In some approaches, patients are selected for treatment based on signs, symptoms, clinical phenotypes and/or biomarkers. In some embodiments, they may be assessed via a clinical exam, including but not limited to imaging and morphological assessments, such as magnetic resonance imaging (MRI), biopsy, or bloodwork for the detection of circulating tumor cells or cell-free DNA from tumor cells.

[0132] In some aspects, patients receiving therapy with the nucleic acid and/or with a specific kinase inhibitor may include those which have previously not responded to conventional anti-cancer treatment, such as chemotherapy or radiotherapy. In certain aspects, patients receiving therapy with the nucleic acid and/or with a specific kinase inhibitor may include those which have previously not responded to a kinase inhibitor treatment. In some embodiments, the patient has not responded to a treatment involving a MEK inhibitor, a MAPK inhibitor, and/or a BRAF, and/or any other kinase inhibitor. In some aspects, patients include those that show resistance to a kinase inhibitor treatment. In some aspects, patients include those that show resistance to a MEK inhibitor treatment, a MAPK inhibitor treatment, and/or a BRAF inhibitor treatment. In some aspects, the resistance is an acquired resistance. In some aspects, the resistance is an intrinsic resistance.

[0133] In certain embodiments, patients receiving therapy with the nucleic acid and/or with a specific kinase inhibitor may include those which have newly diagnosed cancer. In some embodiments, the cancer treated with the nucleic acid and/or with a specific kinase inhibitor described herein is recurrent cancer. In another embodiment, the cancer is recurrent skin cancer.

[0134] In one aspect, administration of the nucleic acids and/or the specific kinase inhibitor is performed at a very early stage disease progression may provide superior therapeutic benefit. For example, treatment may be performed prior to the appearance of signs or symptoms of cancer. Thus, provided herein are methods and compositions for preventing development of cancer. In some approaches, the patient has no symptoms of cancer.

[0135] In some approaches, patients are assessed by genotyping to determine their individual genetics (e.g., by assessing the presence of risk alleles associated with one or more cancers described below) and associated risk of disease. In some embodiments, patients include those that carry a NRAS-mutation. In some embodiments, patients disclose those who carry a BRAF-mutation. Accordingly, in some approaches, at the time of first administration of the composition, the patient does not exhibit any of the clinical phenotypes of cancer.

5.2 Cancers

[0136] The compositions and methods described herein find particular use for treatment of patients or subjects with, or at risk of developing, cancer. Examples of cancers include solid cancers and sarcomas, such as skin cancer, melanoma, liver cancer, brain cancer, head and neck cancer, stomach cancer, lung cancer, breast cancer, uterine cancer, ovarian cancer, hepatic cancer, bronchial cancer, epipharynx carcinoma, pharyngeal cancer, esophageal cancer, bladder cancer, pancreatic cancer, prostate cancer, colon cancer, osteosarcoma, thyroid cancer, parathyroid cancer, ureteral cancer and cervical cancer, and malignant tumors formed in hemopoietic organs or blood, e.g. leukemia such as acute lymphatic leukemia, malignant lymphoma. In some embodiments, the cancer is skin cancer. In some embodiments, the skin cancer is melanoma. Other examples of cancers affecting the skin include basal cell carcinoma and squamous cell carcinoma.

[0137] Accordingly, in some embodiments, the cancer cell that is contacted with the nucleic acid of the present disclosure and/or with a specific kinase inhibitor is a melanoma cell. In some embodiments, the cancer cell is a metastatic melanoma cancer cell. In certain embodiments, the cancer cell is a MEK-therapy resistant cancer cell. In some embodiments, the cancer cell is a MAPK-therapy resistant cancer cell. In some embodiments, the cancer cell is a BRAF-therapy resistant cancer cell.

6. Summary of sequences

LncRNA Nr. 1:
Gene name: BX470102.3

Genecode ID: ENSG00000238279.1 for the gene, ENST00000420695.1 for the trancript
Chromosome: 1
Strand: +
Mature mRNA length: 531nt
Predicted mature mRNA:
>ENST00000420695.1
Ccccacccagtggggacagaagacaacttaattccacaaagttggacccccaagggaagtggggaggtgagaggg
aaagaaggatgtggtctccatctaaagtcaagatctcttccccagaagctagaggtaaacttgcccagctcggac
taggcctagagaggctgaatgatgtggcatcacccggaaacagcgtttaccctccttatcctcttcccttctgcc
tgaaaacactaatccagatgatggacaatgattcaattagtcatcttctctgatgggggctgagatccaggctgg
gatcccgtggaagtgccgggcaatcctctctgcaagtggctctgtgctccctcatcaccaaggacccatgtcact
ttggcattgcttctcctcagctacttctcagttactggtcctcatttggagagatggatatccggctggaagcat
cccctacccgctgggagagtgggtctacagctcagggtctacatgtggaccagggcctcagaatgtgggtaaatg
tgagtc (SEQ ID NO:1)

Antisense oligonucleotide sequences to target BX:
1: AAGGAGGGTAAACGCT ((SEQ ID NO:13)
2: ATCATCTGGATTAGTG (SEQ ID NO:14)
siRNA sequence to target BX:
Sense: CCCAGAAGCUAGAGGUAAAUU (SEQ ID NO:23)
Antisense: UUUACCUCUAGCUUCUGGGUU (SEQ ID NO:24)

LncRNA Nr. 2:
Gene name: AC004540.4
Genecode ID: ENSG00000225792 for the gene
Chromosome: 7
Strand: -
Isoform 1:
Geneocode ID: ENST00000451368
RefSeq ID: NR_136271.1
Mature mRNA length: 611nt
Predicted mature mRNA:
>ENST00000451368.1
Agcccagtcgccgccgccagcggagcggcccgggcgggacgcggcgggagcgcgcgtgtgcgggacgcagcgcgg
gggatgcgcgcgggccgcggaggcgccgcaaccaacaggcggccgagggtgcagccgcgggagcgccaccgccag
tggggtgggggcaaagctataaagaaggcccagaggattcctgcggagctgtatttactttacatccatgtgaa
ctgctgtcatcactactgtgtccaagcccagaggatgaactggaaaagaagagaggggaaaataataaaaagag
gaaattggttttcacaacacactcaaagcctgagtaacagaggagaactttaattatctccagtcacaaagagag
acaggaaatttggacttttaattagccatttggagtgcagttgggtatttttttagctagataatttaaacgcga
ataattcaagtctgactaaatgaaagtcacataatcagaatgcaaataattgaatttctactgcattcattaatt
cagtgtggaggtgtgtgtgaagactactatgatgagctgtcacagctcaataaaatctcagtcaattaatttttt
cattatcttag (SEQ ID NO:2)

Isoform 2:
Genecode ID: ENST00000451264
RefSeq ID: NR_136270.1
Mature mRNA length: 508nt
Predicted mature mRNA:
>ENST00000451264.1
Ccgcccctcaaccaaccccccaggcggcaaggccctctccacgcgcgctctccagcctggcggggccctggaagcc
gggacacgcggaggccgggagggtcatcggcgtttaaggcagcctcccacaccaagtgcaccgcccggatcccct
ctgcacgagggctttctgcttattgctcttttccccagcagccagaatcgtcaccgtagcgcgggaaggggcctc
gcgggccgtctgcagcaggtgcggccgggagccgcaggcccgcgcggattcctgcggagctgtatttactttaca
tccatgtgaactgctgtcatcactactgtgtccaagcccagaggatgaactggaaaagaagagaggggaaaata

ataaaaagaggaaattggttttcacaacacactcaaagcctgagtaacagaggagaactttaattatctccagtc
acaaagagagacaggaaatttggacttttaattagccatttggagtgcagttgggtat (SEQ ID NO:3)

Antisense oligonucleotide sequences to target AC004540.4:
1: GACTGGAGATAATTAA (SEQ ID NO:15) (targets exon region of both isoforms)
2: TGCGCGGCGGAAAGAA (SEQ ID NO:16) (targets intronic region of Isoform 2)
siRNA Sequence to target both Isoforms of AC004540.4:
Sense: GAGUAACAGAGGAGAACUUUU (SEQ ID NO:25)
Antisense: 5'-PAAGUUCUCCUCUGUUACUCUU (SEQ ID NO:26)

lncRNA Nr.3
Gene name: RP11-7011.3
Genecode ID: ENSG00000237950.1 for the gene
Chromosome: 1
Strand: -
Isoform 1:
Genecode ID: ENST00000446167.1
Mature mRNA length: 486nt
Predicted mature mRNA:
>ENST00000446167.1
gggaccacccaataagcaaccgggaaaccacataccatggacagtgctcggggaatttcggctcctcctcatccc
tggaggttccagggatctggcagagaaagaagcccagtctcacagcaatgactcctgaacatcctttgcaaacac
tatttaggacagatggactgaagtaggccctggggagagttgggggcatttccggaggccagaccaaaggtgatc
tccaggagatttggatgttagtgcaggatagctcagagccaagtggcagataagtctttgggagccagaagggct
ctttcttctctaaggaacaagtgtagacctatagggqcaagaacctgtggcaaccctgggagaggtctgcagatt
caggagggaacatcccaaaactcagcagaggaggagagggagctttgttggtcacctggaaccactaccaatcc
atgttcatgtcaaattaaatgatcactttgaagttt(SEQ ID NO:4)

Isoform 2:
Genecode ID: ENST00000445226.1
Mature mRNA length: 294nt
Predicted mature mRNA:
>ENST00000445226.1
caaccgggaaaccacataccatggacagtgctcggggaatttcggctcctcctcatccctggaggttccagggat
ctggcagagaaagaagcccagtctcacagcaatgactcctgaacatcctttgcaaacactatttaggacagatgg
actgaagtaggccctggggagagttgggggcatttccggagggaacatcccaaaactcagcagaggaggagaggg
agcttttgttggtcacctggaaccactaccaatccatgttcatgtcaaattaaatgatcactttgaagt(SEQ
ID NO:5)

Isoform 3:
Genecode ID: ENST00000412378.1
Mature mRNA length: 494nt
Predicted mature mRNA:
>ENST00000412378.1
cagaccggcgcggggcgctgcggcccaactccttagtaggacgacgtgactcgaggggccggaggacggagggct
cctcctcatccctggaggttccagggatctggcagagaaagaagcccagtctcacagcaatgactcctgaacatc
ctttgcaaacactatttaggacagatggactgaagtaggccctggggagagttgggggcatttccggaggccaga
ccaaaggtgatctccaggagatttggatgttagtgcaggatagctcagagccaagtggcagataagtctttggga
gccagaagggctctttcttctctaaggaacaagtgtagacctatagggqcaagaacctgtggcaaccctgggaga
ggtctgcagattcaggagggaacatcccaaaactcagcagaggaggagagggagctttgttggtcacctggaac
cactaccaatccatgttcatgtcaaattaaatgatcactttgaa(SEQ ID NO:6)

Antisense oligonucleotide sequences to target RP11-7011.3:
1: ACATGGATTGGTAGTG (SEQ ID NO:17) [targeting SEQ ID NOS: 4, 5 and 6]
2: GATCATTTAATTTGAC (SEQ ID NO:18) [targeting SEQ ID NOS: 4, 5 and 6]
siRNA Sequence to target both Isoforms of RP11-7011.3:
Sense: AGCAAUGACUCCUGAACAUUU (SEQ ID NO:27) [targeting SEQ ID NOS: 4, 5 and 6]

Antisense: 5'-PAUGUUCAGGAGUCAUUGCUUU (SEQ ID NO:28)

lncRNA Nr.4
Gene name: RN7SL1
Genecode ID: ENSG00000258486.1 for the gene
Chromosome: 14
Strand: +
Isoform 1:
Genecode ID: ENST00000635274.1
Mature mRNA length: 300nt
Predicted mature mRNA:
>ENST00000635274.1
Cgccgggcgcggtggcgcgtgcctgtagtcccagctactcgggaggctgaggctggaggatcgcttgagtccagg
agttctgggctgtagtgcgctatgccgatcgggtgtccgcactaagttcggcatcaatatggtgacctcccggga
gcgggggaccaccaggttgcctaaggaggggtgaaccggcccaggtcggaaacggagcaggtcaaaactcccgtg
ctgatcagtagtgggatcgcgcctgtgaatagccactgcactccagcctgggcaacatagcgagaccccgtctct
(SEQ ID NO:7)

Isoform 2:
Genecode ID: ENST00000618786.1
Mature mRNA length: 300nt
Predicted mature mRNA: 299
>ENST00000618786.1
gccgggcgcggtggcgcgtgcctgtagtcccagctactcgggaggctgaggctggaggatcgcttgagtccagga
gttctgggctgtagtgcgctatgccgatcgggtgtccgcactaagttcggcatcaatatggtgacctcccgggag
cgggggaccaccaggttgcctaaggaggggtgaaccggcccaggtcggaaacggagcaggtcaaaactcccgtgc
tgatcagtagtgggatcgcgcctgtgaatagccactgcactccagcctgggcaacatagcgagaccccgtctct(
SEQ ID NO:8)

siRNA Sequence to target:
Sense: GCACUAAGUUCGGCAUCAAUU (SEQ ID NO:29) [targeting SEQ ID NOS: 7 and 8]

Antisense: UUGAUGCCGAACUUAGUGC (SEQ ID NO:30)
2:
Sense: ACUAAGUUCGGCAUCAAUAUU (SEQ ID NO:31) [targeting SEQ ID NOS: 7 and 8]
Antisense: UAUUGAUGCCGAACUUAGU (SEQ ID NO:32)
3:
Sense: GGACCACCAGGUUGCCUAAUU (SEQ ID NO:33) [targeting SEQ ID NOS: 7 and 8]
Antisense: UUAGGCAACCUGGUGGUCC (SEQ ID NO:34)
4:
Sense: GGGACCACCAGGUUGCCUAUU (SEQ ID NO:35) [targeting SEQ ID NOS: 7 and 8]
Antisense: UAGGCAACCUGGUGGUCCC (SEQ ID NO:36)

lncRNA Nr.5
Gene name: ARF-AS1
Genecode ID: ENSG00000272146 for the gene
Chromosome: 3
Strand: +
Isoform 1:
Genecode ID: ENST00000606192.5
Mature mRNA length: 327nt
Predicted mature mRNA:
>ENST00000606192.5
cttgcttccggaaaggcgagctgagcattatgggttagggtctcactttgtcacccaagctgaagtacagtggca
tcatctcggcttactcaacctcctgggatcaagtgatcctcccacctcagcccccaaagtagctgggactacagg
tcaggcatggtggctcacacctgtaatcccagcatgttgggaggccaagatgggagactcacttgagcccagaag
ttccagaccagccttggcaatatagtgagatgccatttctattttaaaaaatattttaaaaataaaatatttttc
tattcacctttcatcaatacaaaccca(SEQ ID NO:9)

Isoform 2:

Genecode ID: ENST00000607297.1
Mature mRNA length: 437nt
Predicted mature mRNA:
>ENST00000607297.1
Gatgggtattccctgatgccatgaacttacacgtttcacacacgggaccagacgcttgctttagttgacgcatga
agaccggtccggtcttttgcggagaaaagtggttaaaagctgacttgtgggccgagaaactgtggcaccctaatg
agctagggctagacgcttcgaccaccacgccaagtgattctgaagatctctaattctgtcaaggcgagagcgctc
caacacgtgttcatcggctgttgctttttaaagagaaggtcaggcatggtggctcacacctgtaatcccagcatg
ttgggaggccaagatgggagactcacttgagcccagaagttccagaccagccttggcaatatagtgagatgccat
ttctattttaaaaaatattttaaaaataaaatatttttctattcacctttcatcaatacaaa(SEQ ID
NO:10)

Isoform 3:
Genecode ID: ENST00000607782.1
Mature mRNA length: 552nt
Predicted mature mRNA:
>ENST00000607782.1
attccctgatgccatgaacttacacgtttcacacacgggaccagacgcttgctttagttgacgcatgaagaccgg
tccggtcttttgcggagaaaagtggttaaaagctgacttgtgggccgagaaactgtggcaccctaatgagctagg
gctagacgcttcgaccaccacgccaagtgattctgaagatctctaattctgtcaaggcgagagcgctccaacacg
tgttcatcggctgttgctttttaaagagaagggtctcactttgtcacccaagctgaagtacagtggcatcatctc
ggcttactcaacctcctgggatcaagtgatcctcccacctcagcccccaaagtagctgggactacaggtcaggca
tggtggctcacacctgtaatcccagcatgttgggaggccaagatgggagactcacttgagcccagaagttccaga
ccagccttggcaatatagtgagatgccatttctattttaaaaaatattttaaaaataaaatatttttctattcac
ctttcatcaatacaaacccagaagaga(SEQ ID NO:11)

ASO Sequence to target all 3 isoforms:
ATTGATGAAAGGTGAA (SEQ ID NO:19)
ASO sequence targets exonic region of isoform 2 and 3 and intronic region of isoform 1:
GCGTCAACTAAAGCAA
siRNA Sequence:
Sense: GGAAAGGCGAGCUGAGCAUUU (SEQ ID NO:37) [targeting SEQ ID NO: 9]
Antisense: AUGCUCAGCUCGCCUUUCCUU (SEQ ID NO:38)

lncRNA Nr.6
Gene name: AL157871.4
Genecode ID: ENSG00000258666 for the gene
Chromosome: 14
Strand: +
Isoform 1:
Genecode ID: ENST00000557226.1
Mature mRNA length: 385nt
Predicted mature mRNA:
>ENST00000557226.1
Caggagccaaggaagtttatttactctactgggtgacaggagggcagagtgctccagaggagacccagatacatc
aaccaaggacttccctgagatttggctttgctcttccagggtcaggtccttccacagatacttctcgtcatccgt
catctggatgaccaagggcacgttaaatacatcctggagccacctaaagaaacacaggggagaaagctgacgtc
tcatctcccctgtggaggaacgccatcgtgcatctgaaaacacagctcctacttacaacgtatgttaaaacttcc
ttgcctacaaaatcacaatttgaattgtgatatgaatttgactatggataatgataaggtctactaccatttatc
gaccaggtgg (SEQ ID NO:12)

ASO Sequence:
1. AAGTCCTTGGTTGATG (SEQ ID NO:21)
2. GTAAGTAGGAGCTGTG (SEQ ID NO:22)

siRNA Sequence:
Sense:UGGAUAAUGAUAAGGUCUAUU (SEQ ID NO:39)
Antisense: UAGACCUUAUCAUUAUCCAUU (SEQ ID NO:40)

SEQ	Description
1	BX470102.3-008
2	AC004540.4-001
3	AC004540.4-002
4	RP11-7011.3-001
5	RP11-7011.3-003
6	RP11-7011.3-002
7	RN7SL1-202
8	RN7SL1-201
9	ARF-AS1-201
10	ARF-AS1-202
11	ARF-AS1-203
12	AL157871.4-201
13	Antisense oligonucleotide sequence targeting BX470102.3-008
14	Antisense oligonucleotide sequence targeting BX470102.3-008
15	Antisense oligonucleotide sequence targeting AC004540.4-001 and AC004540.4-002
16	Antisense oligonucleotide sequence targeting AC004540.4-001 and AC004540.4-002
17	Antisense oligonucleotide sequence targeting RP11-7011.3-001, 002 and 003
18	Antisense oligonucleotide sequence targeting RP11-7011.3-001, 002, and 003
19	Antisense oligonucleotide sequence targeting ARF-AS1-201, ARF-AS1-202, and ARF-AS1-203
20	Antisense oligonucleotide sequence targeting ARF-AS1-202 and ARF-AS1-203
21	Antisense oligonucleotide sequence targeting AL157871.4-201
22	Antisense oligonucleotide sequence targeting AL157871.4-201
23	siRNA sense strand sequence targeting BX470102.3-008
24	siRNA antisense strand sequence targeting BX470102.3-008
25	siRNA sense strand sequence targeting AC004540.4-001 and AC004540.4-002
26	siRNA antisense strand sequence targeting AC004540.4-001 and AC004540.4-002
27	siRNA sense strand sequence targeting both isoforms of RP11-7011.3-001, 002 and 003

28	siRNA antisense strand sequence targeting both isoforms of RP11-7011.3-001, 002 and 003
29	siRNA sense strand sequence targeting RN7SL1-201 and 202
30	siRNA antisense strand sequence targeting RN7SL1
31	siRNA sense strand sequence targeting RN7SL1
32	siRNA antisense strand sequence targeting RN7SL1
33	siRNA sense strand sequence targeting RN7SL1
34	siRNA antisense strand sequence targeting RN7SL1
35	siRNA sense strand sequence targeting RN7SL1
36	siRNA antisense strand sequence targeting RN7SL1
37	siRNA sense strand sequence targeting ARF-AS1
38	siRNA antisense strand sequence targeting ARF-AS1 isoform 1 (SEQ ID NO:9)
39	siRNA sense strand sequence targeting AL157871.4-201
40	siRNA antisense strand sequence targeting AL157871.4-201
41	Antisense oligonucleotide sequence CTCATGAGCTGTCGTA targeting AC004540.4-001 and AC004540.4-002
42 and 50	Duplex Sequences: 5'-GGUAAAAACAUGAAGCUAAUAGUUA-3' and 3'-ACCCAUUUUUGUACUUCGAUUAUCAAU-5' targeting AC004540.4-001 and AC004540.4-002
43 and 51	Duplex Sequences: 5'-GCCAACAGCAUGUCAAUUCAGUGAT-3' and 3'-GACGGUUGUCGUACAGUUAAGUCACUA-5', targeting AC004540.4-001 and AC004540.4-002
44 and 52	Duplex Sequences: 5'-AUUUCAUGUCUGAAGCAAUUCUACT-3' and 3'-AAUAAAGUACAGACUUCGUUAAGAUGA-5', targeting AC004540.4-001 and AC004540.4-002
45 and 53	Duplex Sequences: 5'-ACAAAGAGAGACAGGAAAUUU-3' and 3'-AUUUCCUGUCUCUCUUUGUUU-5', targeting AC004540.4-001 and AC004540.4-002
46 and 54	Duplex Sequences: 5'-UCACAAAGAGAGACAGGAAUU-3' and 3'-UUCCUGUCUCUCUUUGUGAUU-5', targeting AC004540.4-001 and AC004540.4-002
47	Antisense oligonucleotide sequence GACTGGAGATAATTAA-Cholesterol targeting AC004540.4-001 and AC004540.4-002

48	Antisense oligonucleotide sequence GACCGTAGTTAGAAGG targeting HNRNPA2/B1
49	Antisense oligonucleotide sequence AGATGGCTCTGTAAGA targeting SNX10

EXAMPLE

EXAMPLE 1

[0138] A goal of this work was to explore lncRNAs interacting with the MAPK pathway that are essential for melanoma cell survival and tumor progression. As a result, we identified the oncogenic features of the lncRNA TRASH and the dependency of melanoma to TRASH expression. We suggest that the direct physical interaction of TRASH and hnRNPA2/B1 mediates the oncogenic character of TRASH. Antisense Oligonucleotide mediated TRASH knockdown (TRASHi) leads to concomitant hnRNPA2/B1 knockdown. We found that TRASH prevents apoptosis, which sustain cancer cells' viability. TRASHi efficiently suppresses these anti-apoptotic mechanisms and strongly affects a broad panel of melanoma cell lines, including melanoma that is treatment resistant to the first-line clinical approach of MEK inhibition. [Grimaldi, A. M. et al. *MEK Inhibitors in the Treatment of Metastatic Melanoma and Solid Tumors.* Am J Clin Dermatol 18, 745–754 (2017)] Furthermore, TRASHi leads to strong tumor growth reduction and apoptosis induction in mouse models of standard melanoma cell line xenografts and patient derived tumors. In summary, these findings demonstrate the strong potential of clinical applications of TRASHi.

Results:

Identification of MAPK-pathway activation responsive lncRNAs in melanoma

[0139] The oncogene NRAS is the most upstream member of the MAPK pathway. NRAS mutations seem to be anearly event in melanocytic tumorigenesis and NRAS activation is followed by activation of the downstream targets AKT and ERK.[Khosravi-Far, et al., *Increasing Complexity of Ras Signal Transduction: Involvement of Rho Family Proteins.* in Advances in Cancer Research vol. 72 57–107 (Elsevier, 1997).; Brazil, et al. *Ten years of protein kinase B signalling: a hard Akt to follow*. Trends in Biochemical Sciences **26**, 657–664 (2001).; Platz, et al., *Human cutaneous melanoma; a review of NRAS and BRAF mutation frequencies in relation to histogenetic subclass and body site*. Molecular Oncology **1**, 395–405 (2008).] To identify lncRNA transcripts that respond to MAPK pathway upregulation we transduced an $NRAS^{Q61}$ mutant plasmid into primary human melanocytic

cell lines (PHM^{Q61}). **(Fig. 7a-b)** PHM^{Q61} cells showed upregulated levels of phosphorylated ERK and AKT (pERK and pAKT). **(Fig. 7c)** Activating NRAS mutations like $NRAS^{Q61}$ are commonly diagnosed in benign nevi and additional transformations are needed to fully unfold the malignant potential of melanocytes. [Poynter, et al. B*RAF and NRAS mutations in melanoma and melanocytic nevi.* Melanoma Research **16**, 267–273 (2006)] No significant differences in cell proliferation could be measured comparing the PHM^{Q61} and PHM cell lines transduced with an empty vector (PHM^{e}), indicating that a sole $NRAS^{Q61}$ mutation is not sufficient to equip melanocytic cell lines with profound melanoma cell characteristics. **(Fig. 7b-d)**

[0140] **Figure 1a** represents a schematic workflow overview of the combined in silico and in vitro processes to identify MAPK pathway activation responsive lncRNAs that are essential for melanoma cell survival. First, we compared pair-end non-poly A enriched 101-bp RNASeq data from PHM, PHM^{E}, PHM^{Q61}, and two melanoma cell lines (D04, MM415) harboring MAPK pathway hyperactivating mutations. 237 transcripts were differently expressed (DE) in PHM^{Q61}, D04, and MM415 when compared to standard melanocytes (PHM^{Q61}ΔPHM^{E}; DO4ΔPHM; M415ΔPHM). **(Fig 1b-c)** 120 of the DE genes were lncRNA transcripts**.** 28 of those transcripts were also expressed (FPKM values > 0.2) in >90% of patient derived melanoma samples from the TCGA dataset This process led to the identification of several lncRNA transcripts that respond to MAPK pathway activation, including the transcript AC004540.4, which is located on the reverse strand of chromosome 7. Based on our functional studies, which will be discussed in later parts of this study, we named the novel transcript: TRanscript ASociated with HNRNPA2B1 (TRASH).

[0141] Endoribonuclease-prepared siRNA (esiRNA) is an efficient and specific method for RNAi screens in mammalian cells.[Kittler, R. et al. *An endoribonuclease-prepared siRNA screen in human cells identifies genes essential for cell division.* Nature **432**, 1036–1040 (2004)] RNAi screening using TRASH targeting esiRNA libraries led to strong cell viability decrease in melanoma cell lines, while no such impact could be observed in melanocytic cell lines. **(Fig. 1d)** To reduce the chance of measuring off target effects, we subsequently conducted siRNA mediated RNAi screening. As expected, siRNA mediated TRASH silencing showed significant cell viability decrease in melanoma cell lines, but not melanocytic cell lines **(Fig. 1e)**. These findings unveil that our pipeline identified a MAPK activation responsive lncRNA that is essential for melanoma cell survival.

TRASH is a nuclear regulator of hnRNPA2/B1

[0142] The regulatory functions of lncRNAs are closely related to their subcellular localization and lncRNAs are primarily localized to the nucleus.[Karakas, et al., *The Role of LncRNAs in Translation*. Noncoding RNA **7**, 16 (2021).; Derrien, et al. *The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression.* Genome Research **22**, 1775–1789 (2012).]To identify the role of TRASH in melanoma, we performed subcellular fractionation followed by qPCR, demonstrating that TRASH is highly enriched in the nuclear compartment versus the cytoplasmic compartment in melanoma. **(Fig. 2a)** Nuclear enriched lncRNAs often exist in inefficiently spliced states. [Statello, et al. *Gene regulation by long non-coding RNAs and its biological functions.* Nat Rev Mol Cell Biol **22**, 96–118 (2021)] Using 4 different primer pairs for comparison of relative quantification of different intronic/exonic regions of TRASH through qPCR further showed that exonic, intronic and exon/intron transition regions of TRASH were detected in different quantities, indicating that TRASH transcripts may exist to a certain extent in inefficient spliced states. **(Fig. 2b)** Genomic juxtapositioning of lncRNAs and protein coding genes can result in co-expression. The closest genomic same strand protein coding gene to TRASH is the oncogene coding for hnRNPA2/B1. [Statello, et al. *Gene regulation by long non-coding RNAs and its biological functions.* Nat Rev Mol Cell Biol **22**, 96–118 (2021)] HnRNPA2/b1 is part of the family of heterogeneous nuclear ribonucleoproteins (hnRNPs), a group of protein[s that have at least one RNA-binding motif and regulate nucleic acid metabolism.[Singh, R. & Valcárcel, J. *Building specificity with nonspecific RNA-binding proteins*. Nat Struct Mol Biol **12**, 645–653 (2005).] HnRNPA2/B1 interacts with lncRNAs and exerts regulatory functions in MAPK pathway signaling. [Gupta, A. et al. *The HNRNPA2B1–MST1R–Akt axis contributes to epithelial-to-mesenchymal transition in head and neck cancer*. Lab Invest (2020) doi:10.1038/s41374-020-0466-8.; Barceló, C. et al., *Ribonucleoprotein HNRNPA2B1 Interacts With and Regulates Oncogenic KRAS in Pancreatic Ductal Adenocarcinoma Cells*. Gastroenterology **147**, 882-892.e8 (2014).; Chen, Z. et al. *Integrative Analysis of NSCLC Identifies LINC01234 as an Oncogenic lncRNA that Interacts with HNRNPA2B1 and Regulates miR-106b Biogenesis.* Molecular Therapy **28**, 1479–1493 (2020).; Liu, B. et al. E*nzalutamide-Induced Upregulation of PCAT6 Promotes Prostate Cancer Neuroendocrine Differentiation by Regulating miR-326/HNRNPA2B1 Axis*. Front. Oncol. **11**, 650054 (2021).; Shen, Y. et al. l*ncRNA ST3GAL6-AS1 promotes invasion by inhibiting hnRNPA2B1-mediated ST3GAL6 expression in multiple myeloma.* Int J Oncol

58, 5 (2021).; Wang, H. et al. *Long noncoding RNA miR503HG, a prognostic indicator, inhibits tumor metastasis by regulating the HNRNPA2B1/NF-κB pathway in hepatocellular carcinoma.* Theranostics **8**, 2814–2829 (2018).; Shilo, A. et al. *Splicing factor hnRNP A2 activates the Ras-MAPK-ERK pathway by controlling A-Raf splicing in hepatocellular carcinoma development.* RNA **20**, 505–515 (2014).] To identify possible co-interactions and dependencies of TRASH and hnRNPA2/B1 we explored the correlation between the genes of interest in contrast to permutations of randomly chosen genes in patient derived melanoma and healthy skin samples. Most notably, RNA expression of each gene is significantly higher in melanoma. **(Fig 2c)** Correlation of TRASH and hnRNPA2/B1 is almost always significantly stronger in melanoma than the average correlation of each gene to 10 sets of random genes ($p<0.05$ 10/10 for TRASH and 8/10 for hnRNPA2/B1). However, in healthy skin samples, no significant difference could be seen in any of the 20 comparisons. **(Fig. 8a-d)** Inhibition of TRASH expression did not significantly affect hnRNPA2/B1 RNA abundance, indicating that TRASH does not regulate hnRNPA2/B1 gene expression. **(Fig. 2d)** To investigate if inhibition of TRASH expression affects hnRNPA2/B1 protein expression, we visualized protein levels of hnRNPA2/B1 1 and 2 days after TRASH expression was inhibited. Immunoblot probing for HnRNPA2/B1 detected strong and stable protein expression reduction. **(Fig 2e)** To investigate if the regulating effect of TRASH expression on hnRNPA2/B1 protein levels may rely on direct RNA-protein binding, we pulled down hnRNPA2/B1 from melanoma cell lysate and compared TRASH enrichment to negative control pulldown. HnRNPA2/B1 pulldown samples showed >65-fold enrichment of TRASH compared to the control samples, indicating that the lncRNA TRASH and the protein hnRNPA2/B1 directly interact. **(Fig. 2f)**

[0143] Taken together, these findings indicate that melanoma is characterized by TRASH and hnRNPA2/B1 upregulation and both molecules seem to physically interact with each other. Most notably, TRASH expression seems to be essential for maintaining stable hnRNPA2/B1 protein levels in melanoma.

<u>TRASH serves as MAPK and PI3K-Akt signaling cascade relevant anti-apoptotic regulator in melanoma.</u>

[0144] It is common practice to use synthetic nucleic acids such as siRNA and Antisense Oligonucleotides (ASOs) for silencing gene expression and these methods have the potential to be widely used in future clinical therapeutic approaches. [Winkle, et al., *Noncoding RNA*

therapeutics — challenges and potential solutions. Nat Rev Drug Discov **20**, 629–651 (2021).; Deleavey et al. *Designing Chemically Modified Oligonucleotides for Targeted Gene Silencing.* Chemistry & Biology **19**, 937–954 (2012)] Both methods can lead to off-target effects and unwanted immune system activation.[Kanasty, et al., *Action and Reaction: The Biological Response to siRNA and Its Delivery Vehicles.* Molecular Therapy **20**, 513–524 (2012)] In contrast to siRNA, ASOs allow more chemical modification of synthetic nucleic acids to reduce unwanted side effects. [Kole, et al., *RNA therapeutics: beyond RNA interference and antisense oligonucleotides.* Nat Rev Drug Discov **11**, 125–140 (2012).] Therefore, we focused on GapmeR-type ASO mediated TRASH inhibition (TRASHi) studies.

[0145] In the next step we tested TRASHi in a repository of standard and primary patient derived melanoma cell lines harboring MAPK pathway activating NRAS, BRAF and c-KIT mutations, which is frequently seen in melanoma patients. [Liang, J. et al. *The C-Kit Receptor-Mediated Signal Transduction and Tumor-Related Diseases.* Int. J. Biol. Sci. **9**, 435–443 (2013); Vu, et al., *Targeting mutant NRAS signaling pathways in melanoma.* Pharmacological Research **107**, 111–116 (2016); Dhomen, et al., *BRAF Signaling and Targeted Therapies in Melanoma.* Hematology/Oncology Clinics of North America **23**, 529–545 (2009).] TRASHi induced a strong cell viability decrease in melanoma, but not in melanocytic cell lines. **(Fig 3a)** To measure the impact of TRASHi on the reproductive viability of melanoma cells, we performed clonogenic assays on three different melanoma cell lines. TRASHi drastically reduced the capability of melanoma cells to produce colonies. **(Fig 3b)** Also, ASO mediated inhibition of hnRNPA2/B1 expression (hnRNPA2/B1i) led to significant cell viability decrease. **(Fig. 3c)** Caspase 3 & 7 activity increase is a marker for apoptosis induction.[Lüthi, et al., T*he CASBAH: a searchable database of caspase substrates.* Cell Death Differ **14**, 641–650 (2007).] Caspase -3 & -7 activity was significantly increased by 3-fold after TRASHi and 1.7-fold after hnRNPA2/B1 inhibition. **(Fig. 3d)**

[0146] To examine the functional relevance of TRASH in melanoma DO4 cells were treated with TRASHi and non-targeting control ASOs, RNA was extracted and used for RNA-Seq. Differential expression (DE) analysis showed TRASHi had a global effect on melanoma gene expression. We found that 574 genes were down-regulated, and 493 genes were up-regulated. GO term analysis revealed the top enriched GO term cluster among the down-regulated genes is relevant to “ECM-receptor interaction” and “PI3K-Akt signaling pathway”; the top enriched GO term cluster among the up-regulated genes included terms

like “protein tyrosine kinase activity (GO: 0004713)” and “Ras guanyl-nucleotide exchange factor activity (GO0005088”). These GO terms consisted of genes encoding growth factors, tyrosine kinases, G protein coupled receptor subunits and collagen subunits.

[0147] These findings indicate that the functional mechanisms of TRASH are linked to genes situated at the top of the MAPK and PI3K-Akt signaling cascade. TRASH expression seems to be a common apoptosis inhibiting dependency in MAPK-pathway activated melanoma. Some of the anti-apoptotic functions of TRASH may rely to its stabilizing effect on hnRNPA2/B1. Furthermore, these findings allow the conclusion that TRASH may excise its regulatory functions upstream of many kinase-pathway cascades.

Kinase activity profiling reveals unique anti-apoptotic features of TRASH expression

[0148] Considering the results that TRASH seems to serve as an anti-apoptotic regulator in melanoma that broadly affects kinase activity states, we used the novel technique of HTKAM to thoroughly investigate kinase activity shifts followed by TRASHi.

TRASH knockdown shows characteristics that can be of high clinical value

[0149] The MEK inhibitor (MEKi) trametinib is a FDA approved drug for the treatment of melanoma as mono- and combinatorial therapy and used in clinics worldwide.[Wright, et al.,. *Trametinib: First Global Approval.* Drugs **73**, 1245–1254 (2013).] Drug resistance is the main limiting factor in modern oncology.[Vasan, et al., *A view on drug resistance in cancer.* Nature **575**, 299–309 (2019).] Therefore therapeutic applications that reduce growth of drug resistant tumors are urgently needed. TRASHi in a panel of cell lines that are resistant to the MEK-Inhibitor Trametinib (MEKi) led to significant cell viability decrease, comparable to the effect seen in their nonresistant naïve cell line counterparts. **(Fig. 3a+4a)** Combinational application of drugs is a common strategy in clinical oncology to synergize drug effects and to hamper the development of drug resistance.[Sawyers, C. L. *Perspective: Combined forces.* Nature **498**, S7–S7 (2013); Kling, J. *Bundling next-generation cancer therapies for synergy.* Nat Biotechnol **24**, 871–872 (2006).] Synergistic effects could be measured in a broad panel of concentration combinations in a standard melanoma cell line and in directly patient derived melanoma cells when testing dual TRASHi and MEKi. Synergy strongly increased with higher concentrations of TRASHi. More importantly, no notable inhibitory effects of could be observed. **(Fig. 4b)**

[0150] Next, we rescued cells that survived initial TRASH knockdown and after a phase of regrowth in ASO free media, we repeated TRASHi. Cells that survived initial TRASHi kept their vulnerability to TRASHi. **(Fig 5d)** To further evaluate the clinical potential of targeting TRASH dependency in melanoma, we aimed to test the effects of TRASHi in mouse models. ASO mediated inhibition of RNA expression has been proven to lead to effective tumor growth reduction in vivo.[Shi, L. et al. *A KRAS-responsive long non-coding RNA controls microRNA processing.* Nat Commun **12**, 2038 (2021).; Leucci, E. et al. *Melanoma addiction to the long non-coding RNA SAMMSON.* Nature **531**, 518–522 (2016).] We used xenograft models harboring a standard melanoma cell line (D04), patient derived primary melanoma cells (AV5) and a melanoma PDX model. A treatment regimen of 60ug subcutaneous ASO injections twice a week, co applied with an in vivo transfection reagent, reduced tumor growth in all three mouse models significantly. **(Fig. 4c)** The PDX tumor model TM01341 showed extremely high rates of tumor growth. While tumor growth could be significantly hampered in the TRASHi group, mice of the control group had to undergo euthanization before desired endpoint of the experiment, due to UCSF- IACUC guidelines for maximum acceptable tumor sizes. To simulate the experiment to the desired endpoint, we tumor growth in the PDX control group was forecasted using a regression model. **(Fig. 4c)** In none of the three melanoma type groups significant differences in weight change could be seen in between the TRASHi and control treatment group. **(Fig. 4c)** Essentially, RT-qPCR of tumor tissue extracted after end of treatment period showed that in vivo TRASHi strongly reduced TRASH expression. **(Fig. 4d)** In some circumstances GapmeR ASOs can show toxic side effects, in particular hepatotoxicity.[Kasuya, T. et al., *Ribonuclease H1-dependent hepatotoxicity caused by locked nucleic acid-modified gapmer antisense oligonucleotides.* Sci Rep **6**, 30377 (2016)] Liver tissue of treated mice was extracted for H+E staining after end of treatment period. Neither for animals receiving TRASHi, nor for animals receiving control ASOs detectable pathologic changes in liver tissue could be shown. **(Fig. 4e)** Furthermore, IHC staining of tumor tissue that was harvested from mice at the end of treatment period shows high levels of the apoptosis marker cleaved caspase 3 in tumors that underwent TRASHi compared to tumors of mice that received control ASO. **(Fig. 4e)**

[0151] In summary these findings show that TRASHi could help to bypass the recent limitation of MEKi resistance in clinical melanoma therapy and also has the potential amplify MEKi treatment. To our knowledge no data regarding resistance building against GapmeR ASO mediated RNA depleting therapy in mammalian cells exists yet. Our findings highlight

that no early onset treatment resistance building could be observed for TRASHi in melanoma. Additionally, TRASHi significantly reduces TRASH expression and tumor growth in vivo while showing no signs of toxicity.

Discussion

[0152] MAPK pathway activation is a common and initiating event in melanoma genesis and regulating elements of its protein kinase cascades serve as effective targets for oncological treatment.[Luke, et al., *Targeted agents and immunotherapies: optimizing outcomes in melanoma*. Nat Rev Clin Oncol **14**, 463–482 (2017).; Hodis, E. et al., *A landscape of driver mutations in melanoma*. Cell **150**, 251–263 (2012).] There has been major progress in the development of melanoma therapeutics in the past 10 years. However, many patients do not benefit from these advances due to initial or acquired treatment resistance. Therefore, additional treatment options are urgently needed. Here, we present a bioinformatic pipeline that is composed of analytical steps including a broad set of *in silico* and *in vitro* derived data which lead to the identification of the oncogenic lncRNA TRASH. TRASH expression is responsive to MAPK activation and essential for MAPK-dependent melanoma cell survival. Our findings highlight the potential of TRASH as a therapeutic RNA target in melanoma.

[0153] With the ultimate goal of being able to develop a method of TRASH silencing with clinical utility, we used ASOs to inhibit TRASH expression (TRASHi), a gene silencing method that has already been utilized in clinical trials for various diseases. [Bedikian, et al., *Dacarbazine with or without oblimersen (a Bcl-2 antisense oligonucleotide) in chemotherapy-naive patients with advanced melanoma and low–normal serum lactate dehydrogenase: 'The AGENDA trial'*. Melanoma Research **24**, 237–243 (2014).; Beer, T. M. et al. *Custirsen (OGX-011) combined with cabazitaxel and prednisone versus cabazitaxel and prednisone alone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (AFFINITY): a randomised, open-label, international, phase 3 trial.* The Lancet Oncology **18**, 1532–1542 (2017).]

[0154] TRASHi induces apoptosis and inhibits colony formation capabilities in a broad panel of MAPK-dependent melanoma cell lines and primary melanoma cells, while having no effect on melanocytic cell lines. Our findings highlight that TRASH may exert regulatory mechanisms upstream of the MAPK and PI3K-Akt pathway. Some of the oncogenic features of TRASH may rely on the stabilizing effect it exerts on its protein binding partner which is

the product of the anti-apoptotic oncogene hnRNPA2/B1. Analysis of patient derived melanoma and non-melanoma skin tissue points toward the direction that gene expression correlation and upregulation of TRASH and hnRNPA2/B1 expression may be a melanoma specific mechanism. Therefore, we propose that the functional axis of TRASH and hnRNPA2/B1 is concomitant of melanoma.

Our results underline the high clinical potential of TRASHi. The precise role of TRASH expression in drug resistance mechanisms to melanoma goes beyond the scope of this research project. However, we show that MEKi-resistance does not desensitize melanoma cells to their TRASH dependency, indicating that TRASHi can serve as treatment for melanoma refractory to small molecule MEK inhibiting therapy. Dual application of TRASHi and MEKi amplifies the effects of mono-application, demonstrating the synergistic effects of multi-drug regimens that clinical dermato oncologists strive for.

[0155] Consistent with our in vitro results, we show that TRASH silencing is a powerful tool to reduce tumor growth through apoptotic cell death in PDX and xenograft melanoma mouse models, while showing no signs of hepatotoxicity or TRASHi-related weight loss.

[0156] MAPK hyperactivation propels expression of essential oncogenic elements and our findings indicate that the lncRNA TRASH is one of them. We unveiled a network of anti-apoptotic kinases that are affected by TRASHi and to our knowledge, such a pattern of apoptosis specific kinase activity shifts through inhibiting a druggable lncRNA target have never been reported.

[0157] Given the robust anti-melanoma effects of TRASHi and the development of RNA targeting therapy as a promising new method in next generation cancer therapy, we propose that TRASHi is a promising lncRNA targeting cancer therapy, from which many patients, including the subset of melanoma patients with MEKi resistance, could benefit.

Methods

Bioinformatic pipeline for identifying MAPK-responsive lncRNAs

Reference Annotation

[0158] A custom reference annotation of total 75,506 transcripts, referring to 35,101 genes, of which 16,405 were classified as noncoding, was built by integrating 13,870 lncRNA genes from the GENCODE (V19, July 2013 freeze, GRCh37, downloaded March 2015) into the

RefSeq database (release 57, downloaded March 2013). Cuffcompare (version 2.1.1) was used to cut out redundant transcripts.

Assembly and identification of previously unidentified lncRNAs

[0159] After alignment to the human genome with TopHat (version 2.0.11), the reads were assembled into transcripts with Cufflinks (version 2.1.1). To discover novel lncRNAs, we excluded all transcripts that overlapped with any genes from our initial reference annotation. To filter out transcriptional noise, we kept only multi-exonic transcripts which were > 200bp and had at least one intron region > 10bp. Next, isoforms were merged with Cuffcompare into 1,311 transcripts.

Coding Potential Assessment of Transcripts

[0160] To identify transcripts with a coding potential, we ran (i) the HMMER3 algorithm (considering all 6 open reading frames) for each of the 1,311 transcripts to identify any protein family domain as noted in the Pfam database (release 27.0, Pfam-A and Pfam-B domains considered) and (ii) the Coding Potential Assessment Tool (CPAT v1.2.1). 479 transcripts were categorized as TUCPs (331 transcripts called by Pfam only, 70 transcripts called by CPAT only, and 78 transcripts called by both). The other 832 transcripts were classified as previously unidentified lncRNAs, or "novel lncRNAs". The final reference annotation had a total of 76,817 transcripts referring to 35,961 genes.

Filter for DE genes

[0161] Cuffdiff (v.2.1.1) was used to identify differential gene expression analysis between PHM^{E} and PHM^{Q61}. From a reference of 35,905 genes, we discarded genes with FPKM < 0.2 in both conditions (14,790 genes) and kept genes with log2fold change > 1 or < -1 (1021 genes). Cufflinks was used to obtain FPKM values of the 1021 genes in Seq-Data from the D04 and MM415 melanoma cell lines. Log 2 transformations were performed to calculate expression fold change in the comparisons: 1) PHM^{E} vs. PHMQ61, 2) PHM vs. D04, 3) PHM vs. MM415. The value of 1 was added to all FPKM values before calculating log2fold change. Genes that had a log 2-fold change > 1 or < -1 were considered as differentially expressed.

Animal models

[0162] Rodent experimental procedures were approved by the Office of Research institutional Animal Care and Use Program (IACUC) at the University of San Francisco (UCSF). All in vivo studies were conducted under the authorized protocol number AN174613-03. Mice were maintained in a pathogen free environment and had free access to food and water. For PDX tumor models, the PDX type TM01341, derived from liver metastasis of a male melanoma patient was engrafted on 4- to 6-week-old NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ mice (Stock.no 005557) on the right posterior dorsal flank (n=4/group). For cell line models 2x10^^{6} D04 (n=5/group) and AV5 (n=3/group) cells in 150ul of PBS and 50ul of Matrigel were subcutaneously injected on the right posterior dorsal flank of 4- to 6-week-old homozygous nude Foxn1^{nu}/Foxn1^{nu} mice (Stock.no 007850). All mice were purchased and PDX tissue was engrafted from the vendor Jackson laboratory. Tumor size was measured using a digital caliper and the formula 0.5 x (length x (width^2)) was used to calculate tumor volume. Mice were treated twice a week with 60ug of TRASH targeting ASOs, or 60ug of non-targeting control ASO and 9.6ul of in vivo JetPEI diluted in an overall amount of 200ul 5% glucose. ASO injections were applied subcutaneously in a 2cm distance to the tumor for a total of 7 injections. Mice were weighted twice a week and constantly observed for signs of distress or disorder. Mice were euthanized after three weeks of ASO application or when tumors reached a diameter of >2cm. All experiments were performed in accordance with the UCSF Laboratory Animal Resource Center (LARC) guidelines. After euthanasia parts of tumors and liver tissue were excised and fixed in formalin solution, followed by storing in 70% ethanol and Immunohistochemistry staining. Parts of tumors were stored in RNAlater™ Stabilization Solution (ThermoFisher) and stored at -20°C. TRIzol solution was used to extract RNA from tissue and qPCR was performed to analyze gene expression.

Cell culture

[0163] Human melanoma cell line VMM39 was purchased from American Type Culture Collection (ATCC). Human melanoma cell lines D04, MM415, WM1366, WM3629, WM3211, Sk-Mel-2 and Sk-Mel-28 were a generous gift from Boris Bastian at the University of California, San Francisco. Primary human melanoma cell line Hs852.T was purchased from the Cell Culture Core Facility (CCCF) at the University of California, San Francisco. Primary human melanoma cell line AV5 was obtained from metastasis of a melanoma patient. All experimental protocols were approved by UCSF Human Research Protection Program Institutional Review Board (IRB# 12-0948), all patients signed informed consent,

and methods were carried out in accordance with relevant guidelines and regulations. Resistant cell lines D04RM, MM415RM, Sk-Mel-2RM and WM3629RM were established as previously described.[Sanlorenzo, M. et al., *The lincRNA MIRAT binds to IQGAP1 and modulates the MAPK pathway in NRAS mutant melanoma.* Sci Rep **8**, 10902 (2018).] Primary human melanocytic cell lines (PHM) from infant foreskin of five healthy donors were available in our cell repository and pooled. Melanoma cell lines were maintained in RPMI 1640 media supplemented with 10% (vol/vol) heat inactivated fetal bovine serum. Melanocytes were maintained in M254 medium with HMGS supplements (1x final solution). All cell lines were incubated at 37 °C under 5% CO2.

Viral transduction

[0164] $NRAS^{Q61R}$ cDNA was cloned into the Gateway entry vector pENTR/D-topo. pENTR/D-topo-$NRAS^{Q61R}$ was subjected to site-directed mutagenesis to generate mutants which were then validated by Sanger sequencing. $NRAS^{Q61R}$ cDNA in pENTR was cloned into the Gateway cloning-enabled destination vector gFG12. After lentiviral transduction, cells were grown for 2 weeks followed by cell sorting facilitating GFP intensity on a FACS Aria II cell sorter.

Cell fractionation

[0165] Total nuclear and cytoplasmic extracts were obtained using the SurePrep Nuclear/Cytoplasmic RNA purification kit according to the manufacturer's instructions. Primers are listed in supplementary table 1.

Sanger Sequencing

[0166] RNA from PHME and PHMQ61 was extracted using Purelink RNA extraction kit (ambion) and transcribed into cDNA. Sanger Sequencing was performed using standard protocol by Quintarabio. Primers are listed in supplementary table 1.

Protein extraction and immunoblotting

[0167] Total protein lysates were homogenized in 1x RIPA buffer and Halt protease and phosphatase inhibitor cocktail (1x final concentration) followed by centrifugation at 14,000 RPM/minute at 4°C. Protein concentration was quantified using the Pierce BCA Assay Kit (ThermoFisher Scientific). Linear absorbance was measured using the BioTek SynergyHT plate reader. Total protein in 1× Laemmli buffer with 10% 2- mercaptoethanol was separated

by SDS/PAGE, transferred for 15 h to a PVDF membrane (IPVH00010; Millipore) by electroblotting with 20% (vol/vol) methanol, and blocked for 1 h in in Intercept (TBS) blocking buffer (LICOR). Membranes were incubated overnight at 4 °C with primary antiserum for hnRNPA2/B1 (abcam, cat.no.: ab31645, dilution 1:750) and Beta-Actin (Cell signaling, cat.no.: 8457, dilution 1:2500) following incubation with secondary Goat Anti-Rabbit serum (LI-COR, cat.no.: 925-68071, dilution 1:5000) for 1 h and scanned using the Li-COR Odyssey Imaging system.

RNA extraction and quantitative real-time PCR (qRT-PCR)

[0168] TRIzol, Phenol:chloroform:isoamyl alcohol (125:24:1) or NucleoSpin RNA kit (TaKaRa) was used for extracting Total RNA from cells and tissues according to the manufacturer's instructions. Total RNA was quantified by NanoDrop ND-1000 (Thermo Scientific) or Quibit 4 (Thermo Fisher). 50ng or RNA was reverse transcribed using the cDNA synthesis and gDNA removal QuantiTect Reverse Transcription Kit. Real time PCR was performed using the iTaq Universal SYBR Green Supermix, 10ng (20ng for RIP Assay) of cDNA and on a QuantStudio™ 5 Real-Time PCR System or a 7500 fast real time PCR system. Relative gene expression was calculated using the comparative Ct method, normalized to GAPDH or β-actin. Primer sequences are listed in Supplementary Table 1.

Oligonucleotide transfection

[0169] EsiRNA was generated following standard protocol.[Kittler, R. et al., *Genome-wide resources of endoribonuclease-prepared short interfering RNAs for specific loss-of-function studies*. Nat Methods **4**, 337–344 (2007).] Primer sequences TCACTATAGGGAGAGACACTCAAAGCCTGAGTAACAGA and TCACTATAGGGAGACTGACTGAGATTTTATTGAGCTGTG were used to create TRASH targeting esiRNA. SiRNA was purchased from Dharmacon, using the siDESIGN software. For TRASH targeting siRNA design, the sequence ACAAAGAGAGACAGGAAAUUU was used. For pooled non-targeting control siRNA design, the sequences UGGUUUACAUGUCGACUAA, UGGUUUACAUGUUGUGUGA, UGGUUUACAUGUUUUCUGA and UGGUUUACAUGUUUUCCUA were used.

[0170] ASO GapmeRs were purchased from QIAGEN and designed using the GeneGlobe design and analysis hub. For TRASH targeting ASO design, the sequence GACTGGAGATAATTAA was used for *in vitro* experiments and TGCGCGGCGGAAAGAA for *in vivo*. For hnRNPA2/B1 targeting ASO design, the

sequence GACCGTAGTTAGAGG was used. For non-targeting control ASO design, the QIAGEN standard sequence AACACGTCTATACGC was used.

[0171] EsiRNA, siRNA and ASO GapmeRs were transfected in a final concentration of 50nM unless mentioned otherwise and the transfection reagent Lipofectamine 3000 (2ul/ml) was added according to the manufacturer's instructions.

Expression analysis in TCGA and GTEx

[0172] The analysis of TCGA/GTEx gene expression data was done in R. For TCGA data, the SKCM dataset (n=469) was used. The GDCquery function of the TCGAbiolinks package was run with the following parameters: project = "TCGA-SKCM", data.category = "Transcriptome Profiling", data.type = "Gene Expression Quantification", workflow.type = "HTSeq – FPKM". GDCdownload and GDCprepare then produce a RangedSummarizedExperiment. Expression values are then stored in a data frame and converted to TPM by dividing each FPKM value by the total FPKM of each sample and multiplying by 10^6. To retrieve GTEx data (n=394), "GTEx_Analysis_2017-06-05_v8_RNASeQCv1.1.9_gene_tpm.gct.gz" was downloaded from gtexportal.org/home/datasets. Skin samples within the GTEx dataset were identified by referencing https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-5214/samples/?s_page=59&s_pagesize=500&s_sortby=col_8&s_sortorder=ascending. The raw read counts were converted to TPM values and then transformed to log2 scale. A value of 1 was added to avoid taking log of zero. For both TCGA and GTEx, duplicate genes were removed. If a patient provided multiple specimens, only the first would be used. The ensemble ID for our genes of interest were ENSG00000225792 (TRASH) and ENSG00000122566 (hnRNP2/B1). Cor.test was applied to find the correlation between each gene and TRASH, and the same for hnRNPA2/B1. Spearman's correlation coefficient (ρ) was used to measure rank correlation. 2000 random genes were sampled from both datasets. The correlation of TRASH and hnRNPA2/B1 was ranked against 200 random gene correlations with TRASH and hnRNPA2/B1 each for 10 iterations.

Cell viability assay

[0173] Dependent on cell doubling time, 0.7-2 x $10^{\wedge 3}$ cells were seeded in 96 well plates. 1 day after seeding cells were incubated in media with oligonucleotide concentration and/or MEKi and transfection reagent. 3 (synergy experiments) or 5 (solely ASO) days after transfection Total luminescence was measured on the SynergyHT plate reader (BioTek) using

Gen5 software. Cell viability decrease always is shown in relation to cell viability of cells incubated with non-targeting control ASOs.

Caspase Glo 3/7 assay

[0174] Dependent on cell doubling time, 2-3 x 10^3 cells were seeded in 96 well plates. 1 day after seeding cells were incubated in media with 50nM oligonucleotide concentration and transfection reagent. 1 day after transfection Total luminescence was measured on the SynergyHT plate reader (BioTek) using Gen5 software. Experiments were performed in quadruplicates.

RNA-Binding Protein Immunoprecipitation

[0175] The Magna RIP™ Kit (Millipore) was used following standard protocol. 10ug of Antibody for Rabbit IgG (Millipore, Cat.no.: PP64B) and hnRNPA2/B1 (Proteintech, Cat.no.: 14813-1-AP) was used to load magnetic beads. RNA precipitate was subjected to qRT–qPCR analysis.

Colony formation Assay

[0176] Dependent on cell doubling time, 1-2 x 10^3 cells were seeded in 6 well plates. 1 day after seeding cells were incubated in media with 50nM oligonucleotide concentration and transfection reagent. 6 days after transfection, cells were washed with PBS, fixed with 10% neutral buffered formalin, and stained with 0.1% crystal violet solution. Colonies were defined as cell conglomerates with >50 cells. Digital Images of plates were evaluated by two independent reviewers for colony counts. The final counts were calculated as the average count of both reviewers for all triplicates.

Statistics and reproducibility

[0177] Error bars in all the plots indicate mean ± S.D. P-value < 0.05 was considered statistically significant. ***p-value < 0.001, **p-value < 0.01, *p-value <0.05 by one tailed Student's t-test. All experiments were performed at least three times, unless otherwise indicated. Statistics was calculated with Microsoft Excel Version 2107.

RNA sequencing

[0178] Total RNA was isolated using the RNeasy mini Kit (QIAGEN) following the manufacturer's protocol. Quality check for extracted RNA was done using 2100 Bioanalyzer (Agilent Technologies, USA) or Tapestation System (Agilent Technologies, USA). All

samples had a RIN score >8. cDNA sequencing libraries were prepared using the Illumina TruSeq Total RNA Sample kit. For samples used for identification of MAPK-responsive lncRNAs, paired-end, 101-bp sequencing was performed by Centrillion Genomic Services (Centrillion Biosciences, USA) on an Illumina HiSeq 2000. For DE gene analysis of ASO-transfected D04 samples, paired-end, 2x150-bp sequencing was performed by Genewiz (USA) on a Illumina HiSeq.

[0179] Sequence reads were aligned to the human genome (hg19) using TopHat (Version 2.0.11).

Analysis of TRASHi induced DE gene expression

[0180] Differential expression (DE) analysis was done using DESeq2. Differentially expressed genes were defined by more than 1.5-fold changes (log_2 >0.58 or <-0.58) in expression with FDR<0.05. GO term analysis was done using DAVID Functional Annotation Clustering analysis.

Target	Experiment	Forward	Reverse
NRAS	Sanger Sequencing	CGCACTGACAATCCAGCTAA	TCGCCTGTCCTCATGTATTG
TRASH	Subcellular enrichment	TCACAACACACTCAAAGCCTG	ACCCAACTGCACTCCAAATG
TRASH 1	knockdown evaluation, splicing efficiency, RIP	TCACAACACACTCAAAGCCTG	ACCCAACTGCACTCCAAATG
TRASH 2	splicing efficiency	TAGCAGCAAAGACAAGCGGT	TTAGCTGCGCAAACTCTGGT
TRASH 3	splicing efficiency	CATCATGACAGTGAGCTTTAGGT	TTCCCCCTCTCTTCTTTTCCAG
TRASH 4	splicing efficiency	CATCGGCGTTTAAGGCAGC	CGCTACGGTGACGATTCTGG
hnRNPA2/B1	knockdown evaluation	ATGGGAGAGTAGTTGAGCCAAA	TCAGTATCTTCTTTAATTCCGCC

Supplementary Table 1. List of all primers and the according experiments that they were used for

EXAMPLE 2

[0181] We mapped and compared the phospho-catalytic profile of kinases of D04, MM415 and D04RM cells that were incubated with TRASH targeting ASOs (SEQ ID NO:15), ASOs targeting the oncogenic lncRNA Malat1 and non-targeting control ASOs. Therefore, we used the high-throughput system HTKAM to measure the enzymatic activity of kinases using biological peptide targets as phospho-sensors to reveal kinase dependencies in cell lines.

[0182] The results show significantly decreased activity levels of the kinases CDK1, LYN, YES1, CHEK1, PKA, PKCa, PIM1 and the kinases of the Akt-family. These kinases fulfill an anti-apoptotic function in cells. The observed effect is specific to TRASH-inhibition and not a general effect that is seen upon ASO targeting of lncRNAs, as no such kinase activity shifts could be measured upon Malat1 inhibition.

EXAMPLE 3

[0183] ASO targeting BX470102.3 (SEQ ID NO: 13) leads to significant cell viability decrease in melanoma (D04, MM415, WM1366, VMM39, Sk-Mel-2, Hs852.T, Hs940.T, WM3629, AV5, AV4, Sk-Mel-28, WM3211, A375, MM485, WM3060, Sk-Mel-5), trametinib resistant melanoma (D04RM, MM415RM, Sk-Mel-2-RM, WM3629RM), Glioblastoma (U138-MG, T98G, A-172, U87-MG), Neuroblastoma (Sk-N-AS), multiple myeloma (H929), lung cancer (H82, SW1271, H1299, H2228) colon carcinoma (SW480, HCT116) and osteosarcoma (U2OS) cell lines.

[0184] ASO targeting BX470102.3 (SEQ ID NO: 14) leads to significant cell viability decrease in melanoma (D04, MM415, WM1366, VMM39, Sk-Mel-2, Hs852.T, WM3629, AV5, Sk-Mel-28, WM3211, MM485, WM3060, Sk-Mel-5), trametinib resistant melanoma (D04RM, MM415RM, Sk-Mel-2-RM, WM3629RM), Glioblastoma (U138-MG, T98G, A-172, U87-MG), Neuroblastoma (Sk-N-AS), multiple myeloma (H929, L363), lung cancer (H82, SW1271, H1299) colon carcinoma (SW480, HCT116) and osteosarcoma (U2OS) cell lines.

[0185] siRNA targeting BX470102.3 (SEQ ID NO: 23) leads to significant cell viability decrease in melanoma (D04, AV5, Sk-Mel-28) cell lines.

[0186] ASO targeting AC004540.4 (TRASH) (SEQ ID NO: 15) leads to significant cell viability decrease in melanoma (Hs940.T, AV4, WM3060, Sk-Mel-5, MaMel30), Glioblastoma (U138-MG, T98G, A-172, U87-MG), Neuroblastoma (Sk-N-AS), multiple myeloma (H929), lung cancer (H82, SW1271, H1299, H2228) colon carcinoma (SW480, HCT116, LS174) and osteosarcoma (U2OS) cell lines.

[0187] siRNA targeting AC004540.4 (SEQ ID NO: 25) leads to significant cell viability decrease in the melanoma AV5 cell line.

[0188] ASO targeting RP11-7011.3 (SEQ ID NO: 17) leads to significant cell viability decrease in melanoma (D04, MM415, WM1366, VMM39, Sk-Mel-2, Hs852.T, WM3629, AV5, AV4, AV1, Sk-Mel-28, WM3211, WM3060, Sk-Mel-5, MaMel30), trametinib resistant melanoma (D04RM, MM415RM, Sk-Mel-2-RM, WM3629RM), Glioblastoma (U138-MG, T98G, A-172, U87-MG), Neuroblastoma (Sk-N-AS), multiple myeloma (H929, L363, XG-1), lung cancer (H82, SW1271, H2228) colon carcinoma (SW480, HCT116) and osteosarcoma (U2OS) cell lines.

[0189] ASO targeting RP11-7011.3 (SEQ ID NO: 18) leads to significant cell viability decrease in melanoma (D04, MM415, WM1366, VMM39, Sk-Mel-2, Hs852.T, WM3629, Sk-Mel-28, WM3211, MM485, WM3060, Sk-Mel-5), trametinib resistant melanoma (D04RM, MM415RM, Sk-Mel-2-RM, WM3629RM), Glioblastoma (U138-MG, T98G, A-172, U87-MG), Neuroblastoma (Sk-N-AS), multiple myeloma (H929, L363), lung cancer (H1299, SW1271) colon carcinoma (SW480, HCT116) and osteosarcoma (U2OS) cell lines.

[0190] siRNA targeting RP11-7011.3 (SEQ ID NO: 27) leads to significant cell viability decrease in melanoma (D04, AV5, Sk-Mel-28) cell lines.

[0191] siRNA targeting RN7SL1 (Pooled SEQ ID NOs: 29,31,33,35) leads to significant cell viability decrease in melanoma (D04, AV5, Sk-Mel-28) cell lines.

[0192] ASO targeting ARF-AS1 (SEQ ID NO: 19) leads to significant cell viability decrease in melanoma (D04, MM415, Sk-Mel-2, Sk-Mel-28, MaMel30) and Neuroblastoma (Sk-N-AS) cell lines.

[0193] ASO targeting ARF-AS1 (SEQ ID NO: 20) leads to significant cell viability decrease in melanoma (D04, MM415, Sk-Mel-2, Sk-Mel-28) and Neuroblastoma (Sk-N-AS) cell lines.

[0194] siRNA targeting ARF-AS1 (SEQ ID NO: 37) leads to significant cell viability decrease in the melanoma cell line D04.

[0195] ASO targeting AL157871.4 (SEQ ID NO: 21) leads to significant cell viability decrease in melanoma (D04, MM415, Sk-Mel-2, Sk-Mel-28) and Neuroblastoma (Sk-N-AS) cell lines.

[0196] ASO targeting AL157871.4 (SEQ ID NO: 22) leads to significant cell viability decrease in melanoma (D04, MM415, Sk-Mel-2, Sk-Mel-28, MaMel30) and neuroblastoma (Sk-N-AS) cell lines.

[0197] siRNA targeting AL157871.4 (SEQ ID NO: 39) leads to significant cell viability decrease in the D04 melanoma cell line.

EXAMPLE 4

In vitro results of additional TRASH-targeting oligonucleotides:

Cell viability

[0198] In vitro treatment with TRASH targeting ASO (SEQ ID NO: 15) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the hepatocellular carcinoma cell line HepG2 and the sarcoma cell line SK-LMS-1. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0199] In vitro treatment with TRASH targeting ASO (SEQ ID NO: 41) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell lines D04, MM415, WM1366, VMM39, Sk-Mel-2, Hs852.T, WM3629, AV5, Sk-Mel-28, WM3211, in the hepatocellular carcinoma cell line HepG2 and the sarcoma cell line SK-LMS-1. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0200] In vitro treatment with TRASH targeting ASO (SEQ ID NO: 16) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell lines D04, MM415, WM1366, VMM39, Sk-Mel-2, Hs852.T, WM3629, AV5, Sk-Mel-28 and WM3211, in the hepatocellular carcinoma cell line HepG2 and the sarcoma cell line SK-LMS-1. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0201] In vitro treatment with TRASH targeting siRNA (SEQ ID NO: 42) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell lines D04, MM415, and Sk-Mel-2. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0202] In vitro treatment with TRASH targeting siRNA (SEQ ID NO: 43) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell lines D04, Sk-Mel-2 and WM3629. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0203] In vitro treatment with TRASH targeting siRNA (SEQ ID NO: 44) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell lines D04, Sk-Mel-2, MM415 and WM3629. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0204] In vitro treatment with TRASH targeting siRNA (SEQ ID NO:45) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell lines D04 and MM415. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0205] In vitro treatment with TRASH targeting siRNA (SEQ ID NO:46) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell lines D04 and MM415. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0206] In vitro treatment with TRASH targeting ASO (SEQ ID NO:47) and additional Cholesterol modification, with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell lines D04, MM415 in the hepatocellular carcinoma cell line HepG2 and the sarcoma cell line SK-LMS-1. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0207] In vitro treatment with hnRNPA2/B1 targeting ASO (SEQ ID NO: 48) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell line D04. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

[0208] In vitro treatment with SNX10 targeting ASO (SEQ ID NO: 49) with a final concentration of 50nM in media and an incubation time for 120hrs lead to significant cell viability decrease in the melanoma cell line D04. Cell viability was compared to treatment with non-targeting control ASO-treatment. Lipofectamine3000 concentration was 2ul/ml.

Intravenous in vivo treatment

[0209] In 4- to 6-week-old NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice, D04 cells in 150µl of PBS and 50µl of Matrigel were subcutaneously injected on the right and left posterior dorsal flank of 4- to 6-week-old homozygous nude Foxn1nu/Foxn1nu mice (Stock.no 007850). Mice were obtained from JAX®. Tumor size was measured using a digital caliper and the formula 0.5 x (length x (width^2)) was used to calculate tumor volume. Mice were treated twice a week with 700µg of (SEQ ID NO: 16) or non-targeting control-ASO. No

transfection reagent was co-applied. ASO injections were applied intravenously as tail vein injections. Mice were weighted twice a week and observed for signs of distress or disorder. Mice in the TRASH-ASO treatment group showed significantly reduced tumor growth, when compared to mice in the group that received non-targeting control ASOs.

Intratumoral in vivo treatment

[0210] In 4- to 6-week-old NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice D04, cells in 150µl of PBS and 50µl of Matrigel were subcutaneously injected on the right posterior dorsal flank of 4- to 6-week-old homozygous nude Foxn1nu/Foxn1nu mice (Stock.no 007850). Mice were obtained from JAX®. Tumor size was measured using a digital caliper and the formula 0.5 x (length x (width^2)) was used to calculate tumor volume. Mice were treated twice a week with 400µg of (SEQ ID NO: 16) or non-targeting control-ASO. No transfection reagent was co-applied. ASO injections were applied into the tumor mass. Mice were weighted twice a week and observed for signs of distress or disorder. Mice in the TRASH-ASO treatment group showed significantly reduced tumor growth, when compared to mice in the group that received non-targeting control ASOs.

RNAscope

[0211] Representative images of DAPI-, hnRNPA2/B1-, and AC004540.4 (TRASH)-derived fluorescence in untreated D04 melanoma cells show that AC004540.4 (TRASH) transcripts and hnRNPA2/B1 protein are enriched in the nucleus of melanoma cells. (Figure 5a)

flow cytometry apoptosis

[0212] To confirm activation of apoptosis and cell death in response to TRASH-ASO treatment (SEQ ID NO: 15) D04 cells were either treated with control-ASO or TRASH-ASO (50nM) for 24h. The cells were stained with Alexa 488 Annexin V and propidium iodide (PI) (Invitrogen™ Dead Cell Apoptosis Kits with Annexin V for Flow Cytometry Catalog number: V13241). Increased fractions of apoptotic and dead cells in the overall cell population, were seen followed by TRASH-ASO treatment, when compared to Control-ASO treatment. (Figure 5e)

MEK-inhibitor-induced upregulation

[0213] Relative fold enrichment analysis using RT-qPCR shows that the MEKi trametinib caused dose dependent AC004540.4 (TRASH)-upregulation. D04 cells responded with 3.2-fold upregulation to 20nM MEKi treatment and 5.4-fold enrichment to 40nM MEKi treatment. MM415 cells are less vulnerable to MEKi treatment and reacted with 0.31-fold increase (20nM), respectively 0.36-fold increase of AC004540.4 (TRASH)-expression. Cells were either treated with trametinib (MEKi) or DMSO (control). Treatment period was 72 hours. CT-values were normalized to GAPDH, error bars represent standard deviation. All experiments were performed in triplicates (n=3/group). (Figure 5b)

[0214] AC004540.4 (TRASH)-ASO treatment has a global effect on gene expression and regulates the MAPK and PI3K-AKT signaling cascade

[0215] To examine the biomolecular changes upon TRASH-inhibition in melanoma, D04 cells were treated with TRASH-ASOs (SEQ ID NO:15) and Control-ASOs and RNA was extracted and used for RNA-Seq. Differential expression (DE) analysis showed that TRASH-ASOs had a global effect on gene expression. We found that 574 genes were down-regulated, and 493 genes were up-regulated, when compared to Control-ASO treatment (Cut off was >1.5-fold change and FDR <0.05, Table 1). GO term analysis revealed that the top enriched GO term clusters associated with the down-regulated genes were related to "ECM-receptor interaction" and "PI3K-AKT signaling pathway", while the top enriched GO term clusters associated with the up-regulated genes included the terms "protein tyrosine kinase activity" (GO: 0004713) and "Ras guanyl-nucleotide exchange factor activity" (GO0005088) (Table 2). These GO terms consisted of genes encoding growth factors, tyrosine kinases, G protein coupled receptor subunits, and collagen subunits. Scatter plot diagram showing differential gene expression after TRASH-ASO treatment compared to Control-ASO treatment. (cut-off for significance was adjusted p-value < 0.05). Data was obtained from RNA-Seq of D04 melanoma cells, treatment period was three days. (Figure 5c)

[0216] These findings suggest that TRASH governs melanoma cell survival and inhibits apoptosis to a stronger extent than its protein binding partner hnRNPA2/B1 and that TRASH may execute its anti-apoptotic functions as a regulator of the MAPK and PI3K-AKT signaling cascade.

Kinase activity profiling reveals unique anti-apoptotic features of AC004540.4 (TRASH)-expression

[0217] Kinases cover a wide range of apoptosis regulating functions in cancer. Given the findings that TRASH-ASO treatment (SEQ ID NO:15) strongly affects the transcriptional regulation of genes that are related to kinase signaling pathways, we aimed to perform functional profiling of kinase activity shifts triggered by TRASH-inhibition. To do so, we used a kinase activity screening platform39 (named High Throughput Kinase Activity Mapping – HT-KAM) that enables the simultaneous identification of kinase enzymes functional state in cancer cells across a broad range of kinase families (see Methods for details). We generated protein extracts of two versions of the D04 (D04 – treatment naïve; D04RM – trametinib resistant) and the MM415 melanoma cell-lines, treated with Control-ASOs or TRASH-ASOs. We tested these cell extracts on HT-KAM and performed unsupervised hierarchical clustering of peptide-associated phosphorylation profiles (Fig. 6a) and of kinase activity signatures (Fig 6b). The changes in kinases' activity upon TRASH-ASO treatment indicate conserved responses across cell-lines, whether kinases are up-regulated or down-regulated (respectively in yellow or blue in Fig. 6b).

[0218] Due to the effects of TRASH-ASO treatment on cell viability and apoptosis induction, we focused on kinases with anti-apoptotic functions. We found that the pro-survival/proto-oncogenic kinases AKT1, CDK1, LYN, YES1, CHEK1, PKCA, STK11, PKCa and PIM1 were significantly less active upon TRASH-inhibition (Fig. 6c left panel). These kinases have been reported to regulate the state of caspases and pro-survival pathways including the RAF-MAPK and PI3K-AKT axes.40–47

[0219] To further test if these observations are TRASH-ASO treatment specific, we generated MALAT1-ASO treated extracts from the same cell-line models. MALAT1 is a known oncogenic lncRNA in various types of cancer, including melanoma.48,49 MALAT1-ASO treatment reduced cell-growth but displayed a significantly reduced effect on apoptosis induction in comparison to TRASH-inhibition ($p=0.002$ for 1.6-fold versus 3.0-fold Caspase-3 & -7 activity increase respectively in Fig. 6d and Fig. 3d). Using the HT-KAM platform, we found that the activity of the kinases associated with cell-survival were not down-regulated in MALAT1-ASO treated cells (Fig. 6c right panel), but significantly and specifically down-regulated upon TRASH-ASO treatment (Fig. 6c, $p < 0.00007$; Fig. 6e, kinase signatures of TRASH-, versus MALAT1-ASO treatment). In summary, our data indicate that TRASH-ASO treatment specifically down-regulates the activity of anti-apoptotic kinases and pro-survival signaling pathways in melanoma cells, supporting the potential therapeutic relevance of TRASH-ASO treatment (Fig. 6f).

[0220] In comparison to MEKi-treatment, repetitive TRASH-ASO treatment does not lead to early drug-resistance in melanoma

[0221] Rescuing cells that survived initial TRASH-ASO (SEQ ID NO:15) and MEKi (trametinib) treatment and providing the rescued cells with a phase of regrowth in drug free media, was followed by repetition of the preceding drug treatment. D04 cells responded with increased vulnerability to 50nM TRASH-ASO treatment, implying that no drug resistance could be measured. On the other hand, D04 cells that underwent MEKi treatment with 15nM or 20nM final concentration responded with significantly less cell-growth inhibition to further MEKi, implying that these cells developed resistance mechanisms that decreased vulnerability to MEKi. Incubation time was 120hrs, n=3. (Fig. 5d).

TABLE 1:
List of genes that are down-regulated upon TRASH-ASO treatment.

ID	Gene.name	log2FoldChange	pvalue	padj
ENSG00000137491	SLCO2B1	-2.59274	1.43E-28	1.13E-25
ENSG00000071909	MYO3B	-1.95637	8.37E-05	0.001189679
ENSG00000100154	TTC28	-1.81477	1.22E-09	5.86E-08
ENSG00000214456	PLIN5	-1.69846	0.002436	0.019731641
ENSG00000196119	OR8A1	-1.673	0.002536	0.020342008
ENSG00000239268	AC092691.1	-1.64048	0.000531	0.005683777
ENSG00000204334	ERICH2	-1.6371	0.002101	0.017570757
ENSG00000196376	SLC35F1	-1.61143	8.27E-23	3.20E-20
ENSG00000184856	LINC00308	-1.6094	1.74E-11	1.29E-09
ENSG00000182463	TSHZ2	-1.59808	3.14E-18	6.26E-16
ENSG00000148935	GAS2	-1.59095	0.000169	0.002142374
ENSG00000130600	H19	-1.56999	2.21E-32	3.22E-29
ENSG00000237515	SHISA9	-1.56986	4.34E-10	2.34E-08
ENSG00000106278	PTPRZ1	-1.56748	1.63E-24	8.61E-22
ENSG00000204252	HLA-DOA	-1.56661	4.42E-09	1.84E-07
ENSG00000114757	PEX5L	-1.51992	4.95E-39	1.34E-35
ENSG00000261115	TMEM178B	-1.51369	1.78E-33	2.82E-30
ENSG00000174469	CNTNAP2	-1.50992	0.004949	0.033901177
ENSG00000165495	PKNOX2	-1.50567	2.74E-09	1.20E-07
ENSG00000188859	FAM78B	-1.49819	5.53E-25	3.00E-22
ENSG00000155974	GRIP1	-1.48432	1.76E-15	2.37E-13
ENSG00000164106	SCRG1	-1.47714	1.15E-11	8.97E-10
ENSG00000125780	TGM3	-1.46318	3.43E-05	0.000555836
ENSG00000163273	NPPC	-1.46133	0.000468	0.005136146
ENSG00000176533	GNG7	-1.459	4.36E-06	9.27E-05
ENSG00000256232	LINC02387	-1.45291	1.83E-06	4.34E-05
ENSG00000167617	CDC42EP5	-1.42861	1.02E-05	0.000192688
ENSG00000144668	ITGA9	-1.41719	1.52E-13	1.58E-11
ENSG00000127954	STEAP4	-1.40458	3.03E-19	6.84E-17
ENSG00000198774	RASSF9	-1.40194	6.09E-12	4.93E-10
ENSG00000065717	TLE2	-1.38255	0.000253	0.003053978
ENSG00000266296	ARIH2P1	-1.37762	0.000204	0.002530044
ENSG00000185924	RTN4RL1	-1.34556	1.48E-06	3.62E-05
ENSG00000036565	SLC18A1	-1.33718	9.01E-15	1.08E-12
ENSG00000257252	AC124947.1	-1.33042	8.84E-05	0.001242963
ENSG00000223802	CERS1	-1.32574	0.000347	0.003990157
ENSG00000225649	AC064875.1	-1.32525	1.45E-21	4.83E-19
ENSG00000213606	AKR1B10P1	-1.31707	4.40E-07	1.20E-05
ENSG00000223764	AL645608.1	-1.30979	3.43E-09	1.47E-07
ENSG00000255864	NA	-1.30375	0.003279	0.024952707
ENSG00000231683	AL033397.1	-1.28997	0.000774	0.007770437
ENSG00000170153	RNF150	-1.28344	2.68E-20	7.47E-18
ENSG00000249226	SUCLG2P4	-1.27377	0.00607	0.040019666
ENSG00000171408	PDE7B	-1.27139	7.37E-17	1.20E-14
ENSG00000145824	CXCL14	-1.26291	3.93E-29	3.92E-26
ENSG00000113361	CDH6	-1.25809	1.37E-11	1.05E-09
ENSG00000116117	PARD3B	-1.25733	1.75E-13	1.80E-11
ENSG00000091129	NRCAM	-1.25597	1.81E-15	2.40E-13
ENSG00000179772	FOXS1	-1.24693	0.00582	0.038679779
ENSG00000228651	AC074327.1	-1.24201	1.02E-08	3.88E-07
ENSG00000278616	BEND3P3	-1.24019	8.12E-05	0.0011626

ENSG00000135925	WNT10A	-1.23715	3.27E-06	7.21E-05
ENSG00000260412	AL353746.1	-1.23235	0.00023	0.002819982
ENSG00000151322	NPAS3	-1.22502	3.53E-05	0.000569027
ENSG00000271216	LINC01050	-1.2229	2.55E-05	0.000428671
ENSG00000171864	PRND	-1.21506	0.007983	0.049623263
ENSG00000148848	ADAM12	-1.21482	9.19E-12	7.20E-10
ENSG00000108846	ABCC3	-1.2128	6.79E-29	6.13E-26
ENSG00000102996	MMP15	-1.21185	6.70E-31	7.47E-28
ENSG00000183580	FBXL7	-1.20853	2.65E-08	9.35E-07
ENSG00000134533	RERG	-1.2041	1.50E-23	6.32E-21
ENSG00000205517	RGL3	-1.20067	2.04E-12	1.81E-10
ENSG00000250995	AL391280.1	-1.1929	0.000353	0.004051833
ENSG00000237653	AC026320.2	-1.19234	0.000114	0.001537941
ENSG00000196776	CD47	-1.18982	1.72E-36	3.62E-33
ENSG00000280355	AL132656.4	-1.17588	0.004722	0.032715724
ENSG00000115596	WNT6	-1.17314	2.25E-09	1.00E-07
ENSG00000170915	PAQR8	-1.16477	8.70E-15	1.05E-12
ENSG00000111319	SCNN1A	-1.16331	0.00189	0.016111329
ENSG00000187955	COL14A1	-1.16216	7.59E-06	0.000149681
ENSG00000184371	CSF1	-1.15814	7.16E-17	1.18E-14
ENSG00000151632	AKR1C2	-1.15749	1.22E-19	3.00E-17
ENSG00000100239	PPP6R2	-1.15491	3.58E-36	6.79E-33
ENSG00000183682	BMP8A	-1.1354	0.000608	0.006341081
ENSG00000171873	ADRA1D	-1.12926	0.003176	0.024333664
ENSG00000181444	ZNF467	-1.12657	2.70E-06	6.09E-05
ENSG00000171557	FGG	-1.12275	2.40E-19	5.55E-17
ENSG00000134532	SOX5	-1.11563	3.73E-17	6.37E-15
ENSG00000080573	COL5A3	-1.10808	2.39E-06	5.50E-05
ENSG00000135324	MRAP2	-1.10629	0.004617	0.032122369
ENSG00000089356	FXYD3	-1.10201	1.95E-09	8.79E-08
ENSG00000105967	TFEC	-1.09855	0.003289	0.024994517
ENSG00000272502	AC104958.2	-1.0985	0.000511	0.005513125
ENSG00000248587	GDNF-AS1	-1.09821	0.001376	0.012487738
ENSG00000242808	SOX2-OT	-1.09805	0.000645	0.006643746
ENSG00000196735	HLA-DQA1	-1.09803	2.65E-15	3.44E-13
ENSG00000102313	ITIH6	-1.09802	0.000829	0.008250813
ENSG00000135414	GDF11	-1.09604	3.47E-31	4.11E-28
ENSG00000241168	AC128685.1	-1.09378	0.000867	0.008549537
ENSG00000144481	TRPM8	-1.09349	1.15E-12	1.07E-10
ENSG00000230490	AL139383.1	-1.08952	9.04E-07	2.29E-05
ENSG00000204248	COL11A2	-1.08848	3.01E-08	1.04E-06
ENSG00000149564	ESAM	-1.086	0.007588	0.047658018
ENSG00000174482	LINGO2	-1.08599	2.02E-06	4.72E-05
ENSG00000227471	AKR1B15	-1.08295	2.52E-08	8.96E-07
ENSG00000182050	MGAT4C	-1.08073	7.29E-07	1.89E-05
ENSG00000244694	PTCHD4	-1.08063	3.97E-15	5.09E-13
ENSG00000204655	MOG	-1.07526	0.006692	0.043174454
ENSG00000185305	ARL15	-1.07422	3.73E-12	3.21E-10
ENSG00000154162	CDH12	-1.07121	3.99E-11	2.73E-09
ENSG00000169760	NLGN1	-1.06965	8.42E-17	1.35E-14
ENSG00000021826	CPS1	-1.06652	3.24E-14	3.59E-12
ENSG00000163638	ADAMTS9	-1.06624	4.38E-13	4.32E-11
ENSG00000116981	NT5C1A	-1.06503	0.002495	0.020099296
ENSG00000259803	SLC22A31	-1.06459	1.70E-05	0.000300298

ENSG00000283563	AC098650.1	-1.06287	0.00517	0.035042492
ENSG00000078018	MAP2	-1.06068	1.25E-23	5.64E-21
ENSG00000177570	SAMD12	-1.06062	9.04E-13	8.53E-11
ENSG00000273259	AL049839.2	-1.05974	0.000106	0.001449506
ENSG00000091972	CD200	-1.05153	6.96E-10	3.58E-08
ENSG00000165125	TRPV6	-1.04961	3.25E-08	1.11E-06
ENSG00000234352	AC009264.1	-1.04818	0.002107	0.017617548
ENSG00000138639	ARHGAP24	-1.04723	4.26E-07	1.17E-05
ENSG00000184005	ST6GALNAC3	-1.04577	1.43E-07	4.27E-06
ENSG00000178662	CSRNP3	-1.04503	0.002115	0.017670936
ENSG00000204262	COL5A2	-1.04378	5.42E-23	2.14E-20
ENSG00000104321	TRPA1	-1.04327	8.15E-08	2.59E-06
ENSG00000197892	KIF13B	-1.0421	7.75E-28	5.65E-25
ENSG00000060718	COL11A1	-1.04016	4.17E-18	8.06E-16
ENSG00000117266	CDK18	-1.03668	2.99E-08	1.04E-06
ENSG00000171227	TMEM37	-1.03519	0.002153	0.017917961
ENSG00000185532	PRKG1	-1.03073	5.33E-07	1.42E-05
ENSG00000166292	TMEM100	-1.02975	9.09E-16	1.29E-13
ENSG00000144278	GALNT13	-1.02882	9.06E-05	0.001268043
ENSG00000183625	CCR3	-1.0285	3.11E-05	0.000513654
ENSG00000176463	SLCO3A1	-1.028	2.66E-22	9.71E-20
ENSG00000153902	LGI4	-1.02296	0.003048	0.023644413
ENSG00000170961	HAS2	-1.02244	3.58E-05	0.000575118
ENSG00000154274	C4orf19	-1.02075	7.25E-05	0.001055186
ENSG00000113721	PDGFRB	-1.01777	1.18E-17	2.17E-15
ENSG00000160145	KALRN	-1.01664	9.58E-21	2.88E-18
ENSG00000100346	CACNA1I	-1.01424	2.54E-07	7.24E-06
ENSG00000169744	LDB2	-1.0138	1.26E-09	6.05E-08
ENSG00000152926	ZNF117	-1.01041	0.000144	0.001878874
ENSG00000106605	BLVRA	-1.00941	6.42E-16	9.22E-14
ENSG00000156298	TSPAN7	-1.00771	0.007757	0.048526251
ENSG00000243679	AC018638.5	-1.0053	0.002234	0.018453963
ENSG00000177301	KCNA2	-1.0031	0.00042	0.004662913
ENSG00000250451	HOXC-AS1	-1.0019	0.002393	0.019457151
ENSG00000150760	DOCK1	-1.00182	4.14E-29	3.92E-26
ENSG00000155966	AFF2	-1.00125	1.36E-07	4.10E-06
ENSG00000186480	INSIG1	-1.00074	1.16E-28	9.56E-26
ENSG00000162512	SDC3	-0.99828	1.97E-15	2.59E-13
ENSG00000118322	ATP10B	-0.99655	1.22E-14	1.42E-12
ENSG00000235823	OLMALINC	-0.9945	7.35E-05	0.001067279
ENSG00000231389	HLA-DPA1	-0.98561	2.71E-28	2.05E-25
ENSG00000145362	ANK2	-0.98437	7.08E-18	1.33E-15
ENSG00000215283	HMGB3P24	-0.98329	6.97E-10	3.58E-08
ENSG00000172572	PDE3A	-0.98307	1.81E-08	6.57E-07
ENSG00000065413	ANKRD44	-0.98287	1.12E-07	3.46E-06
ENSG00000164330	EBF1	-0.98179	5.87E-13	5.68E-11
ENSG00000281881	NA	-0.98108	4.98E-06	0.000104434
ENSG00000171502	COL24A1	-0.9807	3.57E-07	9.96E-06
ENSG00000158887	MPZ	-0.97782	5.50E-27	3.47E-24
ENSG00000163618	CADPS	-0.97747	4.21E-23	1.70E-20
ENSG00000099194	SCD	-0.97709	6.58E-22	2.23E-19
ENSG00000171564	FGB	-0.96588	2.94E-07	8.28E-06
ENSG00000084636	COL16A1	-0.96522	1.55E-15	2.10E-13
ENSG00000125931	CITED1	-0.96518	6.91E-14	7.49E-12

ENSG00000114948	ADAM23	-0.95958	7.72E-20	1.98E-17
ENSG00000141744	PNMT	-0.95608	0.000158	0.002025149
ENSG00000163513	TGFBR2	-0.95567	1.12E-26	6.83E-24
ENSG00000260001	TGFBR3L	-0.95414	0.005412	0.036390616
ENSG00000064999	ANKS1A	-0.95115	5.95E-17	9.99E-15
ENSG00000179532	DNHD1	-0.94858	9.37E-10	4.67E-08
ENSG00000196136	SERPINA3	-0.94492	3.01E-12	2.63E-10
ENSG00000232774	AL355916.1	-0.94469	1.02E-20	2.97E-18
ENSG00000146250	PRSS35	-0.94323	0.000325	0.003781602
ENSG00000164125	FAM198B	-0.94321	1.83E-27	1.25E-24
ENSG00000271270	TMCC1-AS1	-0.94256	4.67E-08	1.56E-06
ENSG00000185565	LSAMP	-0.94199	5.67E-16	8.27E-14
ENSG00000253910	PCDHGB2	-0.9415	0.002425	0.019662527
ENSG00000198597	ZNF536	-0.94019	2.25E-13	2.28E-11
ENSG00000133519	ZDHHC8P1	-0.93699	0.000701	0.007117719
ENSG00000121068	TBX2	-0.93622	6.01E-21	1.87E-18
ENSG00000169418	NPR1	-0.93597	3.54E-05	0.000570212
ENSG00000158270	COLEC12	-0.93578	1.45E-05	0.00026297
ENSG00000105894	PTN	-0.93499	9.15E-08	2.87E-06
ENSG00000129009	ISLR	-0.93395	2.90E-09	1.26E-07
ENSG00000281490	CICP14	-0.93377	6.20E-07	1.63E-05
ENSG00000279400	AC008957.3	-0.9335	0.000426	0.004719696
ENSG00000261468	AC096921.2	-0.93054	0.004858	0.03340762
ENSG00000105767	CADM4	-0.92958	7.92E-29	6.83E-26
ENSG00000262454	MIR193BHG	-0.92877	0.00227	0.018659523
ENSG00000267280	TBX2-AS1	-0.92858	1.56E-11	1.18E-09
ENSG00000116132	PRRX1	-0.92821	6.17E-09	2.48E-07
ENSG00000198074	AKR1B10	-0.92451	4.99E-22	1.75E-19
ENSG00000137727	ARHGAP20	-0.92281	8.02E-05	0.00115
ENSG00000149403	GRIK4	-0.92124	0.000655	0.006724913
ENSG00000164418	GRIK2	-0.91732	1.45E-11	1.10E-09
ENSG00000082196	C1QTNF3	-0.91728	4.74E-06	0.000100304
ENSG00000169432	SCN9A	-0.91655	4.60E-15	5.78E-13
ENSG00000134108	ARL8B	-0.912	4.69E-22	1.68E-19
ENSG00000125848	FLRT3	-0.91188	1.48E-22	5.60E-20
ENSG00000250658	AC097652.1	-0.90896	0.006612	0.042817232
ENSG00000137285	TUBB2B	-0.90539	2.15E-10	1.26E-08
ENSG00000163554	SPTA1	-0.90282	1.61E-06	3.87E-05
ENSG00000156475	PPP2R2B	-0.90029	1.02E-09	5.00E-08
ENSG00000178860	MSC	-0.89782	3.04E-24	1.44E-21
ENSG00000105556	MIER2	-0.89672	5.81E-11	3.77E-09
ENSG00000081189	MEF2C	-0.89393	5.13E-21	1.62E-18
ENSG00000083067	TRPM3	-0.89001	1.87E-10	1.11E-08
ENSG00000162630	B3GALT2	-0.89	2.33E-11	1.69E-09
ENSG00000221817	PPP3CB-AS1	-0.88744	6.50E-05	0.000965227
ENSG00000101638	ST8SIA5	-0.882	9.78E-06	0.000185969
ENSG00000133048	CHI3L1	-0.87844	4.75E-19	1.02E-16
ENSG00000248079	DPH6-AS1	-0.8774	3.14E-05	0.000516851
ENSG00000172164	SNTB1	-0.87709	3.23E-27	2.11E-24
ENSG00000082482	KCNK2	-0.87539	0.002731	0.021578122
ENSG00000164176	EDIL3	-0.87187	3.52E-09	1.50E-07
ENSG00000196083	IL1RAP	-0.87119	3.31E-20	8.72E-18
ENSG00000258655	ARHGAP5-AS1	-0.87077	2.07E-11	1.52E-09
ENSG00000140285	FGF7	-0.86661	4.96E-10	2.62E-08

ENSG00000162687	KCNT2	-0.86596	0.003821	0.027929486
ENSG00000167680	SEMA6B	-0.86474	6.82E-24	3.15E-21
ENSG00000151490	PTPRO	-0.86166	7.01E-12	5.60E-10
ENSG00000106302	HYAL4	-0.86142	1.13E-05	0.000210994
ENSG00000138376	BARD1	-0.85724	3.00E-18	6.06E-16
ENSG00000236651	DLX2-AS1	-0.85686	0.001927	0.016380173
ENSG00000162745	OLFML2B	-0.85506	0.000632	0.006540012
ENSG00000168874	ATOH8	-0.85504	4.22E-10	2.29E-08
ENSG00000203883	SOX18	-0.85418	0.001192	0.01112841
ENSG00000169851	PCDH7	-0.85314	1.29E-23	5.68E-21
ENSG00000166448	TMEM130	-0.85307	1.74E-07	5.13E-06
ENSG00000149212	SESN3	-0.85186	4.21E-18	8.07E-16
ENSG00000244342	LINC00698	-0.85013	0.004333	0.030686931
ENSG00000114200	BCHE	-0.84938	2.00E-11	1.47E-09
ENSG00000147434	CHRNA6	-0.84929	5.07E-05	0.000770826
ENSG00000169855	ROBO1	-0.84624	1.27E-17	2.31E-15
ENSG00000112782	CLIC5	-0.84527	0.005444	0.036522616
ENSG00000164756	SLC30A8	-0.8442	0.000234	0.002855168
ENSG00000152127	MGAT5	-0.84393	4.43E-19	9.69E-17
ENSG00000131094	C1QL1	-0.84297	9.35E-05	0.001299079
ENSG00000112559	MDFI	-0.84207	5.61E-06	0.000115494
ENSG00000103528	SYT17	-0.84191	9.43E-07	2.38E-05
ENSG00000109339	MAPK10	-0.83897	0.001337	0.012176905
ENSG00000186376	ZNF75D	-0.83886	6.98E-07	1.82E-05
ENSG00000249669	CARMN	-0.83551	3.70E-10	2.05E-08
ENSG00000183615	FAM167B	-0.83491	0.006451	0.041988732
ENSG00000181035	SLC25A42	-0.83329	0.001234	0.011443029
ENSG00000104324	CPQ	-0.83308	1.49E-09	6.92E-08
ENSG00000189157	FAM47E	-0.83097	0.003693	0.027194946
ENSG00000102287	GABRE	-0.82978	4.29E-13	4.26E-11
ENSG00000079931	MOXD1	-0.8296	1.11E-19	2.78E-17
ENSG00000127863	TNFRSF19	-0.82829	5.36E-20	1.39E-17
ENSG00000114646	CSPG5	-0.82797	9.72E-05	0.001346433
ENSG00000213614	HEXA	-0.82781	2.44E-22	9.05E-20
ENSG00000234535	AL161719.1	-0.82742	0.007087	0.045108485
ENSG00000097033	SH3GLB1	-0.82679	1.71E-20	4.83E-18
ENSG00000165272	AQP3	-0.82505	7.14E-07	1.85E-05
ENSG00000123684	LPGAT1	-0.82405	2.00E-24	9.95E-22
ENSG00000116991	SIPA1L2	-0.82336	8.58E-14	9.19E-12
ENSG00000159307	SCUBE1	-0.81869	2.17E-11	1.59E-09
ENSG00000072310	SREBF1	-0.81558	6.03E-14	6.57E-12
ENSG00000116774	OLFML3	-0.81477	1.24E-08	4.68E-07
ENSG00000260289	AC093515.1	-0.81389	0.000983	0.009515747
ENSG00000256433	AC005840.2	-0.81141	0.007622	0.047822298
ENSG00000163823	CCR1	-0.8105	0.006612	0.042817232
ENSG00000232353	AC026320.1	-0.81018	0.001412	0.012727888
ENSG00000184304	PRKD1	-0.80889	3.45E-11	2.40E-09
ENSG00000108352	RAPGEFL1	-0.80744	3.24E-05	0.000530316
ENSG00000166402	TUB	-0.80674	2.30E-14	2.58E-12
ENSG00000120925	RNF170	-0.80611	8.45E-09	3.30E-07
ENSG00000179104	TMTC2	-0.80599	3.12E-20	8.44E-18
ENSG00000112699	GMDS	-0.80551	5.15E-09	2.11E-07
ENSG00000123739	PLA2G12A	-0.80439	1.63E-17	2.91E-15
ENSG00000100084	HIRA	-0.80401	2.44E-11	1.75E-09

ENSG00000279382	AC018665.1	-0.80383	2.96E-05	0.000491018
ENSG00000187634	SAMD11	-0.80025	9.96E-13	9.34E-11
ENSG00000065361	ERBB3	-0.79939	1.31E-20	3.77E-18
ENSG00000157680	DGKI	-0.79915	6.86E-07	1.79E-05
ENSG00000170381	SEMA3E	-0.79837	8.48E-06	0.000165423
ENSG00000168675	LDLRAD4	-0.79819	2.42E-11	1.74E-09
ENSG00000135363	LMO2	-0.79791	5.48E-07	1.46E-05
ENSG00000168952	STXBP6	-0.79536	5.45E-08	1.79E-06
ENSG00000204272	NBDY	-0.78925	9.87E-11	6.24E-09
ENSG00000184564	SLITRK6	-0.78815	2.47E-11	1.77E-09
ENSG00000144810	COL8A1	-0.78804	9.52E-18	1.77E-15
ENSG00000066382	MPPED2	-0.78768	0.005912	0.039181271
ENSG00000164056	SPRY1	-0.78616	6.54E-08	2.11E-06
ENSG00000278910	BANCR	-0.78517	1.08E-07	3.35E-06
ENSG00000172508	CARNS1	-0.78365	0.005236	0.035408734
ENSG00000071991	CDH19	-0.78153	7.05E-13	6.68E-11
ENSG00000239282	CASTOR1	-0.77922	0.004563	0.031889425
ENSG00000146147	MLIP	-0.77917	0.000349	0.004019244
ENSG00000198753	PLXNB3	-0.779	2.83E-07	7.99E-06
ENSG00000162407	PLPP3	-0.77808	1.24E-15	1.71E-13
ENSG00000143341	HMCN1	-0.77742	7.93E-08	2.53E-06
ENSG00000102038	SMARCA1	-0.77569	2.02E-12	1.80E-10
ENSG00000056998	GYG2	-0.77436	1.08E-11	8.40E-10
ENSG00000279717	AC005336.3	-0.77429	0.003861	0.028155357
ENSG00000183773	AIFM3	-0.77262	9.21E-06	0.000176979
ENSG00000243224	AC006252.1	-0.7723	0.002444	0.01978047
ENSG00000141376	BCAS3	-0.77121	1.21E-16	1.90E-14
ENSG00000143171	RXRG	-0.76861	0.000739	0.007468754
ENSG00000106123	EPHB6	-0.76699	1.87E-13	1.92E-11
ENSG00000160307	S100B	-0.76541	9.50E-16	1.33E-13
ENSG00000154310	TNIK	-0.76474	9.79E-16	1.36E-13
ENSG00000021645	NRXN3	-0.76472	1.03E-08	3.93E-07
ENSG00000090971	NAT14	-0.76469	5.09E-12	4.18E-10
ENSG00000144218	AFF3	-0.76428	0.000255	0.00307443
ENSG00000164946	FREM1	-0.76384	3.33E-12	2.88E-10
ENSG00000007174	DNAH9	-0.76291	2.64E-06	5.98E-05
ENSG00000185561	TLCD2	-0.7628	3.55E-09	1.50E-07
ENSG00000153944	MSI2	-0.7628	1.35E-19	3.27E-17
ENSG00000148655	LRMDA	-0.76091	1.49E-06	3.62E-05
ENSG00000176406	RIMS2	-0.76017	7.99E-06	0.000156993
ENSG00000167588	GPD1	-0.7585	2.24E-07	6.46E-06
ENSG00000176049	JAKMIP2	-0.7585	4.95E-17	8.38E-15
ENSG00000156427	FGF18	-0.75786	0.000381	0.004298311
ENSG00000175538	KCNE3	-0.7558	0.003744	0.027481411
ENSG00000183098	GPC6	-0.75536	8.18E-06	0.00016001
ENSG00000112561	TFEB	-0.75502	1.11E-06	2.76E-05
ENSG00000033327	GAB2	-0.7547	3.09E-06	6.87E-05
ENSG00000169933	FRMPD4	-0.75304	7.28E-05	0.00105688
ENSG00000185189	NRBP2	-0.75225	8.01E-12	6.33E-10
ENSG00000196139	AKR1C3	-0.75127	1.50E-10	9.05E-09
ENSG00000101384	JAG1	-0.75101	2.41E-18	4.97E-16
ENSG00000130150	MOSPD2	-0.75081	1.18E-16	1.87E-14
ENSG00000117643	MAN1C1	-0.75003	1.82E-05	0.000318073
ENSG00000116741	RGS2	-0.74831	6.68E-13	6.36E-11

ENSG00000123405	NFE2	-0.74703	0.001024	0.009848745
ENSG00000165029	ABCA1	-0.74622	2.92E-18	5.96E-16
ENSG00000143167	GPA33	-0.74587	0.001309	0.011973668
ENSG00000183196	CHST6	-0.74518	4.71E-12	3.90E-10
ENSG00000147588	PMP2	-0.74408	8.72E-06	0.000169029
ENSG00000226043	AP000561.1	-0.74251	0.004843	0.033323943
ENSG00000185885	IFITM1	-0.742	0.000136	0.001787648
ENSG00000116194	ANGPTL1	-0.74065	0.002773	0.021861525
ENSG00000254911	SCARNA9	-0.74059	4.40E-08	1.48E-06
ENSG00000226328	NUP50-AS1	-0.73845	4.50E-07	1.23E-05
ENSG00000260035	AC051619.8	-0.73579	0.0012	0.011181936
ENSG00000124766	SOX4	-0.73574	5.70E-11	3.72E-09
ENSG00000183826	BTBD9	-0.7347	1.48E-09	6.89E-08
ENSG00000111728	ST8SIA1	-0.73441	0.000211	0.002612202
ENSG00000138795	LEF1	-0.73345	1.31E-08	4.88E-07
ENSG00000112419	PHACTR2	-0.73312	2.33E-11	1.69E-09
ENSG00000091428	RAPGEF4	-0.73257	0.000387	0.004357826
ENSG00000182168	UNC5C	-0.73235	2.53E-10	1.46E-08
ENSG00000188738	FSIP2	-0.73208	3.59E-05	0.000575889
ENSG00000082293	COL19A1	-0.73205	2.49E-08	8.88E-07
ENSG00000156103	MMP16	-0.73123	2.32E-17	4.03E-15
ENSG00000243244	STON1	-0.72972	5.07E-06	0.000106064
ENSG00000092758	COL9A3	-0.72667	3.53E-09	1.50E-07
ENSG00000251574	AC099520.1	-0.72621	0.006176	0.040617395
ENSG00000130702	LAMA5	-0.7258	4.03E-06	8.67E-05
ENSG00000075213	SEMA3A	-0.72565	8.43E-10	4.24E-08
ENSG00000137266	SLC22A23	-0.72474	1.84E-08	6.66E-07
ENSG00000123700	KCNJ2	-0.72471	0.000135	0.001775122
ENSG00000106078	COBL	-0.72462	0.006009	0.039700517
ENSG00000170624	SGCD	-0.72337	6.90E-05	0.001014739
ENSG00000185432	METTL7A	-0.72256	4.76E-08	1.59E-06
ENSG00000197959	DNM3	-0.72102	1.87E-09	8.46E-08
ENSG00000128655	PDE11A	-0.72097	1.01E-05	0.000191267
ENSG00000130338	TULP4	-0.71932	1.10E-05	0.000205503
ENSG00000253379	NA	-0.71904	7.67E-05	0.001106991
ENSG00000198624	CCDC69	-0.71903	5.93E-07	1.57E-05
ENSG00000103888	CEMIP	-0.71896	8.27E-10	4.19E-08
ENSG00000187140	FOXD3	-0.71852	1.10E-09	5.36E-08
ENSG00000198964	SGMS1	-0.71815	3.26E-15	4.21E-13
ENSG00000224081	SLC44A3-AS1	-0.71779	0.002919	0.022799652
ENSG00000173991	TCAP	-0.71738	0.007462	0.047053227
ENSG00000151834	GABRA2	-0.7168	0.000267	0.003197598
ENSG00000233215	LINC01687	-0.71598	0.001789	0.015455035
ENSG00000137764	MAP2K5	-0.71572	0.00055	0.005858441
ENSG00000158008	EXTL1	-0.71523	1.03E-09	5.06E-08
ENSG00000114023	FAM162A	-0.71465	1.35E-10	8.25E-09
ENSG00000108387	44443	-0.71336	0.003177	0.024333664
ENSG00000155761	SPAG17	-0.71035	4.76E-05	0.000731244
ENSG00000112964	GHR	-0.70807	0.000598	0.00626024
ENSG00000267801	AC087289.5	-0.70801	0.002778	0.021882498
ENSG00000137460	FHDC1	-0.70722	1.56E-08	5.73E-07
ENSG00000091592	NLRP1	-0.70708	9.45E-10	4.70E-08
ENSG00000054282	SDCCAG8	-0.70662	9.67E-10	4.77E-08
ENSG00000009694	TENM1	-0.70593	1.32E-06	3.24E-05

ENSG00000164764	SBSPON	-0.70505	9.99E-05	0.001376626
ENSG00000172264	MACROD2	-0.70496	6.05E-05	0.00090404
ENSG00000196502	SULT1A1	-0.70452	1.19E-10	7.41E-09
ENSG00000261786	AC006058.1	-0.70442	0.001836	0.015778291
ENSG00000060566	CREB3L3	-0.70402	0.00132	0.012050244
ENSG00000020181	ADGRA2	-0.70286	5.32E-09	2.16E-07
ENSG00000120658	ENOX1	-0.7019	1.44E-07	4.31E-06
ENSG00000163590	PPM1L	-0.70169	4.23E-05	0.000660319
ENSG00000106526	ACTR3C	-0.70117	1.29E-05	0.000238167
ENSG00000112276	BVES	-0.70081	1.19E-11	9.21E-10
ENSG00000181449	SOX2	-0.70059	4.72E-07	1.28E-05
ENSG00000077380	DYNC1I2	-0.6997	1.23E-12	1.13E-10
ENSG00000171033	PKIA	-0.69849	3.29E-05	0.000535838
ENSG00000213626	LBH	-0.69724	4.89E-07	1.32E-05
ENSG00000235109	ZSCAN31	-0.69719	1.52E-13	1.58E-11
ENSG00000203727	SAMD5	-0.69693	6.80E-06	0.000135647
ENSG00000070731	ST6GALNAC2	-0.69627	1.02E-08	3.91E-07
ENSG00000223865	HLA-DPB1	-0.69601	3.02E-09	1.31E-07
ENSG00000143995	MEIS1	-0.69546	6.92E-09	2.75E-07
ENSG00000120458	MSANTD2	-0.69544	5.14E-07	1.38E-05
ENSG00000283632	EXOC3L2	-0.69468	0.004006	0.028992759
ENSG00000272622	AC010735.2	-0.69271	5.43E-08	1.79E-06
ENSG00000134121	CHL1	-0.69268	1.23E-08	4.66E-07
ENSG00000278530	CHMP1B2P	-0.69242	2.08E-05	0.000358064
ENSG00000185760	KCNQ5	-0.69193	0.000317	0.003695466
ENSG00000111816	FRK	-0.69113	0.000306	0.003592837
ENSG00000106804	C5	-0.69001	0.000288	0.003410343
ENSG00000247134	AC090204.1	-0.68948	0.000131	0.00174026
ENSG00000278535	DHRS11	-0.6876	2.23E-10	1.30E-08
ENSG00000251129	LINC02506	-0.68697	1.39E-08	5.15E-07
ENSG00000104936	DMPK	-0.68571	3.24E-16	4.84E-14
ENSG00000183853	KIRREL1	-0.68461	1.29E-09	6.12E-08
ENSG00000143512	HHIPL2	-0.68412	0.002365	0.01928157
ENSG00000259786	LINC02109	-0.68402	0.001629	0.014357456
ENSG00000198121	LPAR1	-0.68304	0.001101	0.010430331
ENSG00000079691	CARMIL1	-0.68276	8.45E-14	9.10E-12
ENSG00000164796	CSMD3	-0.68234	3.13E-05	0.000516135
ENSG00000130382	MLLT1	-0.68204	1.67E-05	0.000296534
ENSG00000167676	PLIN4	-0.6819	1.87E-11	1.39E-09
ENSG00000136275	C7orf69	-0.68127	0.003901	0.028331488
ENSG00000115556	PLCD4	-0.68119	8.89E-06	0.00017198
ENSG00000205403	CFI	-0.68025	4.02E-11	2.74E-09
ENSG00000162944	RFTN2	-0.68021	0.004063	0.029307272
ENSG00000166575	TMEM135	-0.67885	4.93E-11	3.25E-09
ENSG00000240583	AQP1	-0.67845	3.38E-08	1.15E-06
ENSG00000115896	PLCL1	-0.6782	0.000209	0.002594612
ENSG00000182752	PAPPA	-0.6776	2.35E-08	8.38E-07
ENSG00000267534	S1PR2	-0.67691	2.77E-08	9.72E-07
ENSG00000196814	MVB12B	-0.67671	1.74E-07	5.13E-06
ENSG00000154529	CNTNAP3B	-0.67494	0.001101	0.010430331
ENSG00000166780	C16orf45	-0.67417	8.27E-10	4.19E-08
ENSG00000099998	GGT5	-0.67408	0.001243	0.01148273
ENSG00000126803	HSPA2	-0.67406	2.21E-15	2.89E-13
ENSG00000169067	ACTBL2	-0.67307	0.004893	0.033605558

ENSG00000128606	LRRC17	-0.67163	2.42E-09	1.07E-07
ENSG00000132535	DLG4	-0.66974	4.94E-05	0.000755296
ENSG00000164175	SLC45A2	-0.66974	1.30E-07	3.93E-06
ENSG00000099957	P2RX6	-0.66857	4.32E-08	1.45E-06
ENSG00000239521	CASTOR3	-0.66834	3.74E-06	8.12E-05
ENSG00000163072	NOSTRIN	-0.66768	0.000499	0.005400948
ENSG00000116353	MECR	-0.66759	2.42E-07	6.92E-06
ENSG00000179403	VWA1	-0.66744	0.001494	0.013333168
ENSG00000071575	TRIB2	-0.66665	9.77E-17	1.56E-14
ENSG00000184903	IMMP2L	-0.66618	3.32E-09	1.43E-07
ENSG00000171951	SCG2	-0.66589	2.80E-10	1.59E-08
ENSG00000144355	DLX1	-0.66555	1.21E-11	9.32E-10
ENSG00000242574	HLA-DMB	-0.66465	1.67E-08	6.11E-07
ENSG00000164683	HEY1	-0.66452	4.39E-09	1.83E-07
ENSG00000141052	MYOCD	-0.66394	8.35E-07	2.14E-05
ENSG00000163637	PRICKLE2	-0.66391	1.67E-09	7.69E-08
ENSG00000125730	C3	-0.66348	8.01E-12	6.33E-10
ENSG00000198756	COLGALT2	-0.66175	1.98E-05	0.000342235
ENSG00000261379	AC010735.1	-0.66175	6.56E-06	0.000131595
ENSG00000048740	CELF2	-0.66116	0.000582	0.006144055
ENSG00000154237	LRRK1	-0.66112	4.48E-06	9.51E-05
ENSG00000243944	AC117386.2	-0.66101	0.000358	0.004097982
ENSG00000119943	PYROXD2	-0.66023	3.35E-06	7.35E-05
ENSG00000169499	PLEKHA2	-0.66013	4.74E-16	6.96E-14
ENSG00000185477	GPRIN3	-0.65996	1.56E-09	7.18E-08
ENSG00000116819	TFAP2E	-0.65975	0.003875	0.028239454
ENSG00000135842	FAM129A	-0.6591	1.53E-12	1.40E-10
ENSG00000162496	DHRS3	-0.65855	1.79E-12	1.60E-10
ENSG00000121858	TNFSF10	-0.65617	3.78E-07	1.05E-05
ENSG00000139044	B4GALNT3	-0.65575	2.25E-10	1.31E-08
ENSG00000180447	GAS1	-0.65423	1.55E-06	3.74E-05
ENSG00000187678	SPRY4	-0.65366	1.65E-05	0.000292853
ENSG00000223564	CYP4F32P	-0.65273	5.24E-06	0.000109167
ENSG00000270885	RASL10B	-0.65264	7.19E-06	0.00014273
ENSG00000120725	SIL1	-0.65207	1.60E-11	1.20E-09
ENSG00000179583	CIITA	-0.65078	1.48E-05	0.000268069
ENSG00000250337	PURPL	-0.64941	2.58E-08	9.12E-07
ENSG00000011105	TSPAN9	-0.64837	9.21E-08	2.89E-06
ENSG00000044524	EPHA3	-0.64701	1.08E-09	5.25E-08
ENSG00000175899	A2M	-0.6461	2.71E-10	1.55E-08
ENSG00000188177	ZC3H6	-0.64485	1.34E-05	0.000246164
ENSG00000165675	ENOX2	-0.64482	1.65E-10	9.86E-09
ENSG00000159733	ZFYVE28	-0.6436	6.10E-05	0.000910061
ENSG00000175745	NR2F1	-0.64333	2.89E-05	0.000480441
ENSG00000170647	NA	-0.6428	0.004492	0.03148652
ENSG00000173930	SLCO4C1	-0.64255	0.005142	0.034893425
ENSG00000154122	ANKH	-0.64143	2.72E-10	1.55E-08
ENSG00000104490	NCALD	-0.64115	7.78E-08	2.49E-06
ENSG00000204287	HLA-DRA	-0.64104	7.49E-11	4.85E-09
ENSG00000119699	TGFB3	-0.64078	2.28E-08	8.16E-07
ENSG00000139173	TMEM117	-0.64051	0.000157	0.002015249
ENSG00000117069	ST6GALNAC5	-0.63973	0.000296	0.003487428
ENSG00000106546	AHR	-0.63906	5.74E-13	5.58E-11
ENSG00000069702	TGFBR3	-0.63903	6.24E-09	2.50E-07

ENSG00000116661	FBXO2	-0.63803	0.000421	0.00467316
ENSG00000137868	STRA6	-0.63693	2.00E-09	8.98E-08
ENSG00000189186	DCAF8L2	-0.63655	1.91E-05	0.000331576
ENSG00000100299	ARSA	-0.63633	2.83E-05	0.000471913
ENSG00000203857	HSD3B1	-0.63562	7.79E-05	0.001119915
ENSG00000267284	AC022031.2	-0.63526	0.001927	0.016380173
ENSG00000175874	CREG2	-0.63515	0.000587	0.006175966
ENSG00000198908	BHLHB9	-0.63474	0.000944	0.009200419
ENSG00000120156	TEK	-0.63469	6.49E-08	2.10E-06
ENSG00000106780	MEGF9	-0.63402	4.05E-12	3.46E-10
ENSG00000196739	COL27A1	-0.63353	1.32E-06	3.25E-05
ENSG00000234323	LINC01505	-0.63288	8.69E-06	0.000168554
ENSG00000135362	PRR5L	-0.63276	4.68E-10	2.50E-08
ENSG00000206567	AC022007.1	-0.63271	0.000514	0.005536832
ENSG00000133055	MYBPH	-0.63218	7.37E-05	0.001068578
ENSG00000257354	AC048341.1	-0.63207	0.003531	0.026291251
ENSG00000157388	CACNA1D	-0.63108	0.002233	0.018453963
ENSG00000115461	IGFBP5	-0.63102	0.000343	0.0039529
ENSG00000248429	FAM198B-AS1	-0.63072	0.004549	0.03183922
ENSG00000198909	MAP3K3	-0.62996	1.31E-09	6.21E-08
ENSG00000188153	COL4A5	-0.62928	2.08E-09	9.29E-08
ENSG00000100321	SYNGR1	-0.62884	5.69E-10	2.96E-08
ENSG00000249395	CASC9	-0.62788	1.21E-06	2.99E-05
ENSG00000010810	FYN	-0.62729	3.99E-11	2.73E-09
ENSG00000073417	PDE8A	-0.62629	8.28E-10	4.19E-08
ENSG00000143248	RGS5	-0.62617	1.57E-08	5.76E-07
ENSG00000141441	GAREM1	-0.62611	5.71E-08	1.87E-06
ENSG00000154493	C10orf90	-0.62597	3.51E-05	0.000567379
ENSG00000258932	AL390334.1	-0.62593	0.005853	0.038867956
ENSG00000135929	CYP27A1	-0.62502	9.82E-11	6.22E-09
ENSG00000172915	NBEA	-0.62488	3.15E-09	1.36E-07
ENSG00000103591	AAGAB	-0.62476	4.07E-12	3.46E-10
ENSG00000138080	EMILIN1	-0.62465	2.43E-10	1.41E-08
ENSG00000188015	S100A3	-0.62455	2.19E-05	0.000373847
ENSG00000115318	LOXL3	-0.62388	1.91E-14	2.19E-12
ENSG00000167566	NCKAP5L	-0.62335	4.28E-06	9.13E-05
ENSG00000158352	SHROOM4	-0.62283	7.83E-06	0.000154026
ENSG00000184557	SOCS3	-0.62055	1.29E-11	9.90E-10
ENSG00000165949	IFI27	-0.61943	0.000277	0.003308989
ENSG00000104368	PLAT	-0.61936	3.49E-11	2.40E-09
ENSG00000064687	ABCA7	-0.61847	2.84E-10	1.61E-08
ENSG00000250479	CHCHD10	-0.61531	1.31E-08	4.88E-07
ENSG00000187720	THSD4	-0.61395	3.19E-05	0.000522234
ENSG00000167964	RAB26	-0.61288	1.71E-10	1.02E-08
ENSG00000149294	NCAM1	-0.61259	4.99E-07	1.34E-05
ENSG00000175662	TOM1L2	-0.61258	3.67E-05	0.000586554
ENSG00000132688	NES	-0.61185	3.91E-10	2.14E-08
ENSG00000120659	TNFSF11	-0.61113	9.69E-07	2.44E-05
ENSG00000018236	CNTN1	-0.61031	0.00048	0.005249173
ENSG00000003249	DBNDD1	-0.60983	1.91E-05	0.000332442
ENSG00000184384	MAML2	-0.60851	6.79E-05	0.001000305
ENSG00000105711	SCN1B	-0.60802	1.82E-06	4.31E-05
ENSG00000087884	AAMDC	-0.60766	0.000613	0.006384028
ENSG00000235501	AC105942.1	-0.6072	0.00709	0.045108485

ENSG00000113248	PCDHB15	-0.60689	0.000102	0.001403793
ENSG00000144642	RBMS3	-0.60608	1.15E-09	5.59E-08
ENSG00000136158	SPRY2	-0.6059	1.53E-10	9.16E-09
ENSG00000283117	AC004949.1	-0.60558	0.00013	0.00172902
ENSG00000239589	LINC00879	-0.60515	0.003655	0.027019627
ENSG00000132530	XAF1	-0.60481	0.007821	0.048824978
ENSG00000185585	OLFML2A	-0.60369	0.00015	0.001943693
ENSG00000108515	ENO3	-0.60257	8.22E-07	2.11E-05
ENSG00000186469	GNG2	-0.60027	3.66E-10	2.03E-08
ENSG00000130203	APOE	-0.60007	2.64E-11	1.88E-09
ENSG00000225285	LINC01770	-0.5999	0.006666	0.043065924
ENSG00000144847	IGSF11	-0.59941	0.00387	0.028212044
ENSG00000142687	KIAA0319L	-0.59917	6.62E-13	6.34E-11
ENSG00000177409	SAMD9L	-0.59785	6.66E-12	5.37E-10
ENSG00000247081	BAALC-AS1	-0.5946	0.00057	0.006042526
ENSG00000116667	C1orf21	-0.59452	7.40E-06	0.000146646
ENSG00000165948	IFI27L1	-0.59447	8.10E-05	0.001160039
ENSG00000250510	GPR162	-0.59346	4.84E-05	0.000741638
ENSG00000049130	KITLG	-0.59246	1.73E-06	4.11E-05
ENSG00000068024	HDAC4	-0.59228	2.65E-07	7.53E-06
ENSG00000120833	SOCS2	-0.5921	0.000113	0.001526906
ENSG00000156869	FRRS1	-0.59061	6.15E-08	1.99E-06
ENSG00000178764	ZHX2	-0.58907	0.000999	0.009643571
ENSG00000089041	P2RX7	-0.58887	0.000524	0.005616314
ENSG00000130164	LDLR	-0.58801	4.01E-12	3.44E-10
ENSG00000171004	HS6ST2	-0.588	3.77E-06	8.17E-05
ENSG00000090565	RAB11FIP3	-0.58693	2.96E-09	1.29E-07
ENSG00000007237	GAS7	-0.58639	3.12E-08	1.07E-06
ENSG00000113594	LIFR	-0.58622	1.36E-12	1.25E-10
ENSG00000164761	TNFRSF11B	-0.58448	1.39E-05	0.000253866
ENSG00000011677	GABRA3	-0.58407	0.003427	0.025758004
ENSG00000006210	CX3CL1	-0.58349	0.001931	0.016394424
ENSG00000112146	FBXO9	-0.58254	1.84E-09	8.37E-08
ENSG00000134013	LOXL2	-0.58243	4.17E-11	2.80E-09
ENSG00000204257	HLA-DMA	-0.58204	4.91E-06	0.000103226
ENSG00000113578	FGF1	-0.58168	0.000723	0.007310412
ENSG00000237187	NR2F1-AS1	-0.58138	0.003896	0.028331488

List of genes that are up-regulated upon TRASH-ASO treatment.

ID	Gene.name	log2FoldChange	pvalue	padj
ENSG00000110244	APOA4	7.546921	4.37E-10	2.35E-08
ENSG00000163295	ALPI	7.152811	1.24E-08	4.68E-07
ENSG00000171487	NLRP5	6.996995	1.00E-08	3.83E-07
ENSG00000130294	KIF1A	6.60377	8.87E-08	2.80E-06
ENSG00000179148	ALOXE3	4.940284	1.07E-05	0.000200717
ENSG00000135750	KCNK1	4.667929	5.17E-07	1.38E-05
ENSG00000120279	MYCT1	3.863058	7.46E-07	1.93E-05
ENSG00000153531	ADPRHL1	3.705736	1.55E-83	1.47E-79
ENSG00000100368	CSF2RB	3.672316	5.20E-06	0.000108627
ENSG00000183778	B3GALT5	3.379573	4.02E-18	7.85E-16
ENSG00000126217	MCF2L	3.366648	9.17E-07	2.32E-05
ENSG00000131737	KRT34	3.320354	4.48E-08	1.50E-06
ENSG00000164266	SPINK1	3.070383	1.78E-31	2.25E-28
ENSG00000101203	COL20A1	2.951345	3.62E-06	7.89E-05

ENSG00000257495	KRT73-AS1	2.887516	3.11E-07	8.75E-06
ENSG00000260220	CCDC187	2.880767	8.57E-06	0.000166792
ENSG00000078549	ADCYAP1R1	2.870417	3.08E-11	2.17E-09
ENSG00000155093	PTPRN2	2.844389	9.16E-07	2.32E-05
ENSG00000026751	SLAMF7	2.821302	3.51E-40	1.11E-36
ENSG00000145113	MUC4	2.705729	1.79E-24	9.17E-22
ENSG00000154133	ROBO4	2.692127	3.05E-08	1.05E-06
ENSG00000157087	ATP2B2	2.6809	1.89E-05	0.000329257
ENSG00000283265	AL356234.3	2.667874	8.17E-11	5.27E-09
ENSG00000114204	SERPINI2	2.644947	1.40E-05	0.00025487
ENSG00000047617	ANO2	2.642934	1.26E-14	1.47E-12
ENSG00000217825	AC099552.1	2.619098	4.85E-09	2.00E-07
ENSG00000283646	LINC02009	2.6101	4.45E-19	9.69E-17
ENSG00000142623	PADI1	2.566464	3.95E-05	0.000623371
ENSG00000162711	NLRP3	2.515037	8.90E-08	2.81E-06
ENSG00000162723	SLAMF9	2.487104	1.88E-06	4.45E-05
ENSG00000167850	CD300C	2.474447	4.43E-15	5.60E-13
ENSG00000162892	IL24	2.41222	########	1.32E-124
ENSG00000258791	LINC00520	2.380053	2.00E-29	2.11E-26
ENSG00000123977	DAW1	2.337999	4.07E-05	0.000638929
ENSG00000123569	H2BFWT	2.335671	3.84E-05	0.000609832
ENSG00000111305	GSG1	2.331529	4.29E-10	2.32E-08
ENSG00000222047	C10orf55	2.330936	0.000209	0.002592579
ENSG00000167751	KLK2	2.320597	0.000146	0.001892105
ENSG00000007314	SCN4A	2.300691	1.19E-09	5.75E-08
ENSG00000175841	FAM172BP	2.272948	1.67E-06	3.99E-05
ENSG00000124343	XG	2.255526	9.00E-06	0.000173821
ENSG00000167642	SPINT2	2.192074	5.45E-07	1.45E-05
ENSG00000125740	FOSB	2.191016	1.39E-23	5.99E-21
ENSG00000197046	SIGLEC15	2.101248	0.000724	0.007323124
ENSG00000144583	44259	2.095246	3.40E-19	7.57E-17
ENSG00000179046	TRIML2	2.081298	1.81E-05	0.000316519
ENSG00000155961	RAB39B	2.060244	4.29E-12	3.62E-10
ENSG00000189320	FAM180A	2.046828	0.000416	0.004621126
ENSG00000133083	DCLK1	2.000771	1.53E-15	2.09E-13
ENSG00000248964	AC131254.1	2.000124	0.000808	0.008060374
ENSG00000238266	LINC00707	1.936375	2.87E-13	2.89E-11
ENSG00000164746	C7orf57	1.917137	2.53E-08	8.99E-07
ENSG00000170454	KRT75	1.914512	1.88E-09	8.52E-08
ENSG00000106018	VIPR2	1.909907	0.000342	0.003945836
ENSG00000240891	PLCXD2	1.881581	2.53E-68	1.60E-64
ENSG00000260604	AL590004.4	1.853096	7.15E-32	9.68E-29
ENSG00000231802	AC009502.2	1.847117	0.000407	0.004537175
ENSG00000172137	CALB2	1.839132	5.41E-12	4.42E-10
ENSG00000230439	AL512488.1	1.823599	1.50E-10	9.04E-09
ENSG00000255145	STX17-AS1	1.8172	0.000595	0.006237548
ENSG00000149968	MMP3	1.814558	1.26E-12	1.16E-10
ENSG00000115423	DNAH6	1.797947	4.83E-11	3.20E-09
ENSG00000197181	PIWIL2	1.786524	5.23E-09	2.14E-07
ENSG00000184515	BEX5	1.77838	5.02E-12	4.14E-10
ENSG00000105877	DNAH11	1.74955	1.33E-09	6.28E-08
ENSG00000240602	AADACP1	1.74415	9.52E-10	4.72E-08
ENSG00000243742	RPLP0P2	1.743845	1.92E-17	3.40E-15
ENSG00000175920	DOK7	1.741274	0.00032	0.00372572

ENSG00000196557	CACNA1H	1.732619	0.002355	0.019229793
ENSG00000187800	PEAR1	1.726431	6.31E-09	2.52E-07
ENSG00000167984	NLRC3	1.712694	2.52E-05	0.000424895
ENSG00000142619	PADI3	1.708203	4.16E-11	2.80E-09
ENSG00000170498	KISS1	1.678698	7.99E-08	2.54E-06
ENSG00000181652	ATG9B	1.674441	2.72E-14	3.04E-12
ENSG00000165105	RASEF	1.673873	1.43E-26	8.45E-24
ENSG00000179242	CDH4	1.66833	0.007678	0.048090506
ENSG00000260653	AC237221.1	1.664886	0.003741	0.027469645
ENSG00000106952	TNFSF8	1.660308	3.52E-06	7.69E-05
ENSG00000234805	AC090505.1	1.656292	4.56E-05	0.000706399
ENSG00000148346	LCN2	1.646988	0.001069	0.010189194
ENSG00000160255	ITGB2	1.646373	0.001655	0.014517829
ENSG00000167992	VWCE	1.638594	9.59E-06	0.000183099
ENSG00000275216	AL161431.1	1.630785	2.06E-09	9.20E-08
ENSG00000233221	AC133785.1	1.627398	0.000576	0.006091198
ENSG00000166816	LDHD	1.622896	1.99E-06	4.66E-05
ENSG00000166922	SCG5	1.620959	9.17E-35	1.58E-31
ENSG00000189001	SBSN	1.620691	0.000204	0.002530217
ENSG00000139973	SYT16	1.619882	0.00096	0.009316604
ENSG00000171346	KRT15	1.605004	1.20E-13	1.27E-11
ENSG00000163833	FBXO40	1.588739	0.007784	0.048628062
ENSG00000182261	NLRP10	1.584479	0.000139	0.001819599
ENSG00000283517	AC005144.1	1.57828	0.000379	0.004273816
ENSG00000236719	OVAAL	1.572278	1.38E-16	2.14E-14
ENSG00000256982	AC135782.1	1.56338	3.63E-07	1.01E-05
ENSG00000253227	AC090192.2	1.560917	5.02E-06	0.000105148
ENSG00000186642	PDE2A	1.552764	7.56E-17	1.22E-14
ENSG00000233521	LINC01638	1.543752	1.76E-08	6.40E-07
ENSG00000229563	LINC01204	1.54317	3.91E-05	0.000618927
ENSG00000101197	BIRC7	1.539998	4.77E-06	0.000100619
ENSG00000156265	MAP3K7CL	1.530035	4.29E-05	0.000668241
ENSG00000240244	GAPDHP33	1.51435	0.00015	0.001947232
ENSG00000002079	MYH16	1.514187	0.000472	0.005177689
ENSG00000126860	EVI2A	1.514132	0.004597	0.032023549
ENSG00000265190	ANXA8	1.512834	9.27E-09	3.58E-07
ENSG00000184368	MAP7D2	1.512689	0.000293	0.003458496
ENSG00000235314	LINC00957	1.503338	2.72E-11	1.93E-09
ENSG00000111348	ARHGDIB	1.500735	6.07E-10	3.14E-08
ENSG00000198574	SH2D1B	1.494503	3.85E-07	1.06E-05
ENSG00000175746	C15orf54	1.488861	4.73E-10	2.52E-08
ENSG00000177699	AC011944.1	1.481254	0.004656	0.032374824
ENSG00000082126	MPP4	1.479352	1.19E-14	1.40E-12
ENSG00000264301	LINC01444	1.478755	0.000436	0.004811326
ENSG00000237870	AC073130.1	1.474273	5.49E-06	0.000113397
ENSG00000205683	DPF3	1.472931	0.000416	0.004623826
ENSG00000181790	ADGRB1	1.472108	1.06E-05	0.000199354
ENSG00000205038	PKHD1L1	1.460494	0.003104	0.023947885
ENSG00000153233	PTPRR	1.4591	2.03E-18	4.22E-16
ENSG00000268758	ADGRE4P	1.451307	0.001653	0.014509777
ENSG00000277778	PGM5P2	1.446654	4.32E-14	4.76E-12
ENSG00000186047	DLEU7	1.438271	0.000131	0.001740879
ENSG00000231131	LINC01468	1.432513	9.08E-09	3.51E-07
ENSG00000258998	LINC02302	1.423816	0.003279	0.024952707

ENSG00000272068	AL365181.2	1.421754	0.000174	0.002197961
ENSG00000166396	SERPINB7	1.414751	6.75E-38	1.60E-34
ENSG00000165215	CLDN3	1.401619	7.07E-06	0.000140416
ENSG00000181126	HLA-V	1.397637	6.58E-08	2.12E-06
ENSG00000163827	LRRC2	1.393556	0.000395	0.004430167
ENSG00000169908	TM4SF1	1.389468	3.72E-48	1.41E-44
ENSG00000113555	PCDH12	1.386405	4.14E-08	1.40E-06
ENSG00000182795	C1orf116	1.381528	1.37E-09	6.45E-08
ENSG00000185567	AHNAK2	1.378785	4.14E-25	2.31E-22
ENSG00000179817	MRGPRX4	1.36715	0.002619	0.020902531
ENSG00000147394	ZNF185	1.367112	1.01E-10	6.31E-09
ENSG00000117152	RGS4	1.365747	1.53E-08	5.63E-07
ENSG00000169252	ADRB2	1.354156	1.68E-19	3.98E-17
ENSG00000259518	LINC01583	1.348012	2.22E-05	0.000379057
ENSG00000186310	NAP1L3	1.339387	1.73E-08	6.33E-07
ENSG00000240476	LINC00973	1.338991	2.52E-24	1.23E-21
ENSG00000258590	NBEAP1	1.338334	0.00022	0.002712453
ENSG00000198573	SPANXC	1.330886	0.001847	0.015845118
ENSG00000132718	SYT11	1.325537	8.29E-53	3.93E-49
ENSG00000167861	HID1	1.325389	0.006454	0.041996029
ENSG00000248596	AC139491.2	1.32206	4.35E-05	0.000676526
ENSG00000188818	ZDHHC11	1.322053	0.006549	0.042499009
ENSG00000165606	DRGX	1.312109	0.00035	0.004028713
ENSG00000146070	PLA2G7	1.311803	3.87E-05	0.000613079
ENSG00000182866	LCK	1.307491	0.00347	0.025955325
ENSG00000119547	ONECUT2	1.305774	0.005584	0.037334439
ENSG00000269927	AC004817.3	1.30341	3.35E-07	9.38E-06
ENSG00000108309	RUNDC3A	1.301551	1.39E-11	1.06E-09
ENSG00000264230	ANXA8L1	1.298886	3.38E-10	1.90E-08
ENSG00000162510	MATN1	1.294304	0.000331	0.00383244
ENSG00000231419	LINC00689	1.29001	7.12E-12	5.67E-10
ENSG00000142910	TINAGL1	1.28676	6.71E-07	1.76E-05
ENSG00000157557	ETS2	1.278725	4.00E-15	5.09E-13
ENSG00000254842	LINC02551	1.274131	5.65E-05	0.000849911
ENSG00000162896	PIGR	1.273727	7.73E-07	1.99E-05
ENSG00000186205	44256	1.273501	3.47E-11	2.40E-09
ENSG00000273760	AC245041.1	1.260656	5.51E-15	6.78E-13
ENSG00000099338	CATSPERG	1.259445	8.68E-06	0.000168549
ENSG00000167895	TMC8	1.258801	3.22E-06	7.13E-05
ENSG00000198576	ARC	1.256936	3.38E-17	5.82E-15
ENSG00000228624	HDAC2-AS2	1.256169	0.000228	0.002798123
ENSG00000230002	ALMS1-IT1	1.246993	3.55E-08	1.21E-06
ENSG00000137709	POU2F3	1.243906	0.00054	0.005759434
ENSG00000187994	RINL	1.242299	1.34E-10	8.20E-09
ENSG00000167083	GNGT2	1.241492	1.81E-06	4.31E-05
ENSG00000162641	AKNAD1	1.238465	0.00306	0.023704106
ENSG00000173237	C11orf86	1.23343	0.00011	0.001494048
ENSG00000197279	ZNF165	1.226168	2.70E-08	9.49E-07
ENSG00000120217	CD274	1.225602	1.78E-15	2.38E-13
ENSG00000082556	OPRK1	1.219692	0.001855	0.015891533
ENSG00000141469	SLC14A1	1.216879	1.85E-27	1.25E-24
ENSG00000050438	SLC4A8	1.214911	3.00E-08	1.04E-06
ENSG00000102003	SYP	1.211392	1.49E-08	5.51E-07
ENSG00000143217	NECTIN4	1.206346	2.66E-06	6.00E-05

ENSG00000112195	TREML2	1.204893	0.007046	0.04492868
ENSG00000124249	KCNK15	1.202639	5.04E-05	0.000767836
ENSG00000101187	SLCO4A1	1.20163	0.000937	0.009154046
ENSG00000267107	PCAT19	1.193064	1.70E-05	0.000300298
ENSG00000197646	PDCD1LG2	1.191989	5.36E-09	2.18E-07
ENSG00000236969	GGT8P	1.181029	0.000696	0.007080786
ENSG00000166111	SVOP	1.177521	0.004191	0.029964216
ENSG00000158023	WDR66	1.173815	9.14E-11	5.87E-09
ENSG00000149418	ST14	1.17029	0.004085	0.029427236
ENSG00000140519	RHCG	1.166277	0.00063	0.006524451
ENSG00000172548	NIPAL4	1.165613	0.002032	0.01706562
ENSG00000095203	EPB41L4B	1.164826	1.38E-14	1.60E-12
ENSG00000144821	MYH15	1.162778	9.90E-15	1.18E-12
ENSG00000234498	RPL13AP20	1.162444	1.08E-05	0.000202908
ENSG00000121797	CCRL2	1.161645	1.37E-08	5.11E-07
ENSG00000236345	AL354719.2	1.160195	4.85E-05	0.000743471
ENSG00000170476	MZB1	1.15844	4.32E-05	0.00067295
ENSG00000134160	TRPM1	1.155214	0.000155	0.00199684
ENSG00000058335	RASGRF1	1.152233	5.57E-06	0.000114667
ENSG00000251127	AC091173.1	1.14897	8.30E-05	0.001181264
ENSG00000164520	RAET1E	1.147446	2.55E-12	2.24E-10
ENSG00000163623	NKX6-1	1.147286	2.49E-06	5.69E-05
ENSG00000127325	BEST3	1.140422	0.006665	0.043065924
ENSG00000129990	SYT5	1.139222	0.003184	0.024373986
ENSG00000125144	MT1G	1.135881	0.00029	0.003429425
ENSG00000188910	GJB3	1.13587	1.87E-07	5.48E-06
ENSG00000163395	IGFN1	1.134446	8.18E-05	0.00116892
ENSG00000117148	ACTL8	1.132791	0.003583	0.026558889
ENSG00000197106	SLC6A17	1.129004	1.37E-08	5.11E-07
ENSG00000129170	CSRP3	1.121505	0.000132	0.00174516
ENSG00000122861	PLAU	1.118466	2.73E-21	8.91E-19
ENSG00000128422	KRT17	1.116168	0.00562	0.037530988
ENSG00000272405	AL365181.3	1.111786	0.005796	0.038575314
ENSG00000184792	OSBP2	1.105607	4.22E-11	2.82E-09
ENSG00000198223	CSF2RA	1.102892	0.002434	0.019725054
ENSG00000221866	PLXNA4	1.100709	0.000108	0.00147294
ENSG00000138356	AOX1	1.098731	1.27E-08	4.75E-07
ENSG00000120129	DUSP1	1.094109	3.70E-21	1.19E-18
ENSG00000180914	OXTR	1.093188	8.98E-08	2.82E-06
ENSG00000189280	GJB5	1.088229	0.001582	0.014011667
ENSG00000238062	SPATA3-AS1	1.081523	0.001147	0.010789159
ENSG00000189410	SH2D5	1.079972	3.81E-10	2.10E-08
ENSG00000130477	UNC13A	1.071155	5.50E-07	1.46E-05
ENSG00000198821	CD247	1.069523	0.001583	0.014011667
ENSG00000230836	LINC01293	1.066065	6.45E-15	7.83E-13
ENSG00000269896	AL513477.1	1.065809	6.73E-05	0.000994188
ENSG00000095752	IL11	1.063873	1.73E-11	1.29E-09
ENSG00000237596	AL138828.1	1.060273	0.000315	0.003678516
ENSG00000276850	AC245041.2	1.060179	3.56E-16	5.27E-14
ENSG00000125538	IL1B	1.058705	0.000682	0.00695638
ENSG00000099812	MISP	1.058017	2.45E-06	5.61E-05
ENSG00000234155	LINC02535	1.053731	0.000279	0.003330447
ENSG00000168497	CAVIN2	1.052654	0.004593	0.032004895
ENSG00000134242	PTPN22	1.051421	2.12E-08	7.61E-07

ENSG00000166923	GREM1	1.047201	0.004131	0.029678915
ENSG00000214274	ANG	1.046853	6.67E-05	0.00098752
ENSG00000119508	NR4A3	1.045508	5.46E-06	0.00011302
ENSG00000254634	SMG1P6	1.044505	0.001597	0.014106434
ENSG00000114854	TNNC1	1.043446	3.31E-06	7.29E-05
ENSG00000173702	MUC13	1.042312	8.02E-19	1.69E-16
ENSG00000249846	LINC02021	1.04012	0.00181	0.015600315
ENSG00000267577	AC010327.3	1.039932	0.000864	0.008535815
ENSG00000137393	RNF144B	1.039622	5.10E-11	3.35E-09
ENSG00000159166	LAD1	1.037752	1.15E-07	3.50E-06
ENSG00000167711	SERPINF2	1.036015	0.002698	0.021351805
ENSG00000164778	EN2	1.027705	4.67E-12	3.88E-10
ENSG00000136167	LCP1	1.021349	3.21E-20	8.56E-18
ENSG00000163376	KBTBD8	1.016859	1.12E-14	1.32E-12
ENSG00000124374	PAIP2B	1.015191	0.005412	0.036390616
ENSG00000232355	AL603650.1	1.014701	0.001744	0.01513957
ENSG00000163254	CRYGC	1.013685	0.003691	0.027194946
ENSG00000237624	OXCT2P1	1.009908	0.002654	0.021076783
ENSG00000235034	C19orf81	0.994811	0.003556	0.026412996
ENSG00000108798	ABI3	0.991306	0.001942	0.016457274
ENSG00000090382	LYZ	0.99009	5.72E-05	0.000859391
ENSG00000271664	AC004890.3	0.987895	0.004175	0.029872477
ENSG00000080166	DCT	0.987414	1.16E-09	5.61E-08
ENSG00000103154	NECAB2	0.987068	1.29E-05	0.000237827
ENSG00000133665	DYDC2	0.987042	3.36E-05	0.000544567
ENSG00000185664	PMEL	0.98308	1.66E-12	1.49E-10
ENSG00000204792	LINC01291	0.982412	1.87E-12	1.67E-10
ENSG00000138675	FGF5	0.978481	1.55E-16	2.39E-14
ENSG00000166455	C16orf46	0.97642	0.000235	0.002864359
ENSG00000184860	SDR42E1	0.976162	1.19E-05	0.000221307
ENSG00000174567	GOLT1A	0.975423	1.67E-07	4.96E-06
ENSG00000223949	ROR1-AS1	0.973222	3.66E-08	1.24E-06
ENSG00000121769	FABP3	0.972382	7.65E-09	3.01E-07
ENSG00000140459	CYP11A1	0.969771	0.00392	0.028428011
ENSG00000128564	VGF	0.969103	2.38E-19	5.55E-17
ENSG00000175894	TSPEAR	0.966216	0.007516	0.047299942
ENSG00000229953	AL590666.2	0.963608	2.41E-05	0.000408672
ENSG00000246273	SBF2-AS1	0.95739	9.94E-08	3.10E-06
ENSG00000145358	DDIT4L	0.954668	0.006271	0.041085389
ENSG00000081923	ATP8B1	0.952218	0.000203	0.002525896
ENSG00000164744	SUN3	0.951789	4.01E-06	8.63E-05
ENSG00000245522	AC026250.1	0.950682	0.000769	0.007726364
ENSG00000163050	COQ8A	0.94887	6.76E-26	3.88E-23
ENSG00000023445	BIRC3	0.948403	3.13E-11	2.20E-09
ENSG00000049759	NEDD4L	0.947616	2.28E-14	2.57E-12
ENSG00000176723	ZNF843	0.940718	0.001281	0.011796187
ENSG00000135636	DYSF	0.939622	0.002314	0.01896068
ENSG00000060762	MPC1	0.939451	2.73E-09	1.19E-07
ENSG00000169548	ZNF280A	0.937206	4.78E-10	2.54E-08
ENSG00000152409	JMY	0.932312	5.32E-19	1.13E-16
ENSG00000235884	LINC00941	0.929195	1.73E-07	5.13E-06
ENSG00000105383	CD33	0.928968	1.74E-05	0.000306466
ENSG00000280744	LINC01173	0.925435	0.000641	0.006610427
ENSG00000226887	ERVMER34-1	0.922213	0.003643	0.026986296

ENSG00000165879	FRAT1	0.914606	0.000613	0.006383117
ENSG00000224596	ZMIZ1-AS1	0.911277	0.000557	0.005929486
ENSG00000108932	SLC16A6	0.909989	4.63E-13	4.55E-11
ENSG00000169715	MT1E	0.89976	1.37E-17	2.48E-15
ENSG00000143367	TUFT1	0.898414	9.41E-20	2.38E-17
ENSG00000270011	ZNF559-ZNF177	0.896471	0.000562	0.005962624
ENSG00000111344	RASAL1	0.895981	0.000216	0.002662148
ENSG00000100867	DHRS2	0.895348	8.65E-10	4.33E-08
ENSG00000134363	FST	0.894689	2.24E-05	0.000382419
ENSG00000248375	AC104066.1	0.89412	0.007835	0.048899267
ENSG00000129910	CDH15	0.892104	5.21E-10	2.72E-08
ENSG00000283235	AC139493.2	0.888217	0.00254	0.020361623
ENSG00000235961	PNMA6A	0.886949	0.004438	0.03118516
ENSG00000163803	PLB1	0.886902	5.23E-06	0.00010897
ENSG00000143365	RORC	0.882521	3.23E-06	7.14E-05
ENSG00000271020	AC112220.2	0.88136	0.001158	0.01087583
ENSG00000100031	GGT1	0.880649	6.47E-13	6.23E-11
ENSG00000147174	GCNA	0.879667	0.000501	0.005421655
ENSG00000183780	SLC35F3	0.879096	0.006708	0.043243123
ENSG00000260160	AC011468.1	0.872073	0.00372	0.027343852
ENSG00000135437	RDH5	0.867611	1.41E-06	3.45E-05
ENSG00000159167	STC1	0.8653	1.52E-19	3.64E-17
ENSG00000198857	HSD3BP5	0.860568	0.000142	0.001851868
ENSG00000119737	GPR75	0.860387	0.000865	0.008540306
ENSG00000280046	AC104581.4	0.856385	0.001356	0.01232554
ENSG00000100994	PYGB	0.855675	5.69E-22	1.96E-19
ENSG00000100385	IL2RB	0.853667	0.006899	0.0442086
ENSG00000178150	ZNF114	0.850673	5.18E-15	6.42E-13
ENSG00000125148	MT2A	0.849194	2.59E-19	5.92E-17
ENSG00000167972	ABCA3	0.848903	0.003681	0.027155635
ENSG00000145088	EAF2	0.847062	0.000553	0.005883876
ENSG00000143322	ABL2	0.844732	3.01E-20	8.27E-18
ENSG00000182324	KCNJ14	0.841577	5.55E-05	0.000837086
ENSG00000122133	PAEP	0.840479	0.000151	0.001953909
ENSG00000226380	AC016831.1	0.837537	3.48E-18	6.86E-16
ENSG00000157168	NRG1	0.83576	5.15E-06	0.000107645
ENSG00000146648	EGFR	0.830474	0.001072	0.010217478
ENSG00000144824	PHLDB2	0.827658	2.15E-23	8.87E-21
ENSG00000112183	RBM24	0.823749	0.000485	0.005293307
ENSG00000086730	LAT2	0.821535	2.48E-05	0.000419187
ENSG00000136244	IL6	0.82091	1.54E-05	0.000276391
ENSG00000105929	ATP6V0A4	0.820715	2.47E-09	1.09E-07
ENSG00000138772	ANXA3	0.816579	1.93E-14	2.20E-12
ENSG00000099834	CDHR5	0.814367	0.002871	0.022480313
ENSG00000122912	SLC25A16	0.814304	4.27E-11	2.85E-09
ENSG00000205426	KRT81	0.813905	4.03E-13	4.02E-11
ENSG00000197632	SERPINB2	0.812676	3.88E-10	2.13E-08
ENSG00000226312	CFLAR-AS1	0.812436	0.003221	0.024596348
ENSG00000188372	ZP3	0.809896	1.38E-05	0.00025212
ENSG00000162413	KLHL21	0.805937	1.02E-20	2.97E-18
ENSG00000072041	SLC6A15	0.805333	6.32E-16	9.15E-14
ENSG00000145194	ECE2	0.801873	5.64E-15	6.90E-13
ENSG00000271643	AC112220.4	0.801342	0.000563	0.005968173

ENSG00000087074	PPP1R15A	0.800673	6.79E-21	2.08E-18
ENSG00000140941	MAP1LC3B	0.79685	5.07E-11	3.34E-09
ENSG00000162458	FBLIM1	0.796693	3.94E-06	8.51E-05
ENSG00000085563	ABCB1	0.795488	0.00161	0.014216484
ENSG00000164604	GPR85	0.792263	6.60E-05	0.000979121
ENSG00000135549	PKIB	0.791705	0.000124	0.001658726
ENSG00000179913	B3GNT3	0.790419	1.93E-06	4.53E-05
ENSG00000125637	PSD4	0.789867	3.23E-07	9.07E-06
ENSG00000187601	MAGEH1	0.78583	3.46E-13	3.47E-11
ENSG00000166073	GPR176	0.784092	1.34E-15	1.83E-13
ENSG00000146054	TRIM7	0.778693	0.001746	0.015142687
ENSG00000132846	ZBED3	0.777962	0.005139	0.034884523
ENSG00000070669	ASNS	0.776597	1.97E-17	3.46E-15
ENSG00000075618	FSCN1	0.776571	4.27E-12	3.61E-10
ENSG00000095383	TBC1D2	0.770926	1.92E-10	1.13E-08
ENSG00000167601	AXL	0.770137	7.97E-16	1.14E-13
ENSG00000167286	CD3D	0.767018	0.001958	0.016575049
ENSG00000153234	NR4A2	0.766436	8.21E-05	0.001171665
ENSG00000070182	SPTB	0.765622	5.01E-05	0.000765277
ENSG00000180071	ANKRD18A	0.764918	0.000121	0.001617678
ENSG00000110031	LPXN	0.763282	4.82E-14	5.28E-12
ENSG00000115008	IL1A	0.763225	6.09E-05	0.000908765
ENSG00000127528	KLF2	0.760239	3.47E-06	7.60E-05
ENSG00000187193	MT1X	0.758114	1.01E-10	6.31E-09
ENSG00000268001	CARD8-AS1	0.757313	4.81E-06	0.000101283
ENSG00000225339	AL354740.1	0.756706	0.007588	0.047658018
ENSG00000169085	C8orf46	0.755657	0.000119	0.001597641
ENSG00000258754	LINC01579	0.755548	3.68E-05	0.000587205
ENSG00000117472	TSPAN1	0.751752	0.002321	0.019008408
ENSG00000140678	ITGAX	0.75009	1.18E-05	0.000219793
ENSG00000119986	AVPI1	0.746885	9.77E-08	3.05E-06
ENSG00000260896	LINC02170	0.745531	3.19E-12	2.77E-10
ENSG00000153237	CCDC148	0.744986	0.000583	0.006145004
ENSG00000110721	CHKA	0.740153	3.48E-10	1.95E-08
ENSG00000268713	AC005261.3	0.73909	0.007945	0.049452825
ENSG00000197872	FAM49A	0.737795	3.69E-08	1.25E-06
ENSG00000082497	SERTAD4	0.73707	1.90E-06	4.48E-05
ENSG00000231298	LINC00704	0.736628	0.006002	0.039667254
ENSG00000113739	STC2	0.733878	6.83E-17	1.14E-14
ENSG00000178695	KCTD12	0.729786	9.56E-09	3.67E-07
ENSG00000134955	SLC37A2	0.729359	5.45E-12	4.43E-10
ENSG00000101680	LAMA1	0.727109	1.36E-10	8.26E-09
ENSG00000076513	ANKRD13A	0.722988	1.56E-16	2.39E-14
ENSG00000183496	MEX3B	0.72291	0.003386	0.025509892
ENSG00000179698	WDR97	0.719459	0.000141	0.001840288
ENSG00000156510	HKDC1	0.716983	1.43E-10	8.68E-09
ENSG00000133134	BEX2	0.715727	4.92E-10	2.61E-08
ENSG00000177606	JUN	0.715009	1.08E-12	1.01E-10
ENSG00000261150	EPPK1	0.714793	0.005034	0.034383881
ENSG00000234465	PINLYP	0.713749	0.005466	0.036611923
ENSG00000163291	PAQR3	0.713377	4.99E-18	9.45E-16
ENSG00000177181	RIMKLA	0.71102	0.000677	0.006912314
ENSG00000053524	MCF2L2	0.709979	0.007729	0.048363104
ENSG00000187801	ZFP69B	0.709262	1.55E-06	3.74E-05

ENSG00000117595	IRF6	0.707798	1.25E-09	5.98E-08
ENSG00000166394	CYB5R2	0.706694	0.00051	0.005505671
ENSG00000106034	CPED1	0.703495	1.37E-07	4.11E-06
ENSG00000166246	C16orf71	0.702636	0.004719	0.032704324
ENSG00000171402	XAGE3	0.699577	0.000964	0.00933961
ENSG00000186472	PCLO	0.697384	1.35E-05	0.000247045
ENSG00000179598	PLD6	0.696003	1.70E-06	4.05E-05
ENSG00000133639	BTG1	0.690026	7.37E-07	1.91E-05
ENSG00000276107	AC037198.1	0.68961	0.004307	0.030551353
ENSG00000135318	NT5E	0.688863	1.60E-16	2.43E-14
ENSG00000196696	AC009022.1	0.68814	8.66E-05	0.001224923
ENSG00000259345	AC013652.1	0.685853	0.005949	0.039410672
ENSG00000185022	MAFF	0.684728	1.42E-09	6.68E-08
ENSG00000162772	ATF3	0.68271	7.39E-07	1.91E-05
ENSG00000139508	SLC46A3	0.681626	0.000957	0.009294322
ENSG00000211772	TRBC2	0.681468	3.18E-05	0.000522234
ENSG00000170989	S1PR1	0.680516	7.37E-05	0.001068412
ENSG00000151014	NOCT	0.679055	5.30E-09	2.16E-07
ENSG00000154319	FAM167A	0.677121	4.08E-09	1.71E-07
ENSG00000181218	HIST3H2A	0.67616	1.24E-10	7.68E-09
ENSG00000006459	KDM7A	0.675097	2.64E-10	1.52E-08
ENSG00000175573	C11orf68	0.672966	4.10E-11	2.77E-09
ENSG00000167767	KRT80	0.669671	6.69E-08	2.15E-06
ENSG00000224959	AC017002.1	0.667922	0.002618	0.020902531
ENSG00000006606	CCL26	0.666661	8.79E-05	0.00123778
ENSG00000196368	NUDT11	0.66545	9.63E-06	0.000183568
ENSG00000144655	CSRNP1	0.663722	9.22E-11	5.89E-09
ENSG00000117597	DIEXF	0.661093	2.36E-16	3.55E-14
ENSG00000188511	C22orf34	0.661019	4.08E-05	0.0006401
ENSG00000141458	NPC1	0.658569	2.82E-08	9.86E-07
ENSG00000229939	AL589880.1	0.657223	0.00375	0.027498203
ENSG00000125378	BMP4	0.65701	0.001815	0.015632737
ENSG00000131019	ULBP3	0.655166	0.000945	0.009205853
ENSG00000104907	TRMT1	0.654994	1.69E-13	1.75E-11
ENSG00000167646	DNAAF3	0.654731	3.34E-05	0.000543195
ENSG00000179431	FJX1	0.653506	1.06E-09	5.18E-08
ENSG00000197608	ZNF841	0.652288	2.93E-10	1.66E-08
ENSG00000065621	GSTO2	0.650325	0.000207	0.002572131
ENSG00000171970	ZNF57	0.649859	0.001036	0.009954619
ENSG00000147676	MAL2	0.649759	5.98E-09	2.41E-07
ENSG00000181873	IBA57	0.64965	6.00E-07	1.58E-05
ENSG00000158125	XDH	0.645136	0.00067	0.006848634
ENSG00000196352	CD55	0.645024	1.34E-13	1.41E-11
ENSG00000256806	C17orf100	0.644038	0.001054	0.010096067
ENSG00000273038	AL365203.2	0.64226	0.00165	0.01449452
ENSG00000156535	CD109	0.641792	6.15E-09	2.47E-07
ENSG00000185338	SOCS1	0.640159	0.006265	0.041085389
ENSG00000169271	HSPB3	0.638532	1.53E-05	0.000275608
ENSG00000163818	LZTFL1	0.638395	2.00E-10	1.17E-08
ENSG00000106366	SERPINE1	0.638272	5.10E-10	2.68E-08
ENSG00000168811	IL12A	0.634991	0.001109	0.010485351
ENSG00000154589	LY96	0.634482	2.38E-06	5.48E-05
ENSG00000196155	PLEKHG4	0.632127	5.13E-15	6.40E-13
ENSG00000133169	BEX1	0.631601	1.40E-10	8.51E-09

ENSG00000096696	DSP	0.63074	2.82E-08	9.86E-07
ENSG00000279541	AC005261.5	0.630184	0.00141	0.012716675
ENSG00000146281	PM20D2	0.62892	3.12E-08	1.07E-06
ENSG00000185697	MYBL1	0.626561	2.81E-11	1.99E-09
ENSG00000143507	DUSP10	0.626358	5.35E-13	5.22E-11
ENSG00000113645	WWC1	0.626111	9.22E-11	5.89E-09
ENSG00000256223	ZNF10	0.625496	4.13E-05	0.000647488
ENSG00000073711	PPP2R3A	0.625288	6.53E-10	3.37E-08
ENSG00000229056	AC020571.1	0.624348	0.000651	0.006686647
ENSG00000129474	AJUBA	0.624058	2.13E-14	2.42E-12
ENSG00000150782	IL18	0.621193	6.97E-06	0.00013879
ENSG00000257605	AC073611.1	0.620706	0.001744	0.01513957
ENSG00000280213	UCKL1-AS1	0.620139	0.001826	0.015711546
ENSG00000086696	HSD17B2	0.619526	5.13E-08	1.70E-06
ENSG00000105327	BBC3	0.619011	4.07E-09	1.71E-07
ENSG00000145990	GFOD1	0.618714	1.39E-09	6.55E-08
ENSG00000214814	FER1L6	0.618079	0.004614	0.032113693
ENSG00000137962	ARHGAP29	0.617815	5.09E-10	2.68E-08
ENSG00000104419	NDRG1	0.617547	2.15E-12	1.90E-10
ENSG00000052749	RRP12	0.614025	4.01E-09	1.69E-07
ENSG00000136997	MYC	0.612116	0.000404	0.004514559
ENSG00000105856	HBP1	0.611567	7.93E-10	4.06E-08
ENSG00000127914	AKAP9	0.608976	2.08E-13	2.12E-11
ENSG00000197915	HRNR	0.608364	4.07E-06	8.73E-05
ENSG00000265843	LINC01029	0.608098	3.32E-11	2.32E-09
ENSG00000105499	PLA2G4C	0.608019	0.000475	0.00520416
ENSG00000164535	DAGLB	0.608011	9.97E-11	6.28E-09
ENSG00000260941	LINC00622	0.607856	0.003155	0.024201071
ENSG00000222724	RNU2-63P	0.605526	0.003549	0.02639039
ENSG00000269906	AL606834.1	0.604301	0.006971	0.044531178
ENSG00000158109	TPRG1L	0.603191	1.79E-08	6.50E-07
ENSG00000215218	UBE2QL1	0.600666	0.002801	0.022014298
ENSG00000158555	GDPD5	0.600509	5.43E-05	0.000821026
ENSG00000117983	MUC5B	0.598975	8.44E-05	0.001196072
ENSG00000181773	GPR3	0.598935	0.00422	0.030125647
ENSG00000176177	ENTHD1	0.598309	0.001385	0.012544869
ENSG00000148908	RGS10	0.597095	5.98E-06	0.000122231
ENSG00000126947	ARMCX1	0.596387	5.90E-08	1.92E-06
ENSG00000279184	NA	0.591966	2.86E-05	0.000477169
ENSG00000177873	ZNF619	0.588426	3.61E-06	7.88E-05
ENSG00000197385	ZNF860	0.587683	6.85E-07	1.79E-05
ENSG00000143479	DYRK3	0.587612	4.49E-09	1.86E-07
ENSG00000184470	TXNRD2	0.586862	3.37E-11	2.35E-09
ENSG00000150593	PDCD4	0.586007	6.03E-06	0.000122612
ENSG00000110046	ATG2A	0.585833	2.26E-06	5.24E-05
ENSG00000144136	SLC20A1	0.584985	4.08E-11	2.77E-09
ENSG00000196754	S100A2	0.580868	0.000326	0.003781602
ENSG00000197415	VEPH1	0.580335	5.49E-07	1.46E-05

TABLE 2
DAVID Functional Annotation Clustering Analysis of genes that are down-regulated upon TRASH-ASO treatment (Enrichment Score >2)

Annotation	Enrichment Score: 2.969365											

Cluster 1	39103503											
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Bonferroni	Benjamini	FDR
GOTERM_CC_DIRECT	GO:0005581~collagen trimer	12	2.3	### ###	ENSG00000196739, ENSG00000158270, ENSG00000188153, ENSG00000131094, ENSG00000204248, ENSG00000060718, ENSG00000138080, ENSG00000082196, ENSG00000204262, ENSG00000171502, ENSG00000187955, ENSG00000082293	460	92	18224	5.1674858	0.006492	0.001085	0
GOTERM_CC_DIRECT	GO:0005788~endoplasmic reticulum lumen	17	3.3	### ###	ENSG00000060718, ENSG00000198756, ENSG00000084636, ENSG00000204262, ENSG00000171502, ENSG00000115596, ENSG00000114200, ENSG00000144810, ENSG00000196739, ENSG00000188153, ENSG00000120725, ENSG00000080573, ENSG0000	460	192	18224	3.5077899	0.009854	0.001238	0

					0204248, ENSG0000 0100299, ENSG0000 0092758, ENSG0000 0187955, ENSG0000 0082293							
GOTERM_MF_DIRECT	GO:0005201~extracellular matrix structural constituent	10	1.9	### ###	ENSG0000 0196739, ENSG0000 0188153, ENSG0000 0204248, ENSG0000 0080573, ENSG0000 0060718, ENSG0000 0133048, ENSG0000 0204262, ENSG0000 0171502, ENSG0000 0187955, ENSG0000 0082293	425	67	16881	5.9283582	0.026912	0.01364	0
GOTERM_BP_DIRECT	GO:0030574~collagen catabolic process	9	1.7	### ###	ENSG0000 0144810, ENSG0000 0156103, ENSG0000 0188153, ENSG0000 0204248, ENSG0000 0080573, ENSG0000 0102996, ENSG0000 0060718, ENSG0000 0204262, ENSG0000 0082293	436	64	16792	5.4159977	0.404694	0.086436	0.1
KEGG_PATHWAY	hsa04974:Protein digestion and absorption	10	1.9	### ###	ENSG0000 0196739, ENSG0000 0188153, ENSG0000 0204248, ENSG0000 0080573, ENSG0000 0060718,	200	88	6879	3.9085227	0.18799	0.021081	0

					ENSG0000 0092758, ENSG0000 0175538, ENSG0000 0204262, ENSG0000 0171502, ENSG0000 0187955							
KEG G_P ATH WA Y	hsa04151 :PI3K-Akt signaling pathway	21	4. 1	0.0 02	ENSG0000 0198121, ENSG0000 0156475, ENSG0000 0112964, ENSG0000 0113578, ENSG0000 0113721, ENSG0000 0060718, ENSG0000 0176533, ENSG0000 0156427, ENSG0000 0204262, ENSG0000 0171502, ENSG0000 0060566, ENSG0000 0144668, ENSG0000 0196739, ENSG0000 0184371, ENSG0000 0188153, ENSG0000 0140285, ENSG0000 0080573, ENSG0000 0204248, ENSG0000 0186469, ENSG0000 0049130, ENSG0000 0120156	20 0	34 5	6879	2.093 6087	0.390 842	0.032 538	0
GOT ER M_ BP_	GO:0030 199~colla gen fibril organizat ion	6	1. 2	0.0 03	ENSG0000 0204248, ENSG0000 0080573, ENSG0000	43 6	39	1679 2	5.925 1941	0.999 074	0.442 383	0. 4

DIRECT					0134013, ENSG00000060718, ENSG00000204262, ENSG00000187955							
KEGG_PATHWAY	hsa04512:ECM-receptor interaction	9	1.7	0.004	ENSG00000144668, ENSG00000196739, ENSG00000188153, ENSG00000204248, ENSG00000080573, ENSG00000060718, ENSG00000196776, ENSG00000204262, ENSG00000171502	200	87	6879	3.5581034	0.542826	0.045052	0
KEGG_PATHWAY	hsa04611:Platelet activation	10	1.9	0.013	ENSG00000196739, ENSG00000204248, ENSG00000080573, ENSG00000185532, ENSG00000060718, ENSG00000171564, ENSG00000010810, ENSG00000171557, ENSG00000204262, ENSG00000171502	200	130	6879	2.6457692	0.94266	0.12911	0.1
KEGG_PATHWAY	hsa05146:Amoebiasis	8	1.6	0.033	ENSG00000119699, ENSG00000196739, ENSG00000188153, ENSG00000204248, ENSG00000080573, ENSG00000060718,	200	106	6879	2.5958491	0.99948	0.265535	0.2

					ENSG00000204262, ENSG00000171502							
KEGG_PATHWAY	hsa04510:Focal adhesion	12	2.3	0.036	ENSG00000109339, ENSG00000144668, ENSG00000196739, ENSG00000188153, ENSG00000204248, ENSG00000080573, ENSG00000113721, ENSG00000060718, ENSG00000010810, ENSG00000150760, ENSG00000204262, ENSG00000171502	200	206	6879	2.0035922	0.999724	0.268149	0.2
Annotation Cluster 2	Enrichment Score: 2.27529592315605											
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Bonferroni	Benjamini	FDR
KEGG_PATHWAY	hsa05150:Staphylococcus aureus infection	11	2.1	######	ENSG00000204257, ENSG00000205403, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000106804, ENSG00000231389, ENSG00000204287, ENSG00000171557,	200	54	6879	7.0063889	5.73E-04	3.21E-04	######

					ENSG00000196735, ENSG00000125730							
GOTERM_BP_DIRECT	GO:0002504~antigen processing and presentation of peptide or polysaccharide antigen via MHC class II	7	1.4	###	ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735	436	17	16792	15.858608	0.006205	0.002862	0
KEGG_PATHWAY	hsa04514:Cell adhesion molecules (CAMs)	17	3.3	###	ENSG00000149294, ENSG00000242574, ENSG00000204252, ENSG00000204287, ENSG00000021645, ENSG00000158887, ENSG00000196735, ENSG00000174469, ENSG00000144668, ENSG00000204257, ENSG00000223865, ENSG00000169760, ENSG00000162512, ENSG00000231389, ENSG00000018236, ENSG00000091129, ENSG00000149564	200	142	6879	4.1177113	6.41E-04	3.21E-04	###
GOTERM_CC_	GO:0042613~MHC class II protein complex	7	1.4	###	ENSG00000204257, ENSG00000223865, ENSG00000	460	22	18224	12.605534	0.004321	8.66E-04	###

DIRECT					0242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735							
GOTERM_MF_DIRECT	GO:0032395~MHC class II receptor activity	6	1.2	######	ENSG00000204257, ENSG00000223865, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735	425	15	16881	15.888	0.014984	0.01364	0
KEGG_PATHWAY	hsa05310:Asthma	7	1.4	######	ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735	200	30	6879	8.0255	0.039307	0.009253	0
KEGG_PATHWAY	hsa05323:Rheumatoid arthritis	11	2.1	######	ENSG00000119699, ENSG00000184371, ENSG00000204257, ENSG00000120659, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000120156, ENSG00000196735	200	88	6879	4.299375	0.044947	0.009253	0

KEGG_PATHWAY	hsa05416:Viral myocarditis	9	1.7	### ###	ENSG00000170624, ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000010810, ENSG00000196735	200	57	6879	5.4307895	0.045217	0.009253	0
KEGG_PATHWAY	hsa05332:Graft-versus-host disease	7	1.4	### ###	ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735	200	33	6879	7.2959091	0.067219	0.011596	0
KEGG_PATHWAY	hsa05330:Allograft rejection	7	1.4	### ###	ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735	200	37	6879	6.5071622	0.124249	0.018948	0
KEGG_PATHWAY	hsa05140:Leishmaniasis	9	1.7	### ###	ENSG00000119699, ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG0000	200	71	6879	4.3599296	0.190156	0.021081	0

					0231389, ENSG0000 0204287, ENSG0000 0196735, ENSG0000 0125730							
KEG G_P ATH WA Y	hsa04940 :Type I diabetes mellitus	7	1. 4	0.0 01	ENSG0000 0204257, ENSG0000 0223865, ENSG0000 0242574, ENSG0000 0204252, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0196735	20 0	42	6879	5.732 5	0.233 242	0.022 948	0
KEG G_P ATH WA Y	hsa05145 :Toxoplas mosis	11	2. 1	0.0 01	ENSG0000 0109339, ENSG0000 0119699, ENSG0000 0204257, ENSG0000 0126803, ENSG0000 0179583, ENSG0000 0223865, ENSG0000 0242574, ENSG0000 0204252, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0196735	20 0	11 0	6879	3.439 5	0.240 84	0.022 948	0
GOT ER M_ CC_ DIR ECT	GO:0030 666~end ocytic vesicle membra ne	8	1. 6	0.0 01	ENSG0000 0158270, ENSG0000 0132535, ENSG0000 0163072, ENSG0000 0223865, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0115596,	46 0	66	1822 4	4.802 108	0.355 871	0.039 96	0

					ENSG0000 0196735							
KEGG_PATHWAY	hsa04612 :Antigen processing and presentation	9	1.7	0.001	ENSG0000 0204257, ENSG0000 0126803, ENSG0000 0179583, ENSG0000 0223865, ENSG0000 0242574, ENSG0000 0204252, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0196735	200	76	6879	4.073 0921	0.281 498	0.025 411	0
KEGG_PATHWAY	hsa04672 :Intestinal immune network for IgA production	7	1.4	0.002	ENSG0000 0204257, ENSG0000 0223865, ENSG0000 0242574, ENSG0000 0204252, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0196735	200	47	6879	5.122 6596	0.382 761	0.032 538	0
KEGG_PATHWAY	hsa05321 :Inflammatory bowel disease (IBD)	8	1.6	0.002	ENSG0000 0119699, ENSG0000 0204257, ENSG0000 0223865, ENSG0000 0242574, ENSG0000 0204252, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0196735	200	64	6879	4.299 375	0.406 205	0.032 538	0
GOTERM_CC_DIRECT	GO:0030 658~transport vesicle membrane	6	1.2	0.003	ENSG0000 0223865, ENSG0000 0164756, ENSG0000 0231389,	460	38	18224	6.255 3776	0.564 495	0.063 862	0.1

					ENSG00000204287, ENSG00000196735, ENSG00000167964							
KEGG_PATHWAY	hsa05320:Autoimmune thyroid disease	7	1.4	0.004	ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735	200	52	6879	4.6300962	0.556219	0.045052	0
GOTERM_BP_DIRECT	GO:0002503~peptide antigen assembly with MHC class II protein complex	3	0.6	0.006	ENSG00000204257, ENSG00000242574, ENSG00000204287	436	5	16792	23.108257	0.999999	0.442383	0.4
GOTERM_MF_DIRECT	GO:0023026~MHC class II protein complex binding	4	0.8	0.007	ENSG00000204257, ENSG00000242574, ENSG00000204252, ENSG00000204287	425	16	16881	9.93	0.987649	0.364905	0.4
GOTERM_BP_DIRECT	GO:0019886~antigen processing and presentation of exogenous peptide antigen via MHC class II	8	1.6	0.01	ENSG00000077380, ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735	436	92	16792	3.3490227	1	0.536219	0.5

KEGG_PATHWAY	hsa04145:Phagosome	11	2.1	0.011	ENSG00000137285, ENSG00000077380, ENSG00000158270, ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735, ENSG00000125730	200	150	6879	2.5223	0.922115	0.125718	0.1
KEGG_PATHWAY	hsa05164:Influenza A	12	2.3	0.012	ENSG00000109339, ENSG00000204257, ENSG00000126803, ENSG00000179583, ENSG00000121858, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000184557, ENSG00000196735	200	174	6879	2.372069	0.929765	0.125718	0.1
GOTERM_BP_DIRECT	GO:0006955~immune response	19	3.7	0.026	ENSG00000196083, ENSG00000179583, ENSG00000242574, ENSG00000204252, ENSG00000069702, ENSG0000	436	421	16792	1.7381508	1	0.750201	0.7

					0204287, ENSG0000 0196735, ENSG0000 0006210, ENSG0000 0145824, ENSG0000 0164761, ENSG0000 0204257, ENSG0000 0120659, ENSG0000 0121858, ENSG0000 0009694, ENSG0000 0223865, ENSG0000 0231389, ENSG0000 0163823, ENSG0000 0164764, ENSG0000 0125730							
KEGG_PATHWAY	hsa05152:Tuberculosis	11	2.1	0.032	ENSG0000 0109339, ENSG0000 0119699, ENSG0000 0204257, ENSG0000 0179583, ENSG0000 0223865, ENSG0000 0242574, ENSG0000 0204252, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0196735, ENSG0000 0125730	200	177	6879	2.1375424	0.99925	0.262231	0.2
GOTERM_MF_DIRECT	GO:0042605~peptide antigen binding	4	0.8	0.032	ENSG0000 0223865, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0196735	425	28	16881	5.6742857	1	0.933291	0.9

GOTERM_CC_DIRECT	GO:0071556~integral component of lumenal side of endoplasmic reticulum membrane	4	0.8	0.036	ENSG00000223865, ENSG00000231389, ENSG00000204287, ENSG00000196735	460	29	18224	5.4644678	0.999994	0.473025	0.5
GOTERM_BP_DIRECT	GO:0060333~interferon-gamma-mediated signaling pathway	6	1.2	0.037	ENSG00000149294, ENSG00000179583, ENSG00000223865, ENSG00000231389, ENSG00000204287, ENSG00000196735	436	71	16792	3.2546841	1	0.871762	0.9
KEGG_PATHWAY	hsa05168:Herpes simplex infection	11	2.1	0.039	ENSG00000109339, ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000106804, ENSG00000231389, ENSG00000204287, ENSG00000184557, ENSG00000196735, ENSG00000125730	200	183	6879	2.067459	0.999851	0.277784	0.3
KEGG_PATHWAY	hsa05322:Systemic lupus erythematosus	9	1.7	0.04	ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000106804, ENSG0000	200	134	6879	2.3101119	0.999885	0.277784	0.3

					0231389, ENSG0000 0204287, ENSG0000 0196735, ENSG0000 0125730							
GOTERM_CC_DIRECT	GO:0012507~ER to Golgi transport vesicle membrane	5	1	0.042	ENSG0000 0223865, ENSG0000 0072310, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0196735	460	52	18224	3.809 3645	0.999 999	0.509 224	0.5
GOTERM_BP_DIRECT	GO:0019882~antigen processing and presentation	5	1	0.054	ENSG0000 0223865, ENSG0000 0242574, ENSG0000 0231389, ENSG0000 0204287, ENSG0000 0196735	436	55	16792	3.501 251	1	0.993 431	1
KEGG_PATHWAY	hsa05166:HTLV-I infection	13	2.5	0.064	ENSG0000 0135925, ENSG0000 0113721, ENSG0000 0242574, ENSG0000 0204252, ENSG0000 0204287, ENSG0000 0196735, ENSG0000 0115596, ENSG0000 0119699, ENSG0000 0204257, ENSG0000 0198909, ENSG0000 0223865, ENSG0000 0163513, ENSG0000 0231389	200	254	6879	1.760 374	1	0.395 228	0.4
GOTERM_	GO:0030669~clathrin-	4	0.8	0.084	ENSG0000 0223865, ENSG0000	460	41	18224	3.865 1113	1	0.683 107	0.7

CC_DIRECT	coated endocytic vesicle membrane				0231389, ENSG00000204287, ENSG00000196735							
GOTERM_BP_DIRECT	GO:0031295~T cell costimulation	5	1	0.144	ENSG00000223865, ENSG00000231389, ENSG00000204287, ENSG00000010810, ENSG00000196735	436	78	16792	2.468 8309	1	1	1
GOTERM_BP_DIRECT	GO:0042102~positive regulation of T cell proliferation	4	0.8	0.203	ENSG00000223865, ENSG00000242574, ENSG00000231389, ENSG00000163554	436	60	16792	2.567 5841	1	1	1
GOTERM_CC_DIRECT	GO:0031902~late endosome membrane	5	1	0.25	ENSG00000134108, ENSG00000196814, ENSG00000204257, ENSG00000242574, ENSG00000204287	460	101	18224	1.961 257	1	1	1
GOTERM_CC_DIRECT	GO:0032588~trans-Golgi network membrane	4	0.8	0.348	ENSG00000223865, ENSG00000231389, ENSG00000204287, ENSG00000196735	460	83	18224	1.909 2719	1	1	1
KEGG_PATHWAY	hsa05169:Epstein-Barr virus infection	5	1	0.472	ENSG00000109339, ENSG00000223865, ENSG00000231389, ENSG00000204287, ENSG00000196735	200	122	6879	1.409 6311	1	1	0.9
GOTERM_BP_DIRECT	GO:0050852~T cell receptor	5	1	0.536	ENSG00000223865, ENSG00000231389, ENSG0000	436	148	16792	1.301 1406	1	1	1

DIRECT	signaling pathway				0204287, ENSG00000010810, ENSG00000196735							
GOTERM_CC_DIRECT	GO:0005765~lysosomal membrane	8	1.6	0.536	ENSG00000134108, ENSG00000204257, ENSG00000223865, ENSG00000242574, ENSG00000204252, ENSG00000231389, ENSG00000204287, ENSG00000196735	460	274	18224	1.1567122	1	1	1
GOTERM_CC_DIRECT	GO:0010008~endosome membrane	4	0.8	0.848	ENSG00000223865, ENSG00000204252, ENSG00000231389, ENSG00000196735	460	185	18224	0.8565922	1	1	1

DAVID Functional Annotation Clustering Analysis of genes that are up-regulated upon TRASH-ASO treatment (Enrichment Score >2)

Annotation Cluster 1	Enrichment Score: 2.1206711907738813											
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Bonferroni	Benjamini	FDR
GOTERM_MF_DIRECT	GO:0004713~protein tyrosine kinase activity	9	2.1	0.005	ENSG00000182866, ENSG00000143479, ENSG00000146648, ENSG00000198223, ENSG00000100368, ENSG00000157168, ENSG00000138675, ENSG0000	334	133	16881	3.4201297	0.906337	0.337463	0.3

					0143322, ENSG0000 0167601							
GOTER M_MF_DIRECT	GO:0005088~Ras guanyl-nucleotide exchange factor activity	8	1.8	0.008	ENSG0000 0146648, ENSG0000 0058335, ENSG0000 0198223, ENSG0000 0127914, ENSG0000 0100368, ENSG0000 0157168, ENSG0000 0100385, ENSG0000 0138675	334	115	16881	3.5159594	0.976867	0.41687	0.4
GOTER M_BP_DIRECT	GO:0018108~peptidyl-tyrosine phosphorylation	9	2.1	0.011	ENSG0000 0143479, ENSG0000 0108798, ENSG0000 0146648, ENSG0000 0198223, ENSG0000 0100368, ENSG0000 0157168, ENSG0000 0138675, ENSG0000 0143322, ENSG0000 0167601	334	153	16792	2.9573794	1	0.894092	0.9

[0222] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A single or double-stranded nucleic acid of 12-50 nucleotides in length comprising at least 12 nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12, wherein introduction of the single or double-stranded nucleic acid into a cell expressing long non-coding RNA (lncRNA) BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201 inhibits expression of the lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201.

2. The single or double-stranded nucleic acid of claim 1 comprising at least 12 contiguous nucleotides complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12.

3 . The single or double-stranded nucleic acid of claim 1, wherein the single or double-stranded nucleic acid is a single-stranded nucleic acid that is an antisense polynucleotide or a ribozyme that targets lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201.

4. The single-stranded nucleic acid of claim 3 comprising the sequence of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO:41 or SEQ ID NO:47.

5. The single or double-stranded nucleic acid of claim 1, wherein the single or double-stranded nucleic acid is a double-stranded nucleic acid that is a small interfering RNA (siRNA) or a short hairpin RNA (shRNA) that targets lncRNA BX470102.3-008, AC004540.4-

001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201.

6. The double-stranded nucleic acid of claim 5 comprising a sense strand and an antisense strand, wherein the sense strand and the antisense comprise the sequence of SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 42 and SEQ ID NO: 50; SEQ ID NO: 43 and SEQ ID NO: 51; SEQ ID NO: 44 and SEQ ID NO: 52; SEQ ID NO: 45 and SEQ ID NO: 53; or SEQ ID NO: 46 and SEQ ID NO: 54.

7. The single or double-stranded nucleic acid of claim 1, wherein the single or double-stranded nucleic acid is a single-stranded nucleic acid that is a guide RNA (gRNA) that targets a polynucleotide encoding lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201.

8. An antisense polynucleotide comprising SEQ ID NO: 48, wherein introduction of the antisense polynucleotide into a cell expressing HNRNPA2/B1 inhibits expression of HNRNPA2/B1.

9. An antisense polynucleotide comprising SEQ ID NO: 49, wherein introduction of the antisense polynucleotide into a cell expressing SNX10 inhibits expression of SNX10.

10. The single or double-stranded nucleic acid of any one of claims 1-11, comprising at least one modified nucleotide.

11. The single or double-stranded nucleic acid of any one of claims 10, wherein the modified nucleotide comprises a modification selected from the group consisting of a sugar modification, a nucleic acid base modification, and a phosphate backbone modification.

12. The single or double-stranded nucleic acid of claim 11, wherein the 2'-sugar modification is selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA, and locked nucleic acid (LNA) modification.

13. The single or double-stranded nucleic acid of claim 11, wherein the phosphate backbone modification is a 5' phosphorylation.

14. The double-stranded nucleic acid of claim 5 or claim 6, wherein the double-stranded nucleic acid and comprises a 1-6 nucleotide overhang.

15. A vector comprising the single or double-stranded nucleic acid of any of claims 1-14.

16. The vector of claim 15, wherein the vector is a viral vector.

17. The vector of claim 16, wherein the viral vector is a retroviral, a lentiviral, or an adeno-associated viral (AAV) vector.

18. A pharmaceutical composition comprising the single or double-stranded nucleic acid of any one of claims 1-14 or the vector of claim 15 and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition of claim 18, further comprising a specific inhibitor of one or more kinases selected from the group consisting of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, and RAF.

20. The pharmaceutical composition of claim 19, wherein the specific inhibitor is selected from the group consisting of trametinib, volasertib, tozasertib, alisertib, Bay-299, and CeMMEC1.

21. The pharmaceutical composition of claim 18, wherein the pharmaceutically acceptable carrier comprises a copolymer, a lipid, or a nanoparticle.

22. The pharmaceutical composition of claim 21, wherein the nanoparticle is a liposomal nanoparticle.

23. A method of inhibiting cancer cell that is dependent on MAPK pathway hyperactivation, the method comprising contacting the single or double-stranded nucleic acid of any one of claims 1-14, the vector of claim 15 or claim 16, or the pharmaceutical composition of any one of claims 18-22 with the cancer cell such that expression of lncRNA BX470102.3-008, AC004540.4-001, AC004540.4-002, RP11-7011.3-001, RP11-7011.3-003, RP11-7011.3-002, RN7SL1-202, RN7SL1-201, ARF-AS1-201, ARF-AS1-202, ARF-AS1-203 or AL157871.4-201 is inhibited.

24. The method of claim 23, wherein the cancer cell is a neuroblastoma ras sarcoma viral oncogene homolog (NRAS)-mutated cancer cell.

25. The method of claim 23, wherein the cancer cell is a BRAF-mutated cancer cell.

26. The method of claim 23, wherein the cancer cell is in a human and the method comprises administering a therapeutically-effective amount of the single or double-stranded nucleic acid to the human.

27. The method of claim 23, further comprising contacting the cancer cell with a specific inhibitor of one or more kinases selected from the group consisting of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, and RAF.

28. The method of claim 27, wherein the specific inhibitor is selected from the group consisting of trametinib, volasertib, tozasertib, alisertib, Bay-299, CeMMEC1.

29. A method of inhibiting a cancer cell that is dependent on MAPK pathway hyperactivation cancer cell, the method comprising contacting the cancer cell with a specific inhibitor of one or more kinases selected from the group consisting of MEK, PLK1, TAF, AURKA, HER, PTK2, PKD, PKC, IKBK, MAP3K, PIM, SRC, PAK, AKT, ERK, and RAF in an amount to inhibit the cancer cell growth.

30. The method of claim 29, wherein the cancer cell is a neuroblastoma ras sarcoma viral oncogene homolog (NRAS)-mutated cancer cell.

31. The method of claim 29, wherein the cancer cell is a BRAF-mutated cancer cell.

32. The method of claim 29, wherein the specific inhibitor is selected from the group consisting of trametinib, volasertib, tozasertib, alisertib, Bay-299, and CeMMEC1.

33. The method of claim 23 or 29, wherein the cancer cell is in a human.

34. The method of claim 23 or 29, wherein the cancer cell is a melanoma cell.

35. The method of claim 23 or 29, wherein the cancer cell is a metastatic melanoma cancer cell.

36. The method of claim 23 or 29, wherein the cancer cell is a MEK-therapy resistant cancer cell.

37. The method of claim 23 or 29, wherein the cancer cell is a liver cancer cell or a melanoma cell.

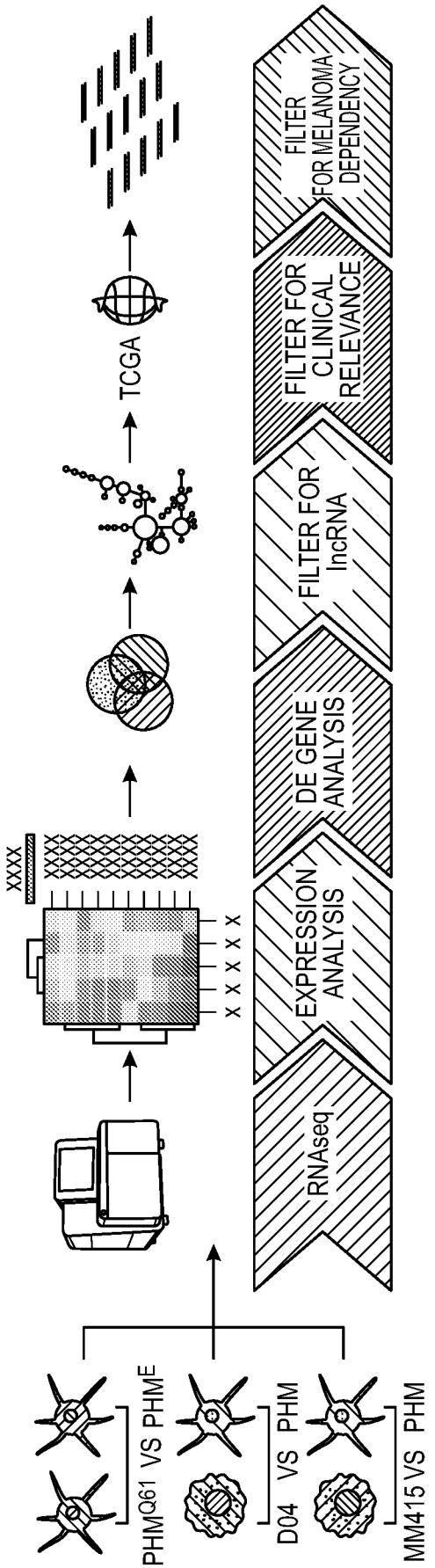
RNAseq
EXPRESSION ANALYSIS
DE GENE ANALYSIS
FILTER FOR lncRNA
FILTER FOR CLINICAL RELEVANCE
FILTER FOR MELANOMA DEPENDENCY
XXXX
X X X X X
TCGA
PHMQ61 VS PHME
D04 VS PHM
MM415 VS PHM

FIG. 1A

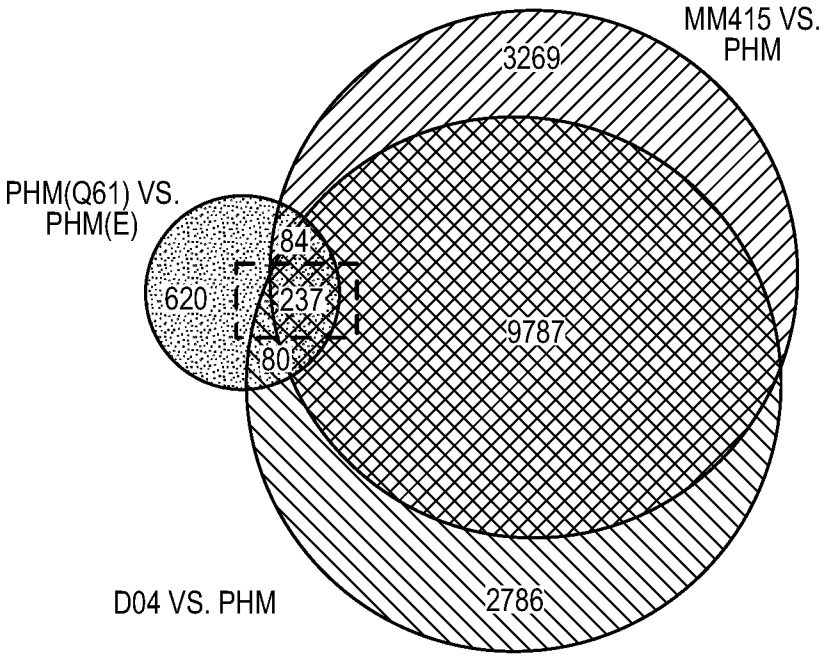
MM415 VS.
PHM
3269
PHM(Q61) VS.
PHM(E)
620
84
237
80
9787
D04 VS. PHM
2786

FIG. 1B

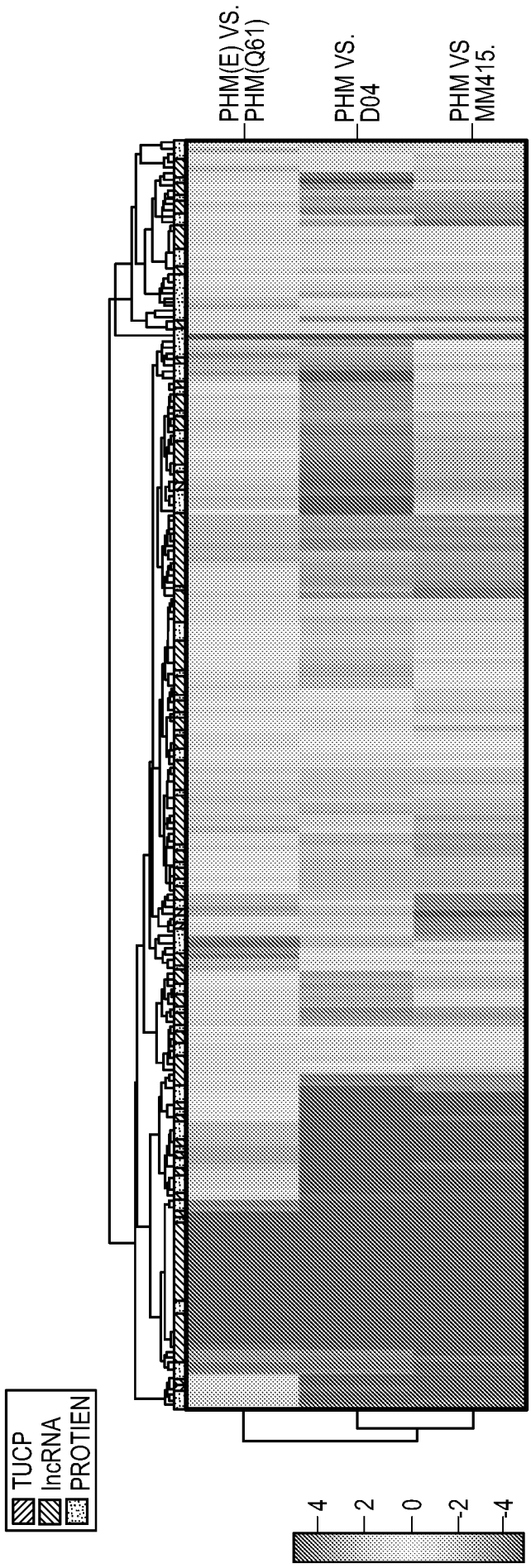
PHM(E) VS. PHM(Q61)
PHM VS. D04
PHM VS MM415.
TUCP
lncRNA
PROTIEN
4
2
0
-2
-4

FIG. 1C

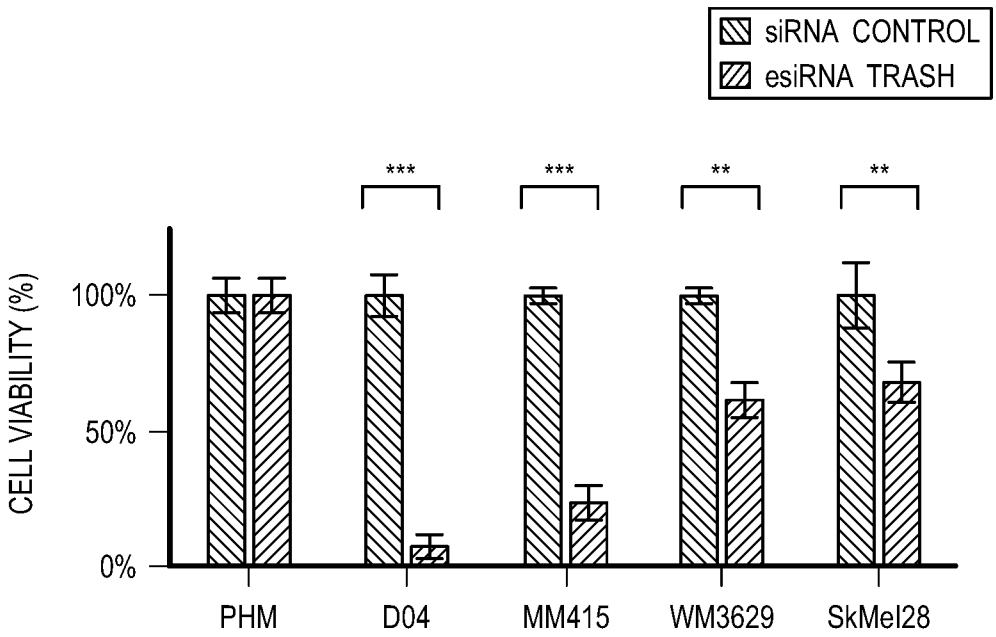
siRNA CONTROL
esiRNA TRASH
***
***
**
**
CELL VIABILITY (%)
100%
50%
0%
PHM
D04
MM415
WM3629
SkMel28

FIG. 1D

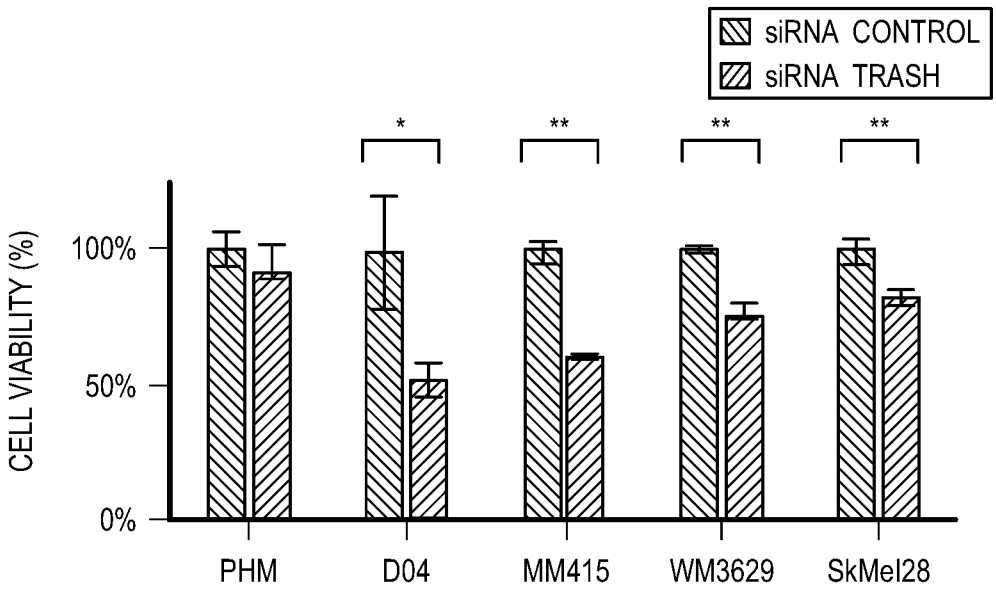
siRNA CONTROL
siRNA TRASH
*
**
**
**
CELL VIABILITY (%)
100%
50%
0%
PHM
D04
MM415
WM3629
SkMel28

FIG. 1E

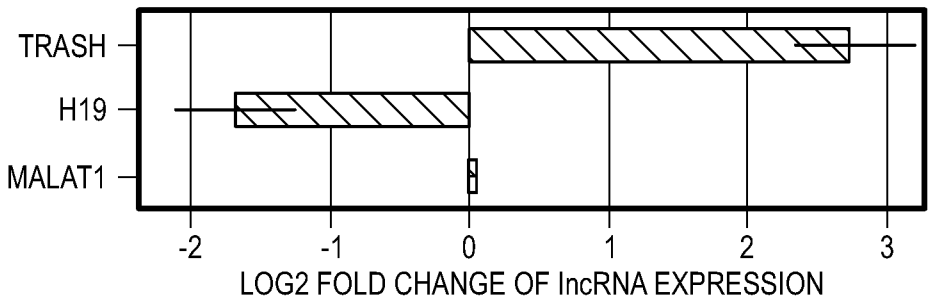

FIG. 2A

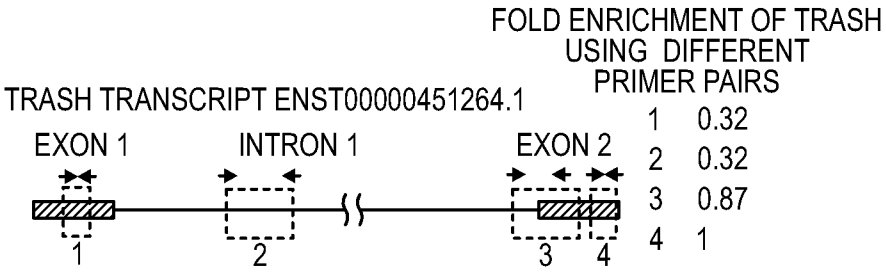

FIG. 2B

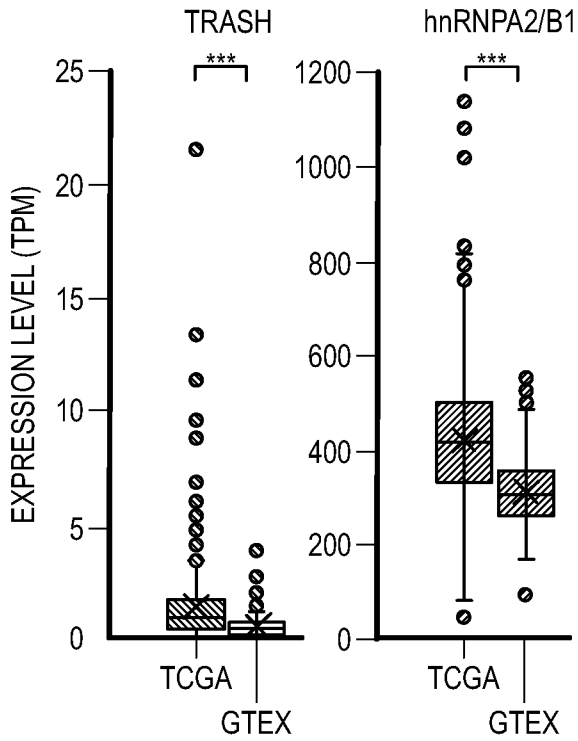

FIG. 2C

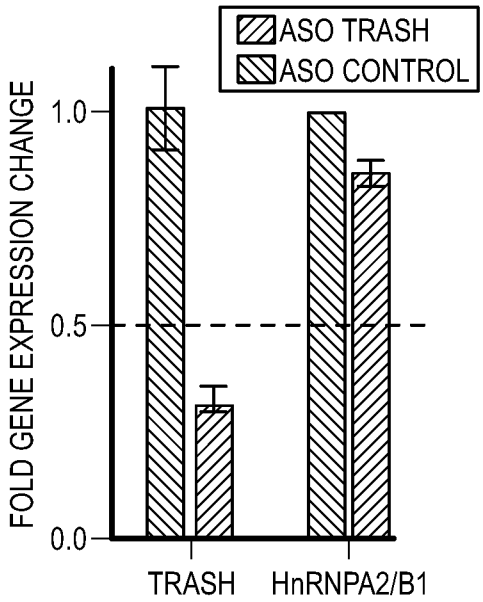

FIG. 2D

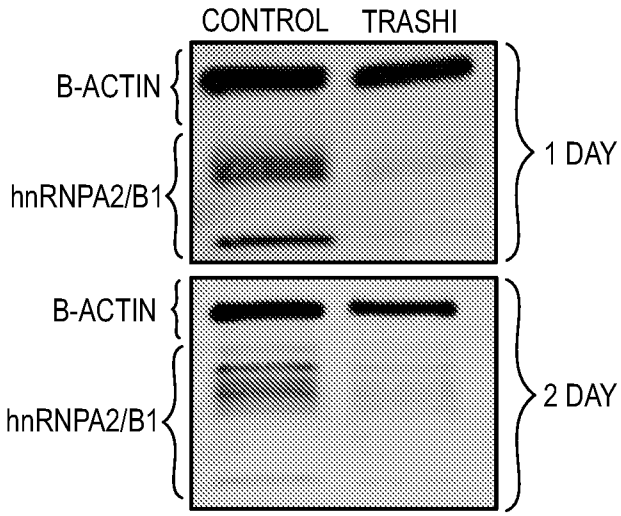

FIG. 2E

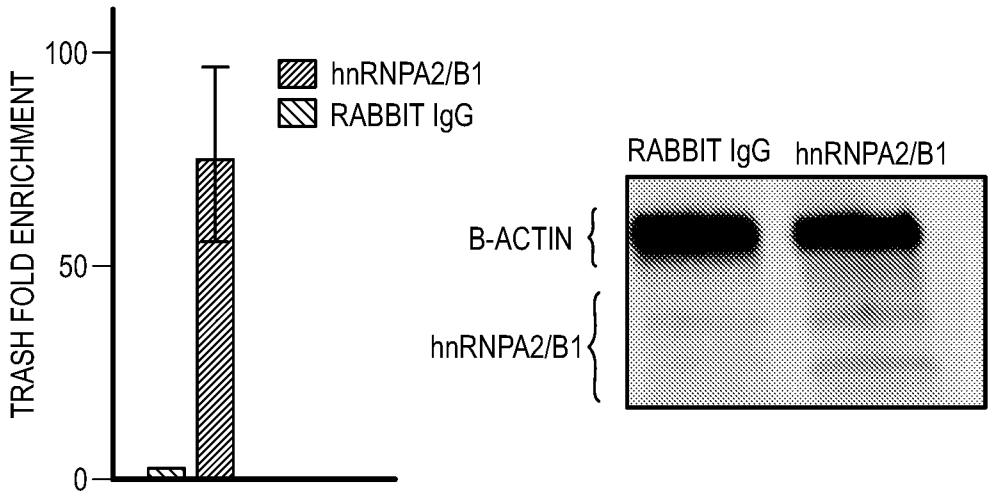

FIG. 2F

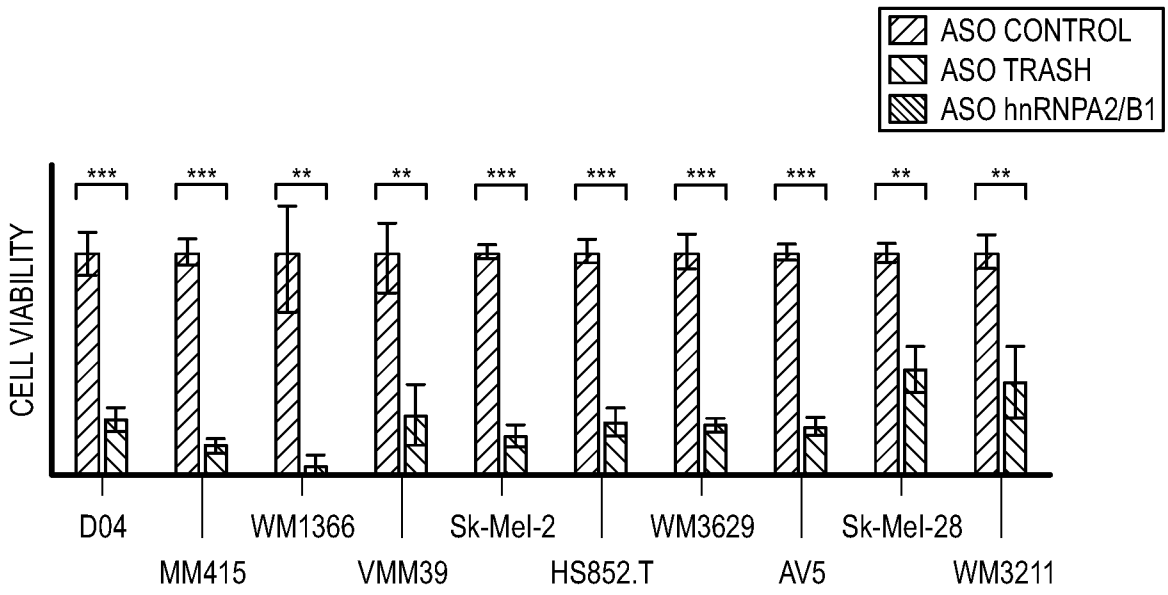
ASO CONTROL
ASO TRASH
ASO hnRNPA2/B1
CELL VIABILITY
***
***
**
**
***
***
***
***
**
**
D04
MM415
WM1366
VMM39
Sk-Mel-2
HS852.T
WM3629
AV5
Sk-Mel-28
WM3211

FIG. 3A

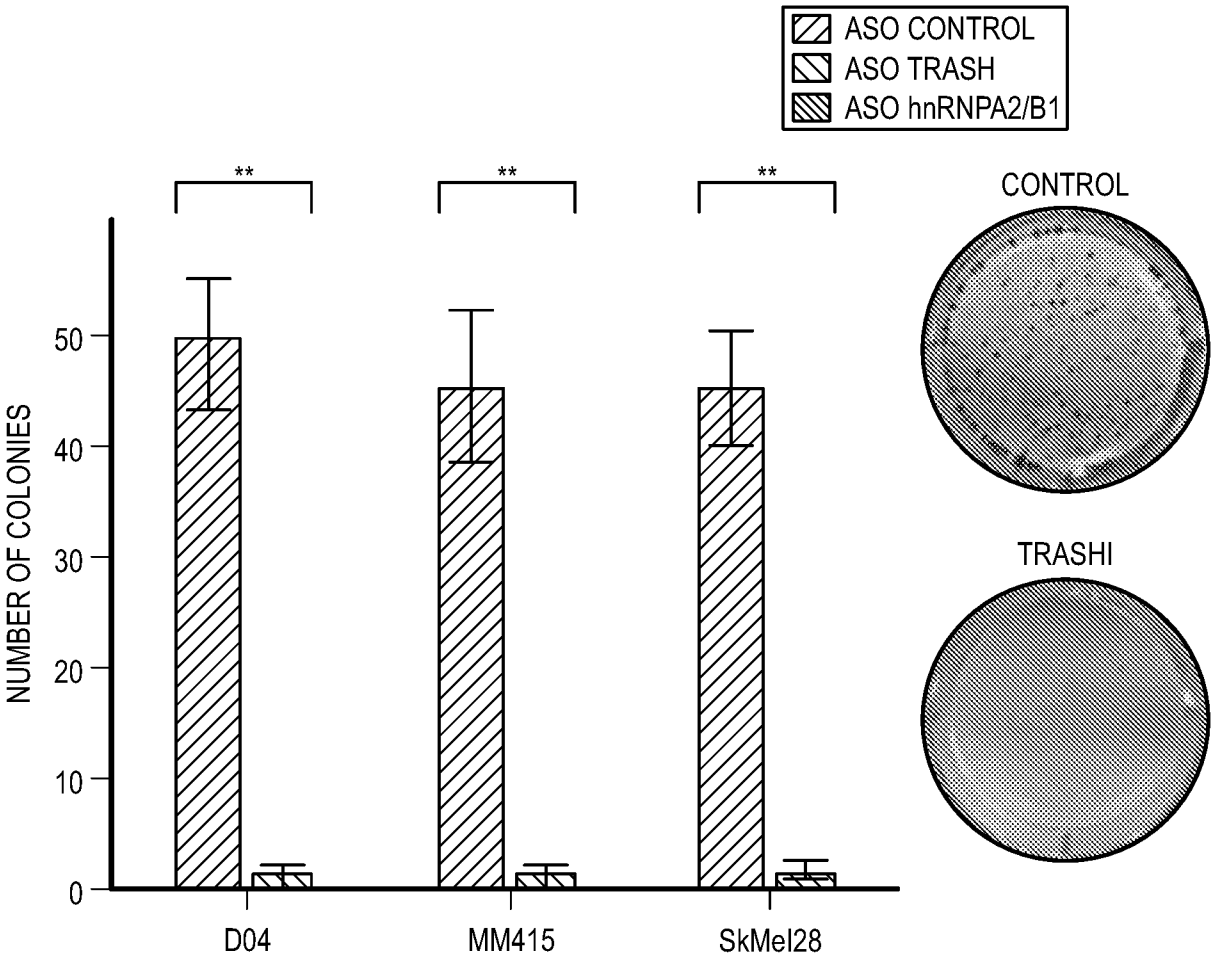
ASO CONTROL
ASO TRASH
ASO hnRNPA2/B1
NUMBER OF COLONIES
0
10
20
30
40
50
**
**
**
D04
MM415
SkMel28
CONTROL
TRASHI

FIG. 3B

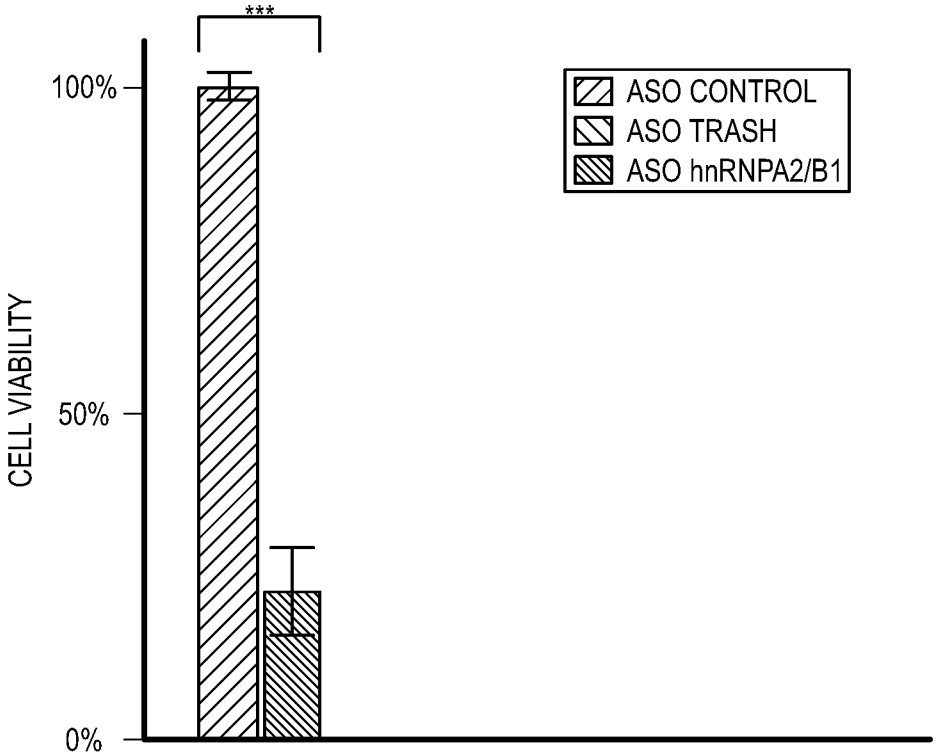
***
100%
50%
0%
CELL VIABILITY
ASO CONTROL
ASO TRASH
ASO hnRNPA2/B1

FIG. 3C

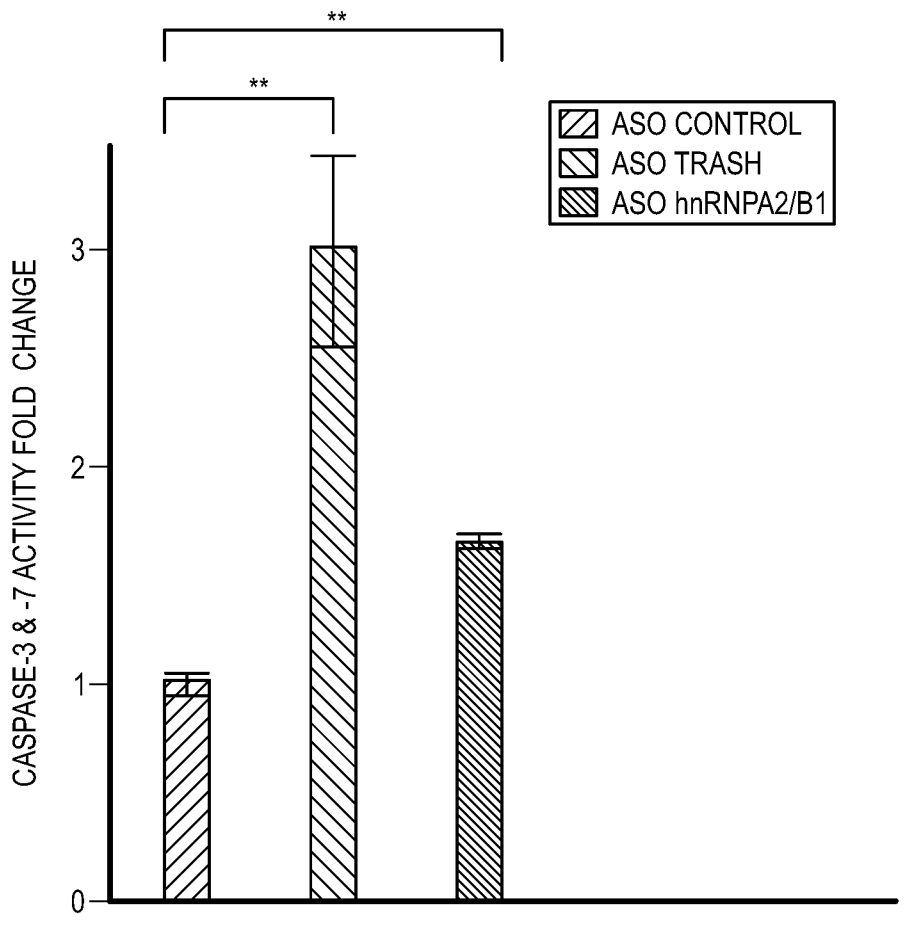
**
**
3
2
1
0
CASPASE-3 & -7 ACTIVITY FOLD CHANGE
ASO CONTROL
ASO TRASH
ASO hnRNPA2/B1

FIG. 3D

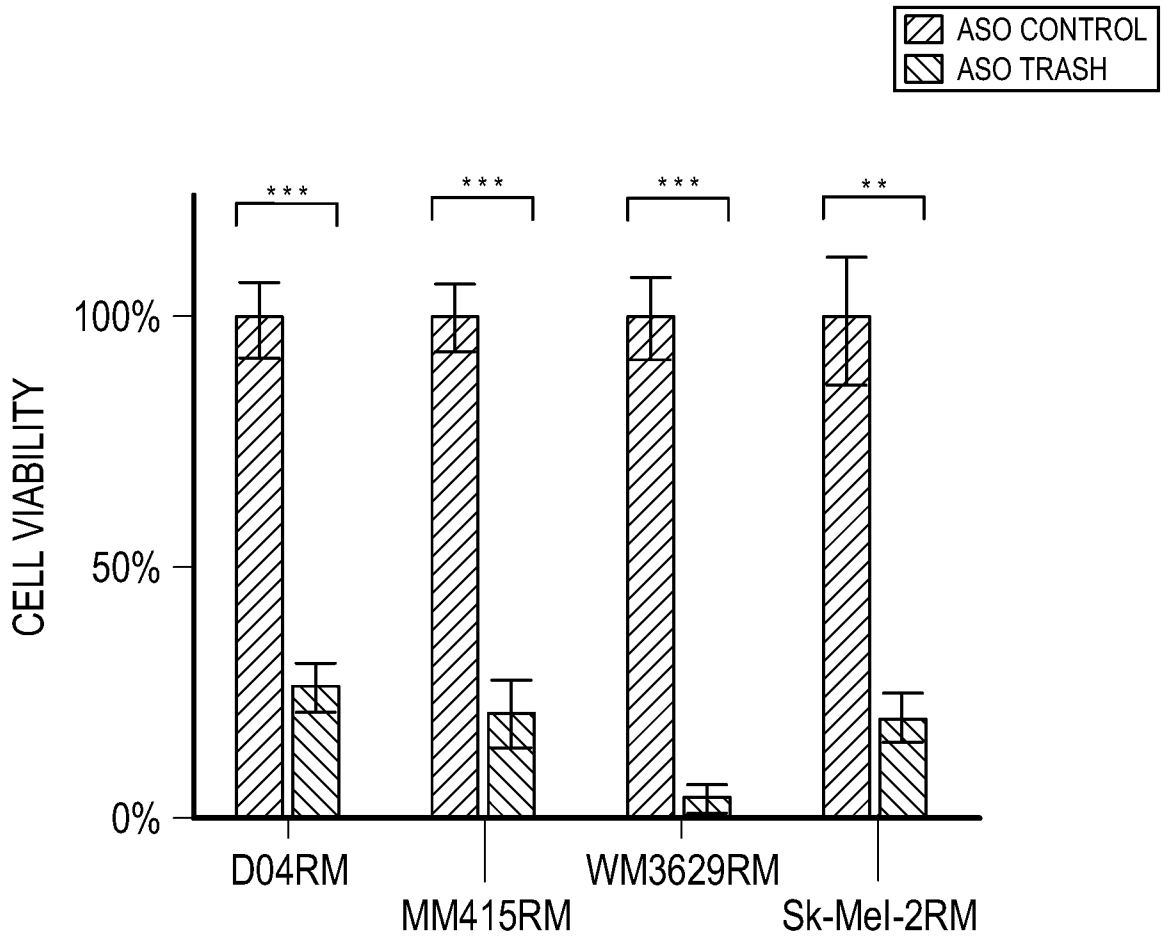
ASO CONTROL
ASO TRASH
***
***
***
**
100%
50%
0%
CELL VIABILITY
D04RM
MM415RM
WM3629RM
Sk-Mel-2RM

FIG. 4A

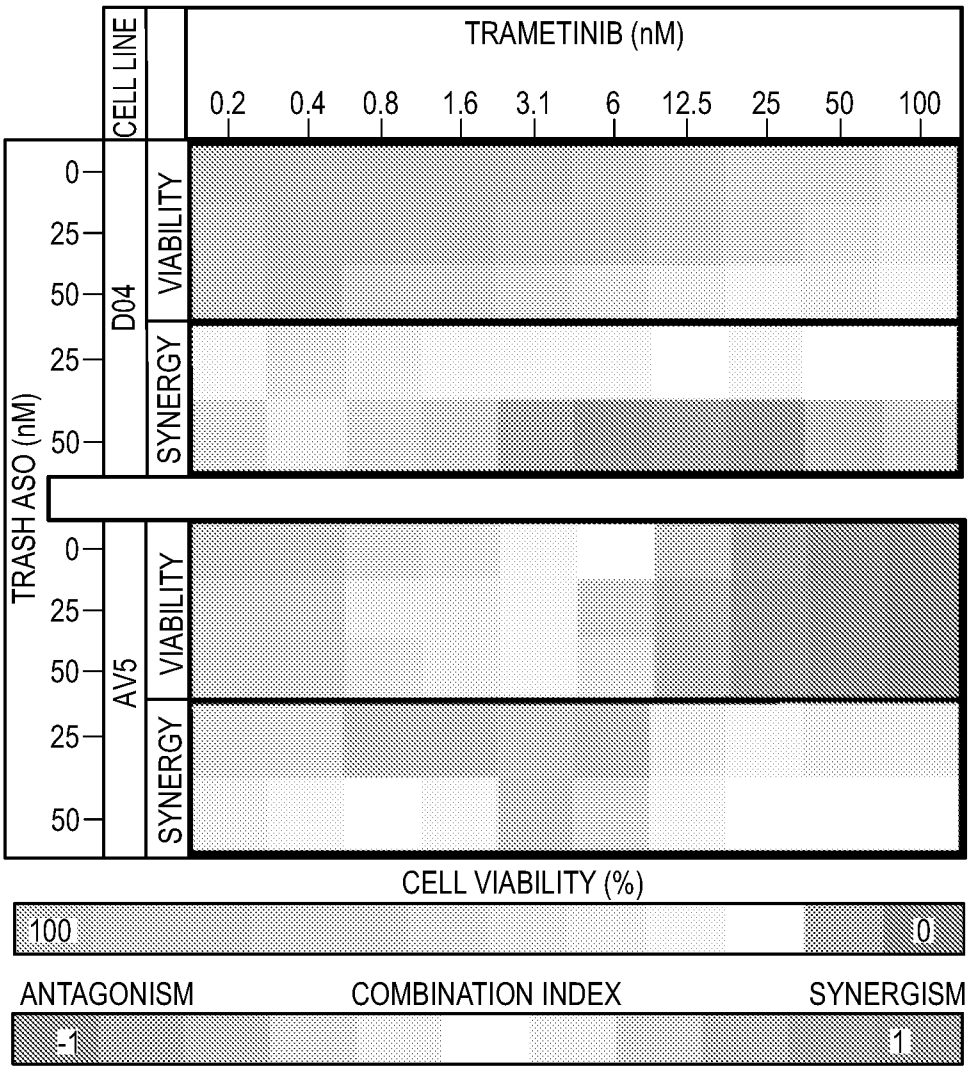
TRAMETINIB (nM)
0.2
0.4
0.8
1.6
3.1
6
12.5
25
50
100
CELL LINE
D04
AV5
VIABILITY
SYNERGY
TRASH ASO (nM)
0
25
50
CELL VIABILITY (%)
100
0
ANTAGONISM
COMBINATION INDEX
SYNERGISM
-1
1

FIG. 4B

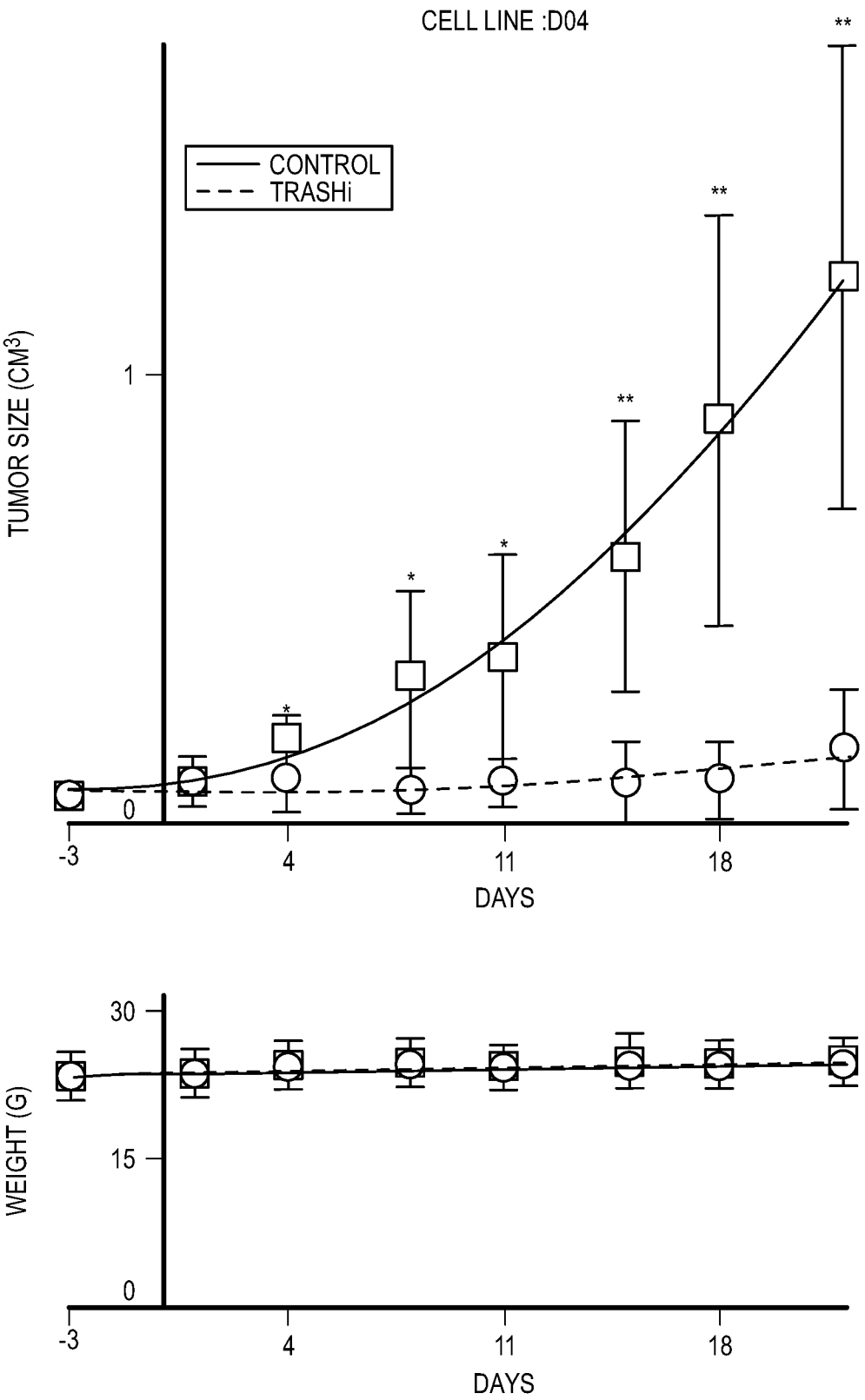
CELL LINE :D04
CONTROL
TRASHi
TUMOR SIZE (CM3)
1
0
-3
4
11
18
DAYS
*
**
WEIGHT (G)
30
15
0
-3
4
11
18
DAYS

FIG. 4C

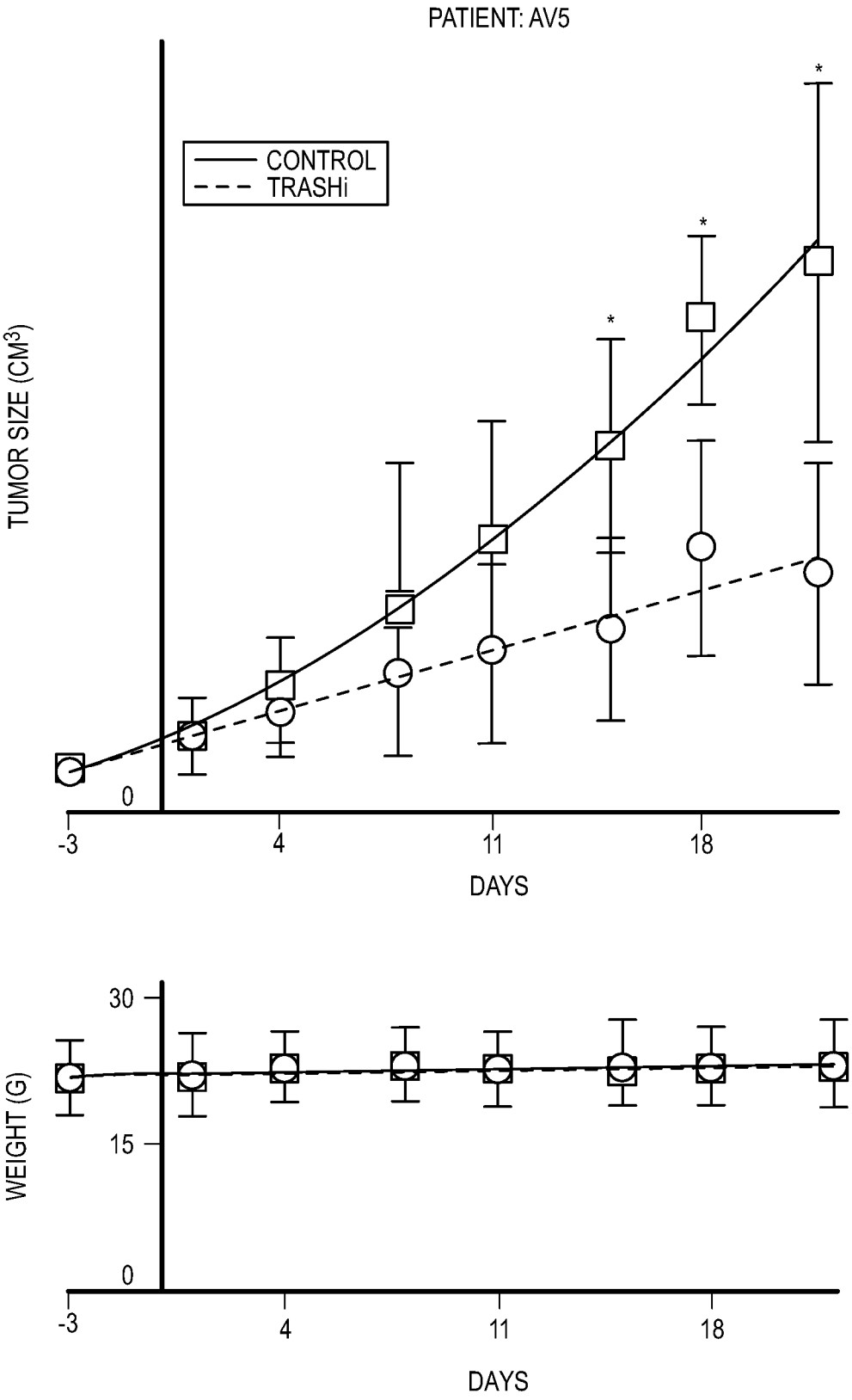

FIG. 4C (CONTINUED)

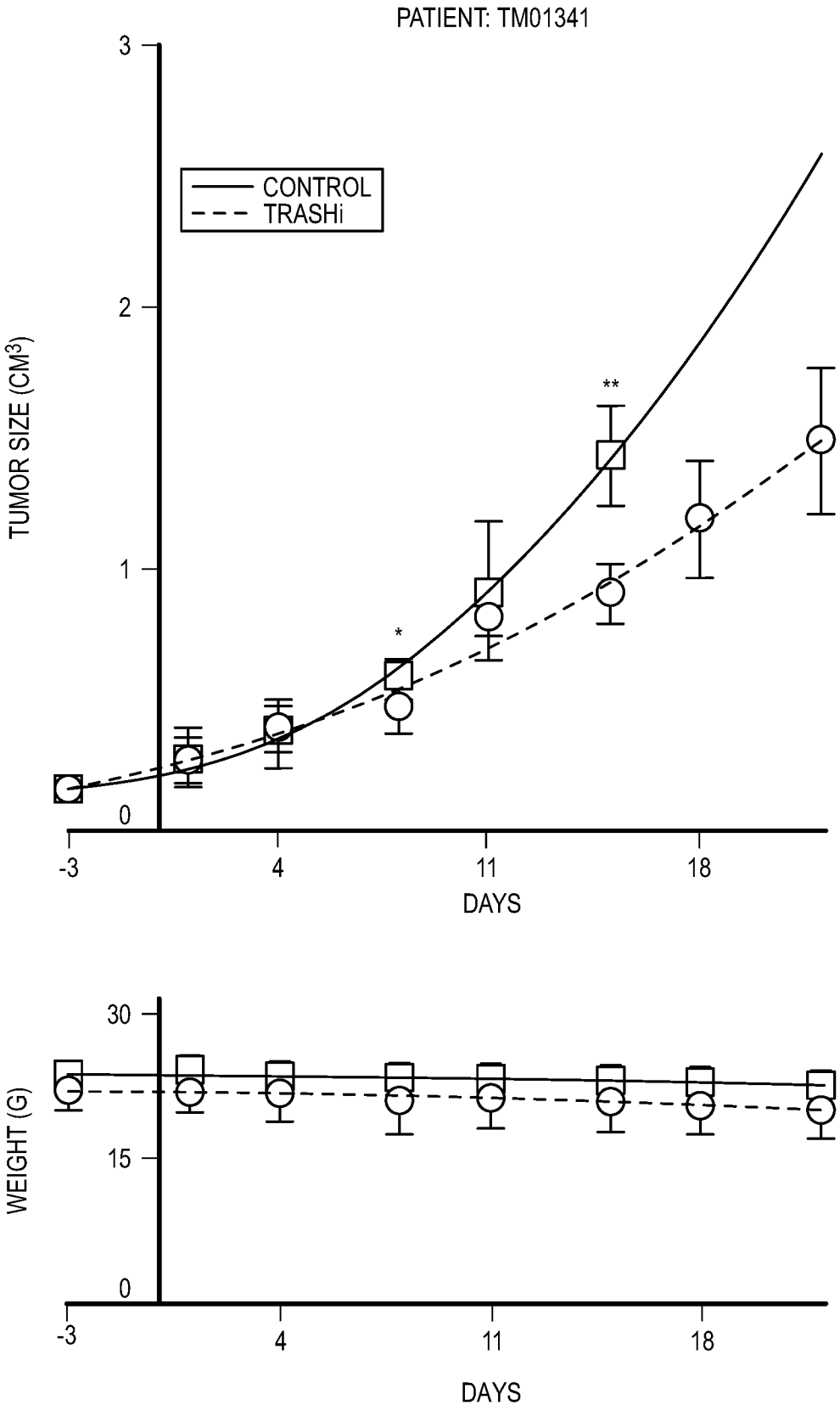

FIG. 4C (CONTINUED)

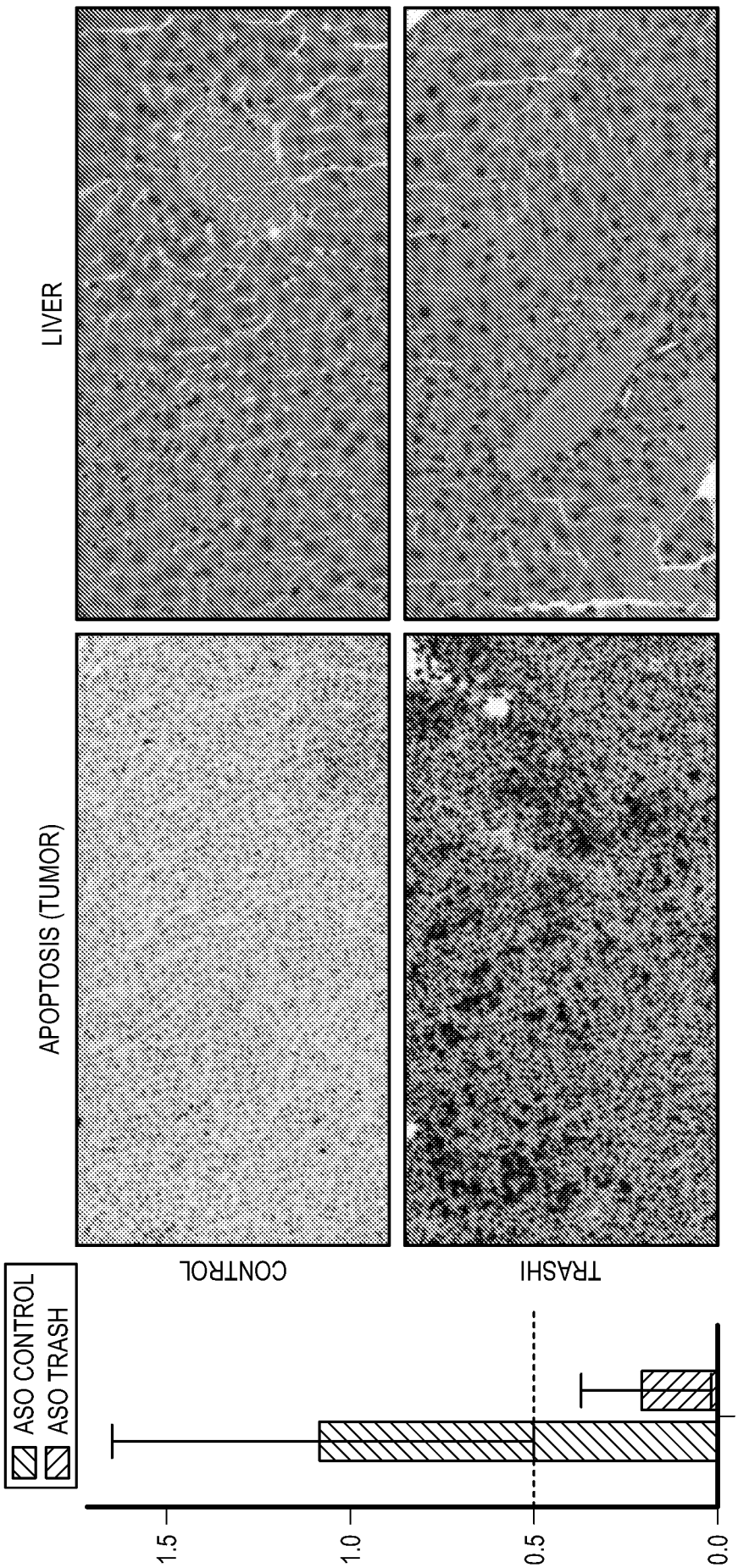
LIVER
APOPTOSIS (TUMOR)
CONTROL
TRASHI
ASO CONTROL
ASO TRASH
TRASH
1.5
1.0
0.5
0.0
FOLD GENE EXPRESSION CHANGE

FIG. 4E

FIG. 4D

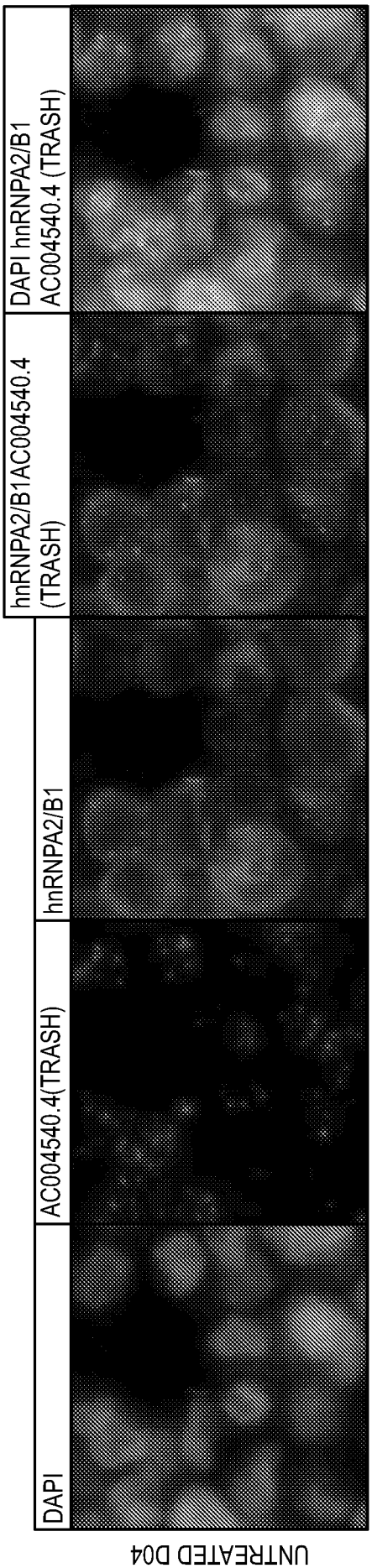
DAPI
AC004540.4(TRASH)
hnRNPA2/B1
hnRNPA2/B1AC004540.4 (TRASH)
DAPI hnRNPA2/B1 AC004540.4 (TRASH)
UNTREATED D04

FIG. 5A

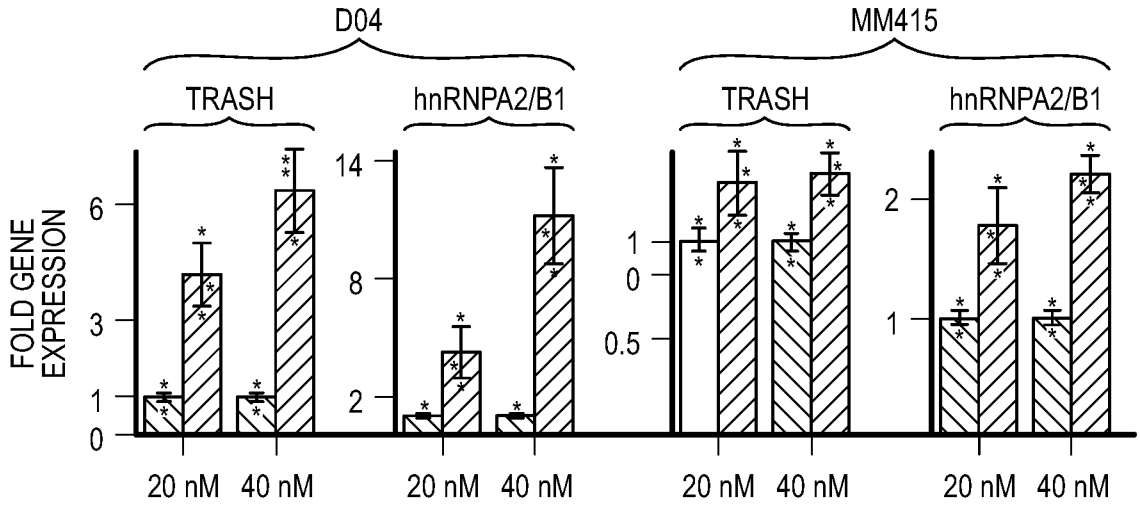
D04
MM415
TRASH
hnRNPA2/B1
TRASH
hnRNPA2/B1
FOLD GENE EXPRESSION
20 nM 40 nM
20 nM 40 nM
20 nM 40 nM
20 nM 40 nM

FIG. 5B

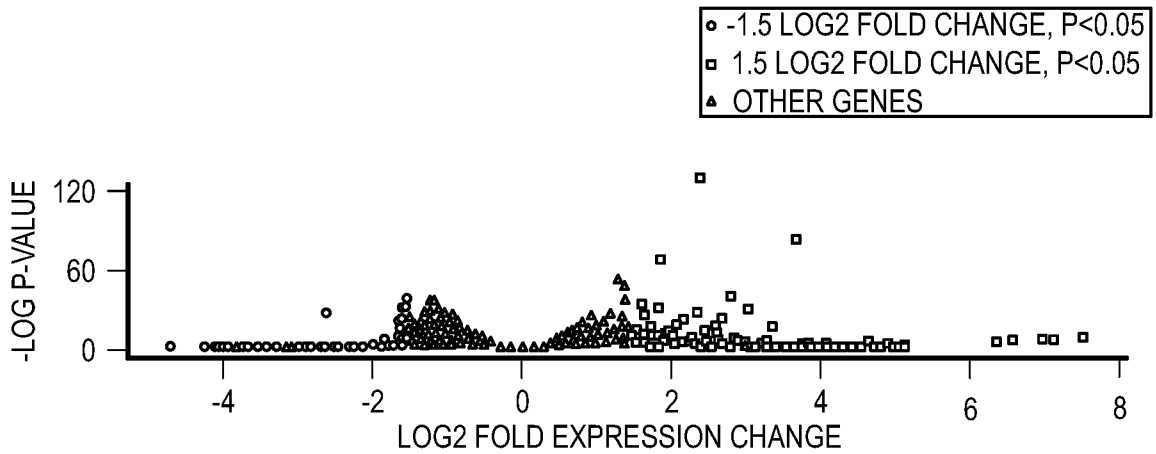
-1.5 LOG2 FOLD CHANGE, P<0.05
1.5 LOG2 FOLD CHANGE, P<0.05
OTHER GENES
-LOG P-VALUE
LOG2 FOLD EXPRESSION CHANGE

FIG. 5C

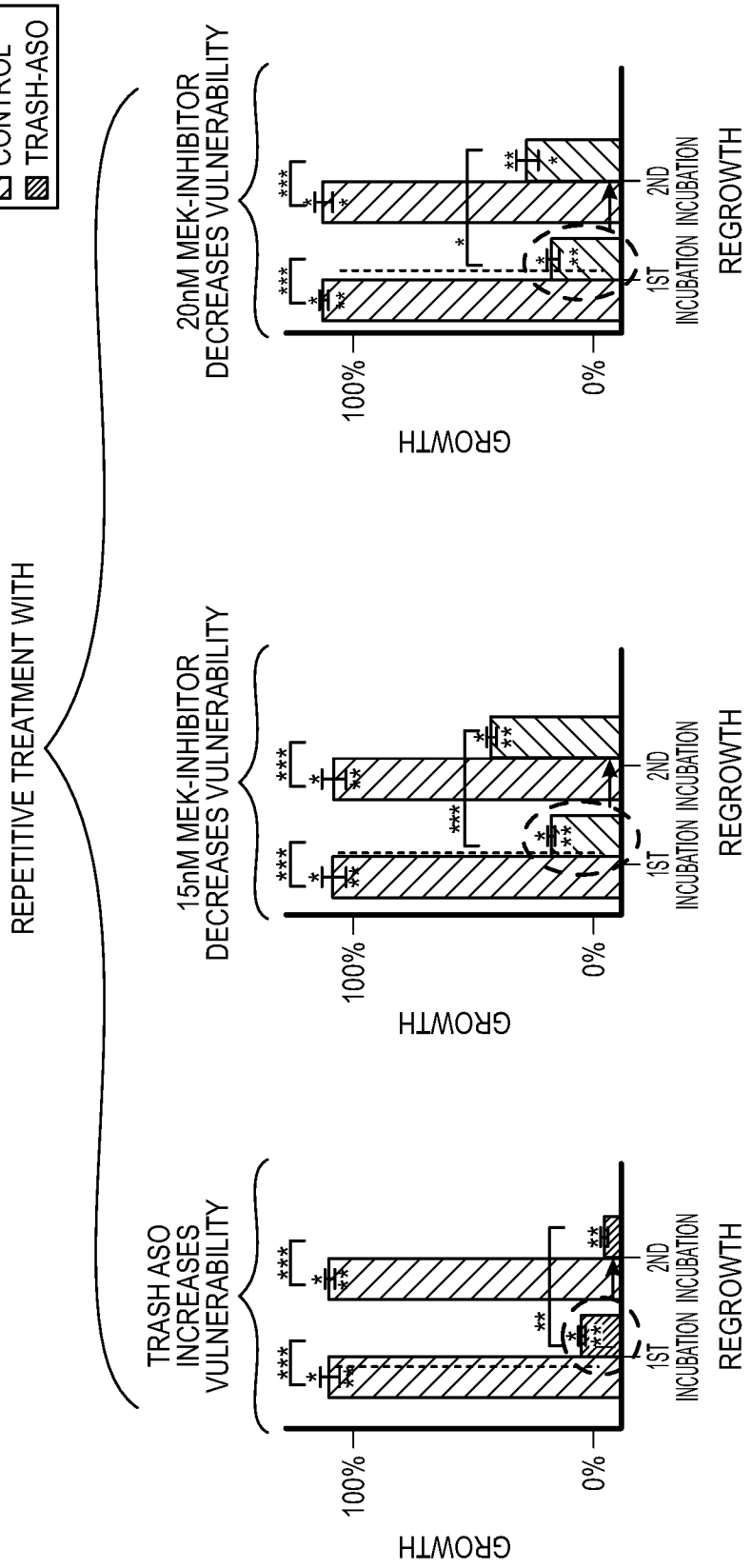
TRAMETINIB
CONTROL
TRASH-ASO
REPETITIVE TREATMENT WITH
TRASH ASO INCREASES VULNERABILITY
15nM MEK-INHIBITOR DECREASES VULNERABILITY
20nM MEK-INHIBITOR DECREASES VULNERABILITY
GROWTH
100%
0%
1ST INCUBATION
2ND INCUBATION
REGROWTH

FIG. 5D

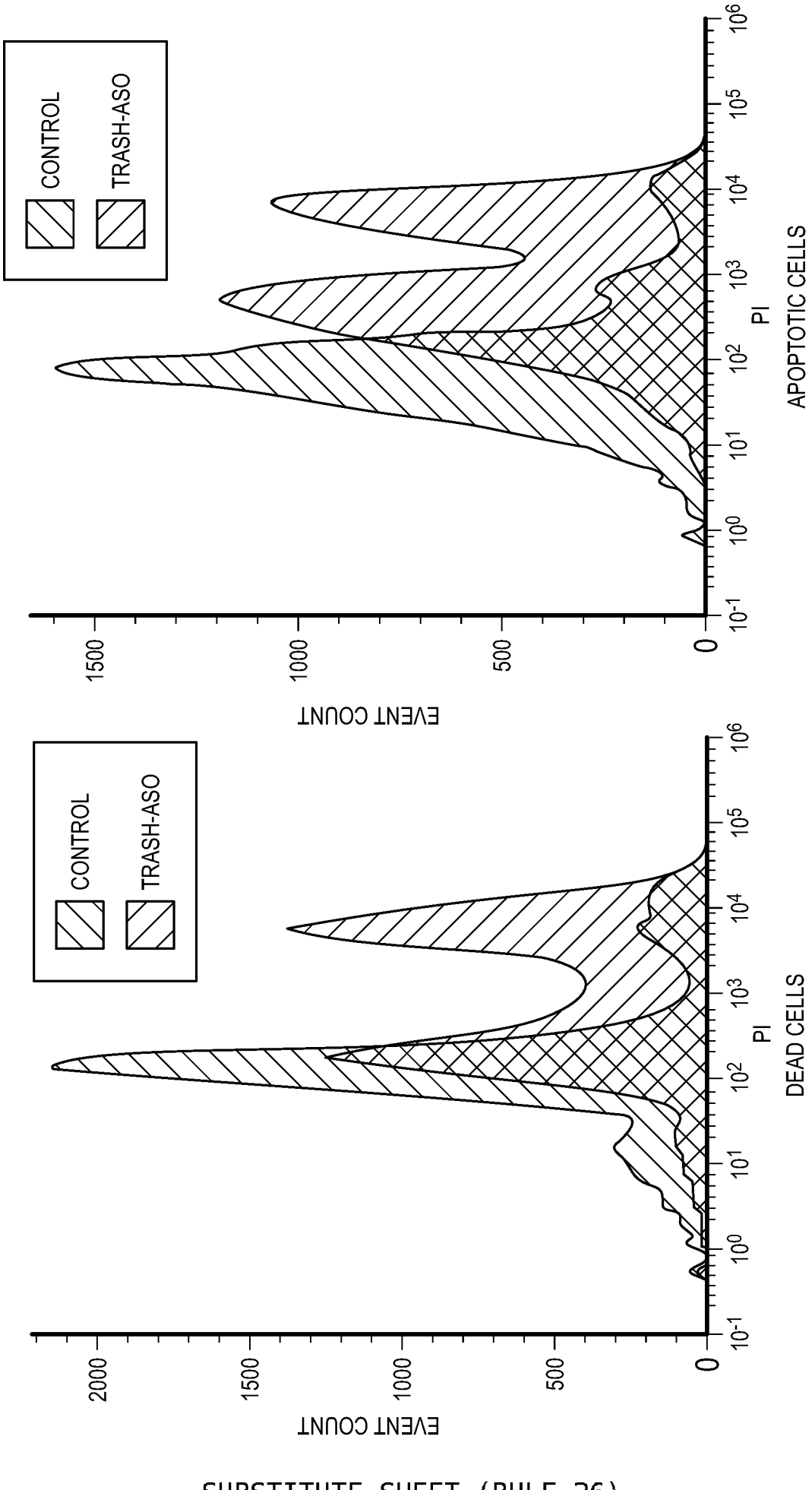
CONTROL
TRASH-ASO
EVENT COUNT
0
500
1000
1500
2000
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
10^{4}
10^{5}
10^{6}
PI
DEAD CELLS
CONTROL
TRASH-ASO
EVENT COUNT
0
500
1000
1500
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
10^{4}
10^{5}
10^{6}
PI
APOPTOTIC CELLS

FIG. 5E

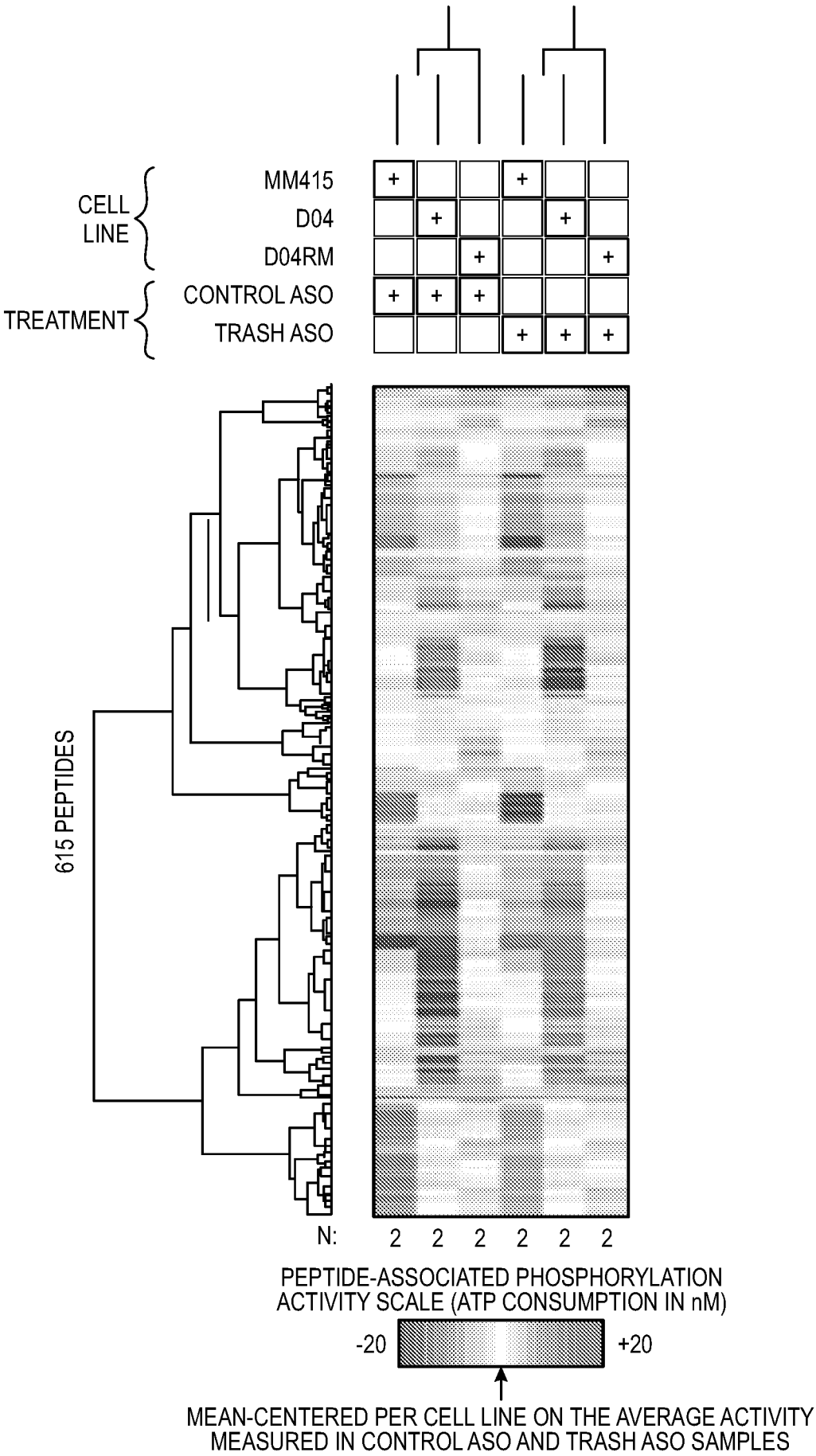
CELL LINE
MM415
D04
D04RM
TREATMENT
CONTROL ASO
TRASH ASO
615 PEPTIDES
N:
2 2 2 2 2 2
PEPTIDE-ASSOCIATED PHOSPHORYLATION ACTIVITY SCALE (ATP CONSUMPTION IN nM)
-20
+20
MEAN-CENTERED PER CELL LINE ON THE AVERAGE ACTIVITY MEASURED IN CONTROL ASO AND TRASH ASO SAMPLES

FIG. 6A

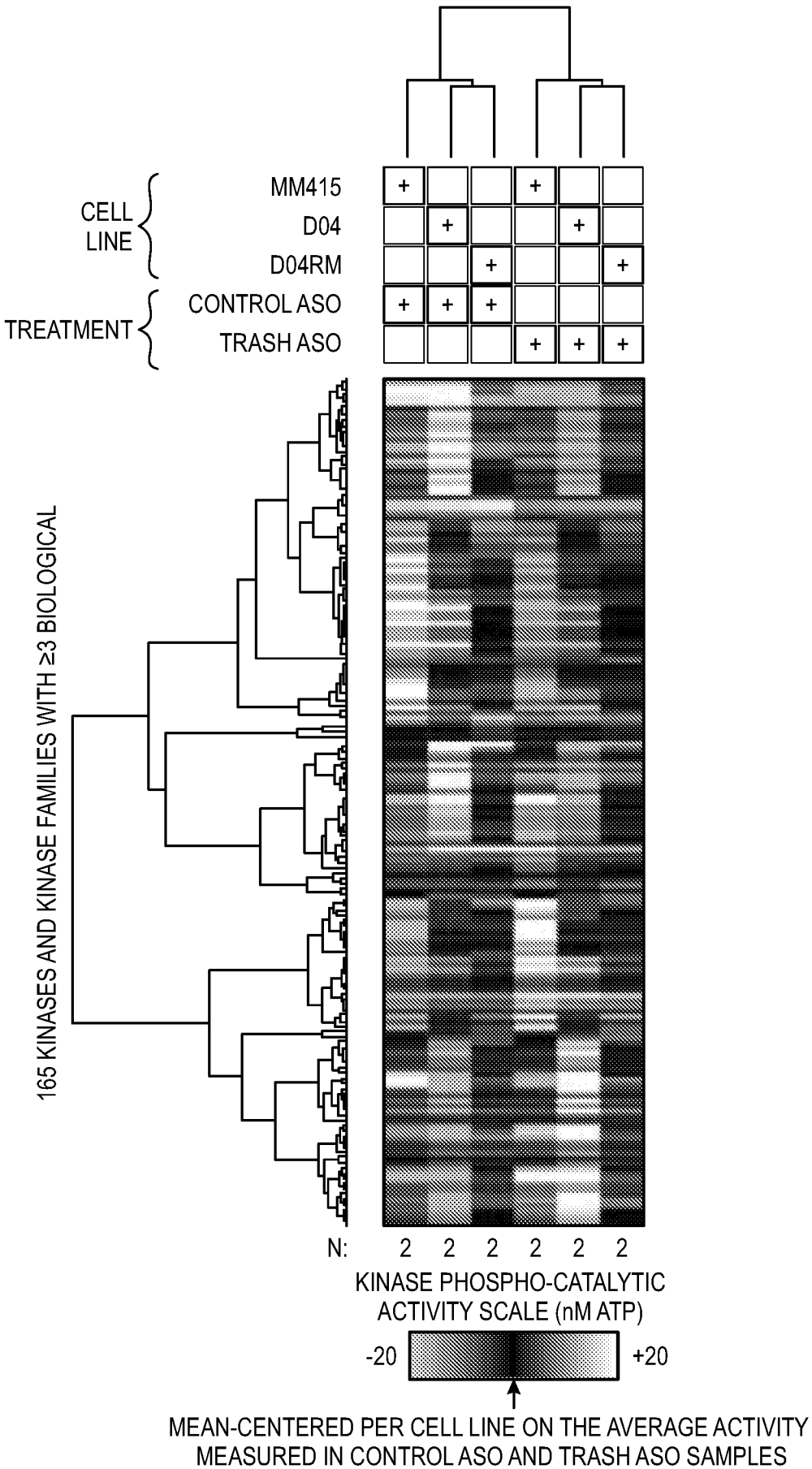
CELL LINE
MM415
D04
D04RM
TREATMENT
CONTROL ASO
TRASH ASO
165 KINASES AND KINASE FAMILIES WITH ≥3 BIOLOGICAL
N: 2 2 2 2 2 2
KINASE PHOSPHO-CATALYTIC ACTIVITY SCALE (nM ATP)
-20
+20
MEAN-CENTERED PER CELL LINE ON THE AVERAGE ACTIVITY MEASURED IN CONTROL ASO AND TRASH ASO SAMPLES

FIG. 6B

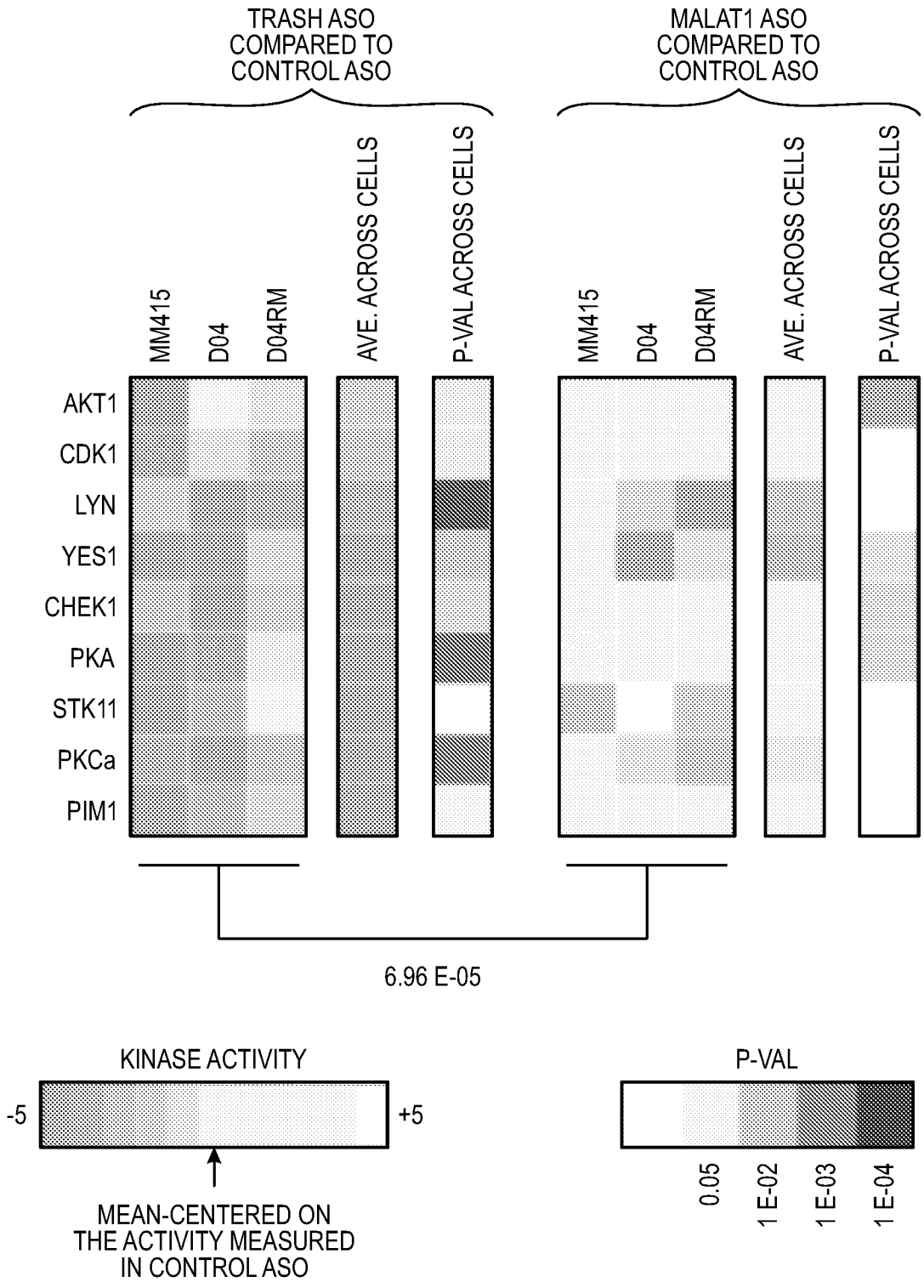
TRASH ASO COMPARED TO CONTROL ASO
MALAT1 ASO COMPARED TO CONTROL ASO
MM415
D04
D04RM
AVE. ACROSS CELLS
P-VAL ACROSS CELLS
AKT1
CDK1
LYN
YES1
CHEK1
PKA
STK11
PKCa
PIM1
6.96 E-05
KINASE ACTIVITY
-5
+5
MEAN-CENTERED ON THE ACTIVITY MEASURED IN CONTROL ASO
P-VAL
0.05
1 E-02
1 E-03
1 E-04

FIG. 6C

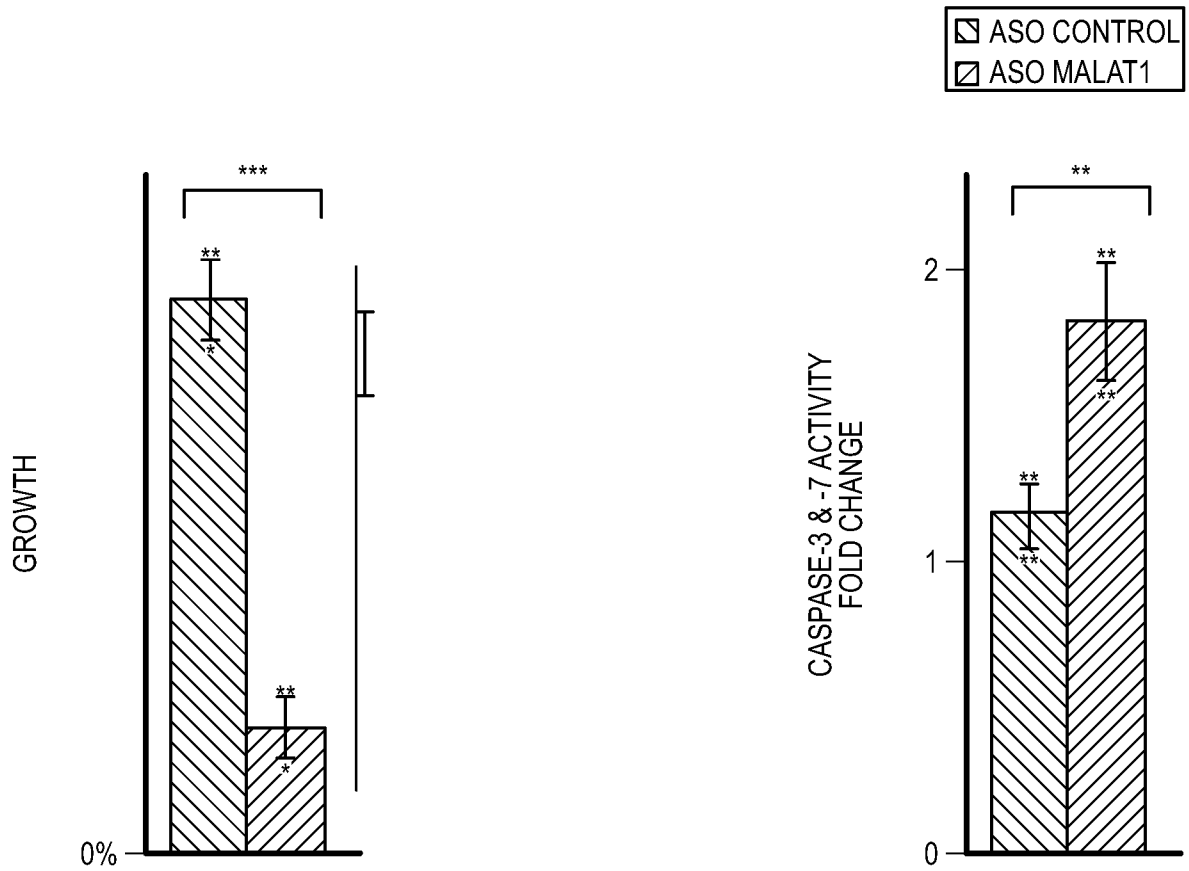
ASO CONTROL
ASO MALAT1
GROWTH
0%
***
**
*
**
*
CASPASE-3 & -7 ACTIVITY
FOLD CHANGE
2
1
0
**
**
**
**
**

FIG. 6D

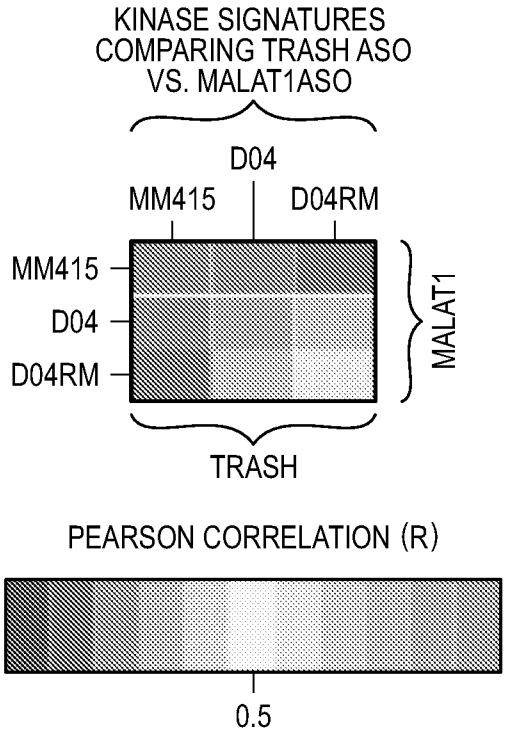
KINASE SIGNATURES
COMPARING TRASH ASO
VS. MALAT1ASO
D04
MM415
D04RM
MM415
D04
D04RM
MALAT1
TRASH
PEARSON CORRELATION (R)
0.5

FIG. 6E

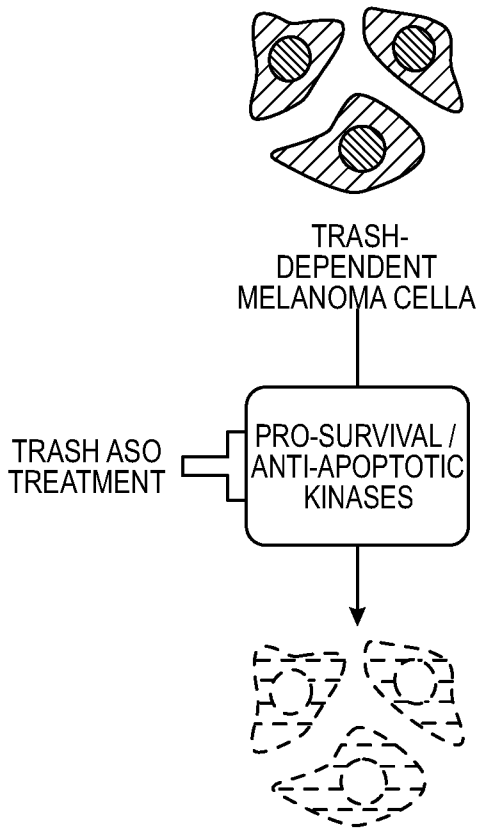
TRASH-
DEPENDENT
MELANOMA CELLA
TRASH ASO
TREATMENT
PRO-SURVIVAL /
ANTI-APOPTOTIC
KINASES

FIG. 6F

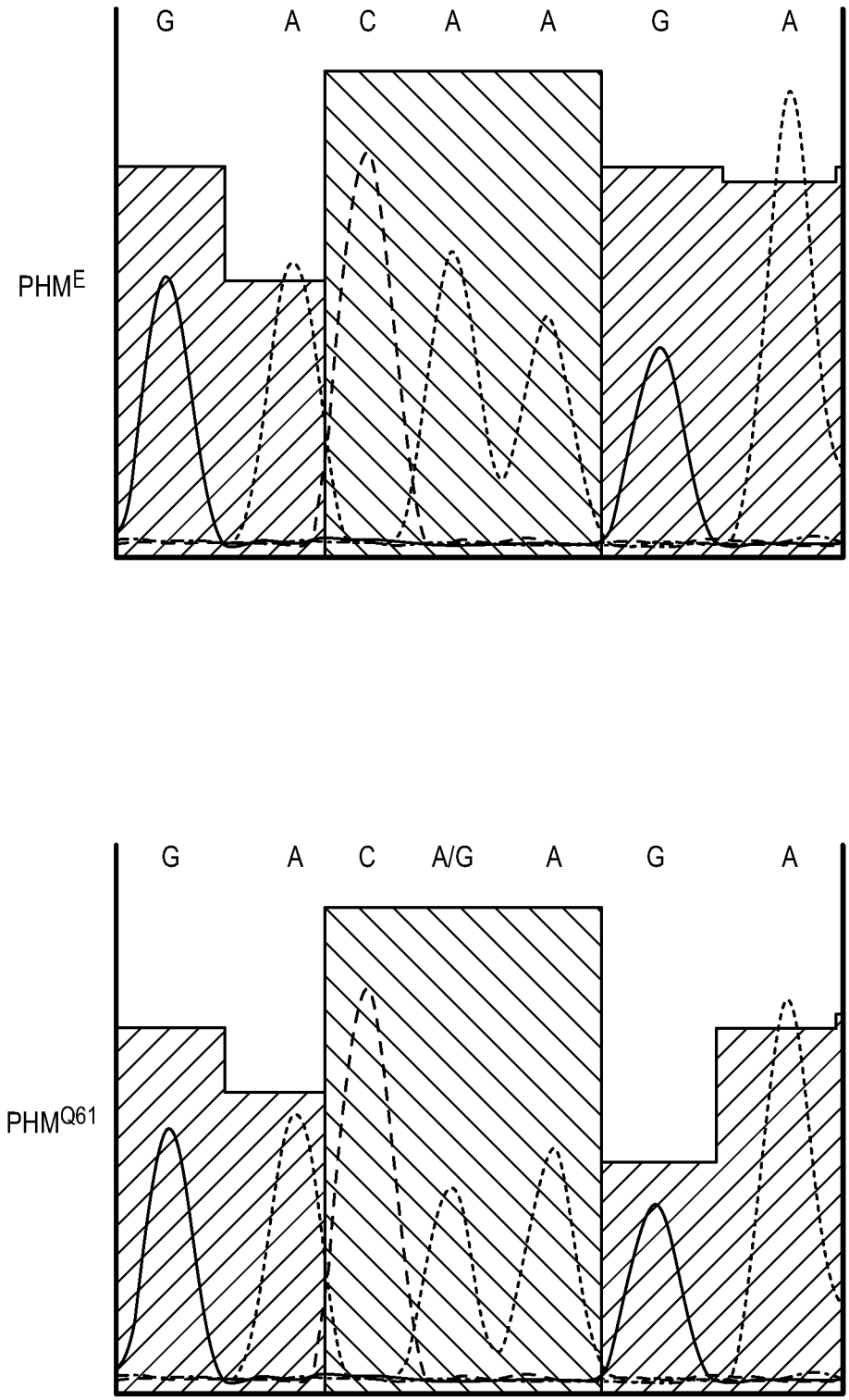

FIG. 7A

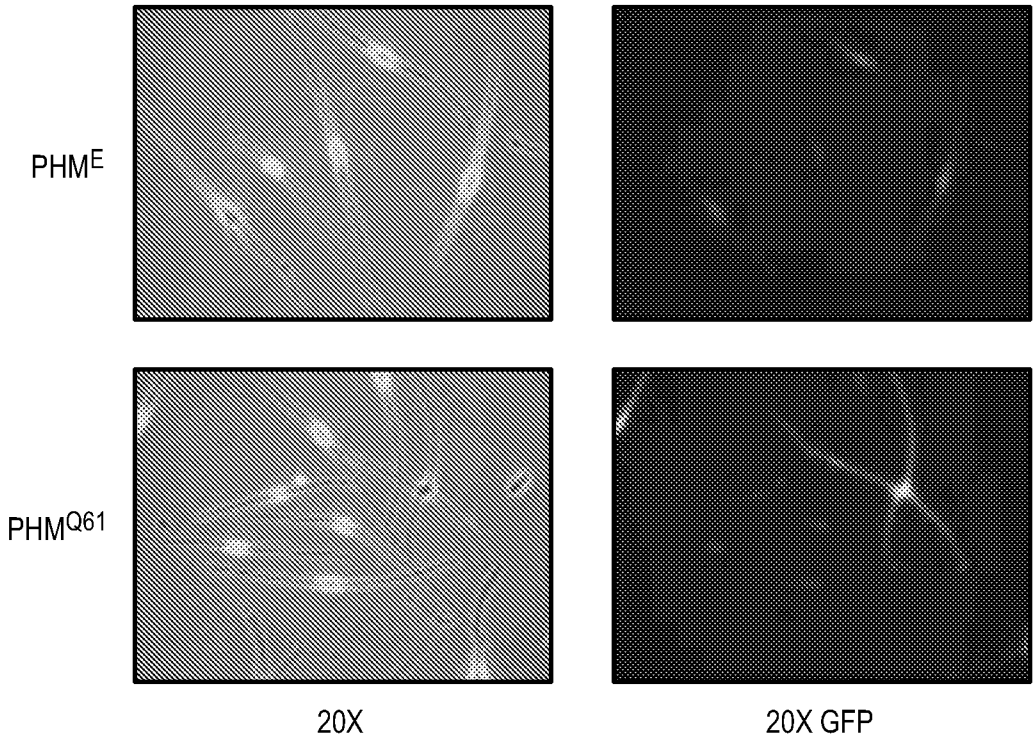
PHM^E
PHM^Q61
20X
20X GFP

FIG. 7B

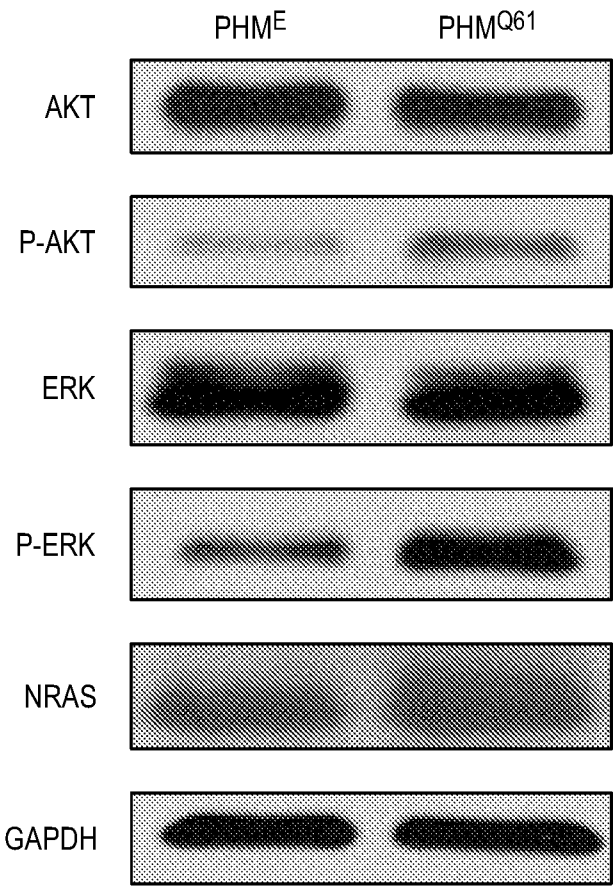
PHM^E
PHM^Q61
AKT
P-AKT
ERK
P-ERK
NRAS
GAPDH

FIG. 7C

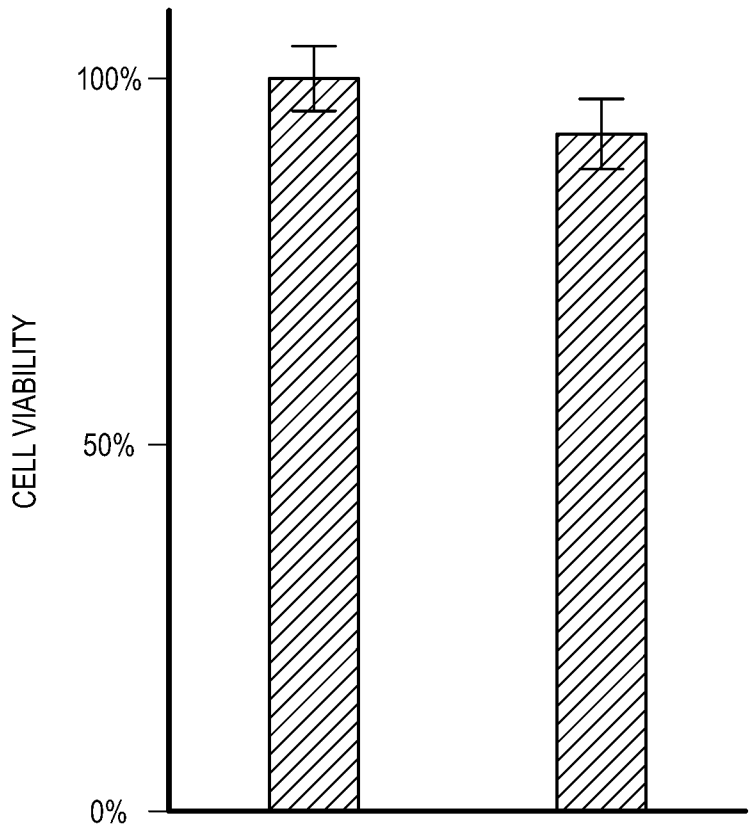

FIG. 7D

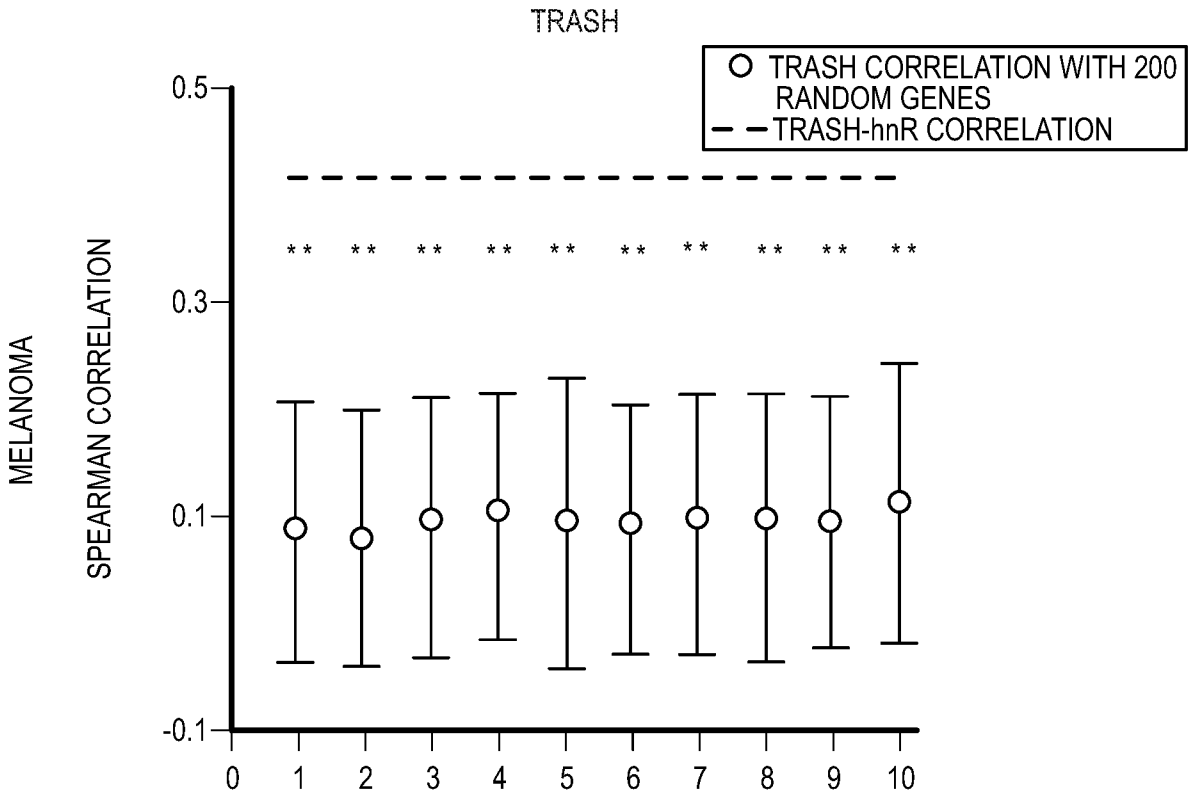
TRASH
TRASH CORRELATION WITH 200 RANDOM GENES
TRASH-hnR CORRELATION
MELANOMA
SPEARMAN CORRELATION
0.5
0.3
0.1
-0.1
0 1 2 3 4 5 6 7 8 9 10

FIG. 8A

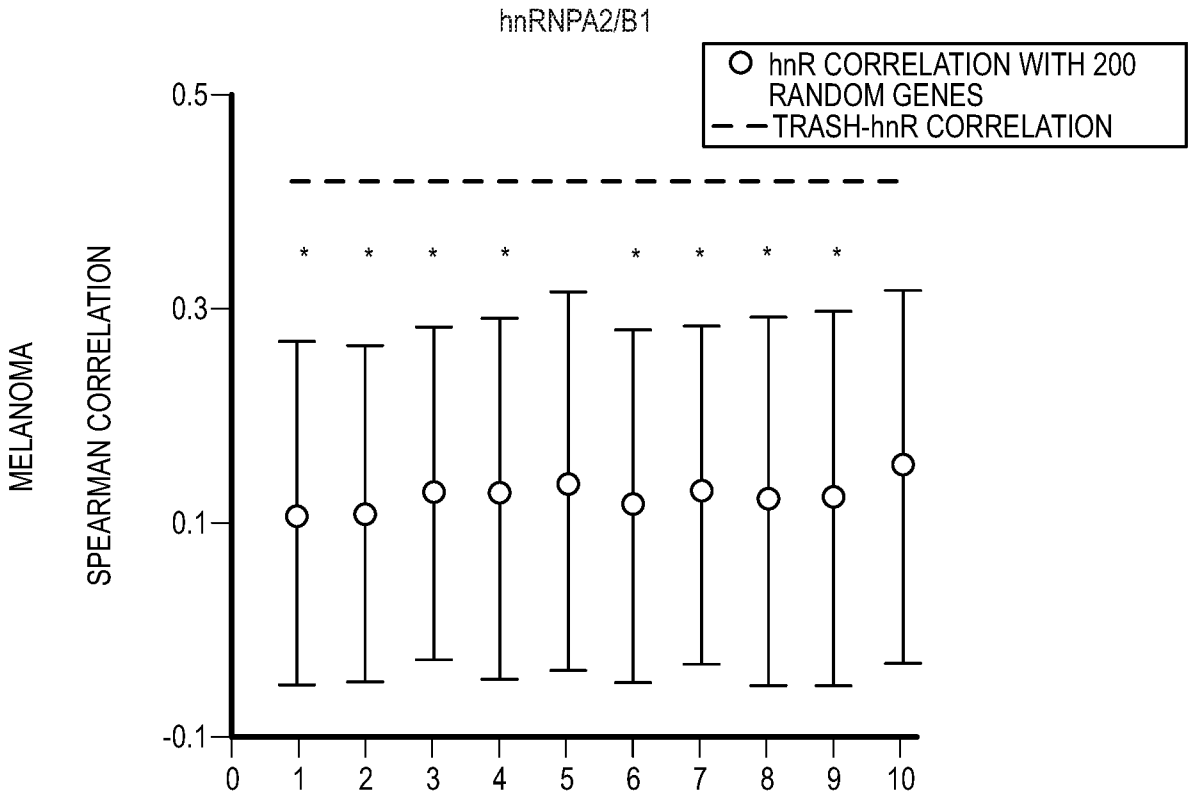
hnRNPA2/B1
hnR CORRELATION WITH 200 RANDOM GENES
TRASH-hnR CORRELATION
MELANOMA
SPEARMAN CORRELATION
0.5
0.3
0.1
-0.1
0 1 2 3 4 5 6 7 8 9 10

FIG. 8B

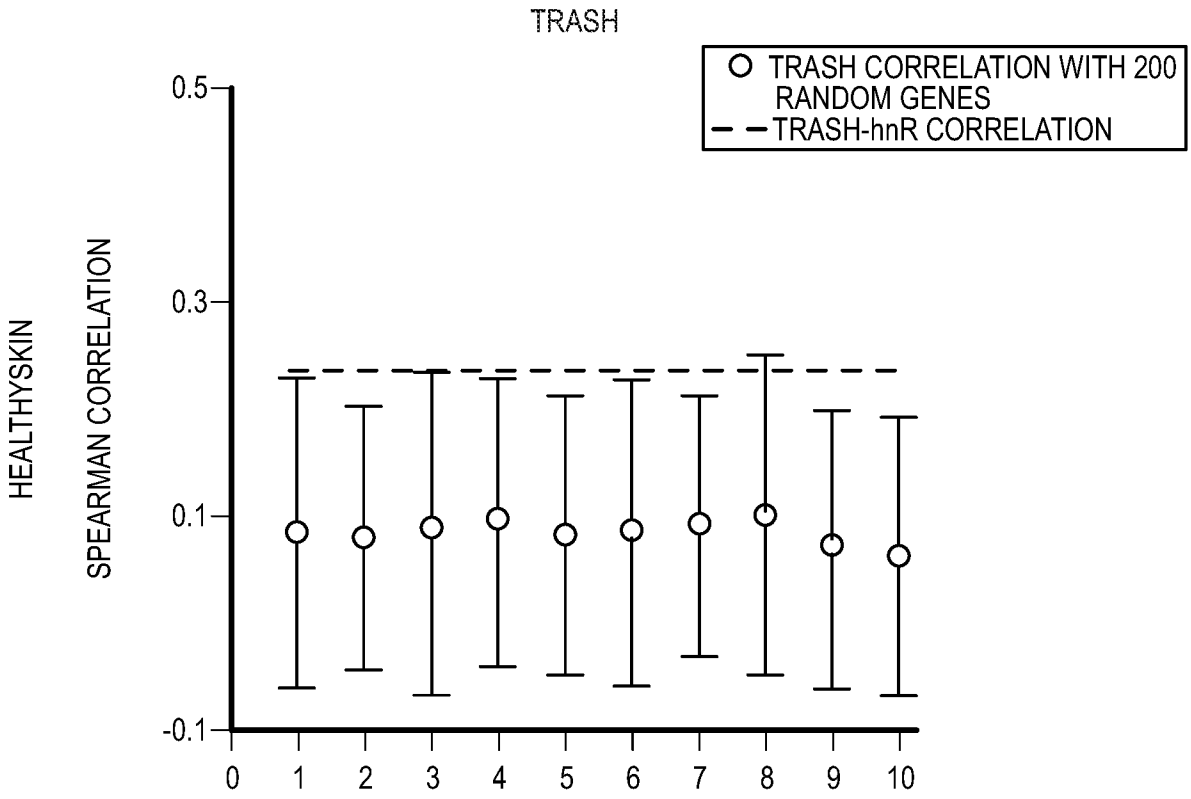
TRASH
TRASH CORRELATION WITH 200 RANDOM GENES
TRASH-hnR CORRELATION
HEALTHYSKIN
SPEARMAN CORRELATION
0.5
0.3
0.1
-0.1
0 1 2 3 4 5 6 7 8 9 10

FIG. 8C

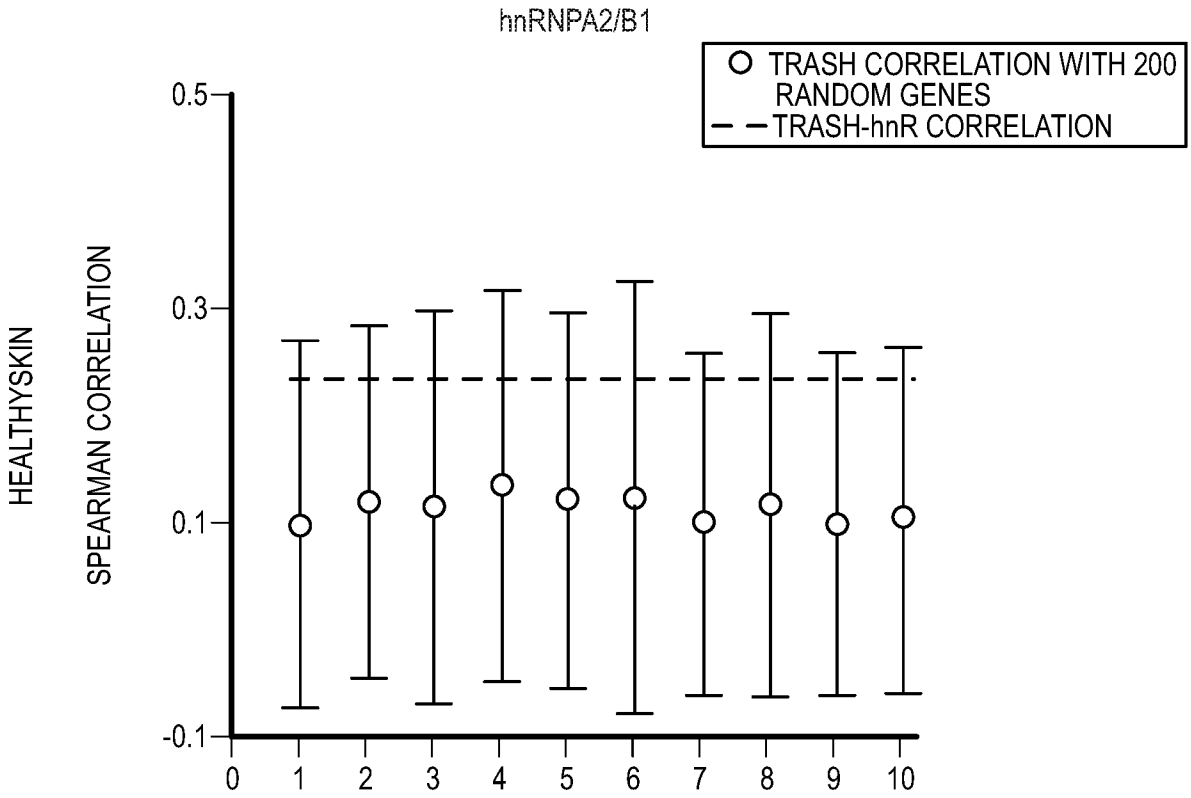
hnRNPA2/B1
TRASH CORRELATION WITH 200 RANDOM GENES
TRASH-hnR CORRELATION
HEALTHYSKIN
SPEARMAN CORRELATION
0.5
0.3
0.1
-0.1
0 1 2 3 4 5 6 7 8 9 10

FIG. 8D