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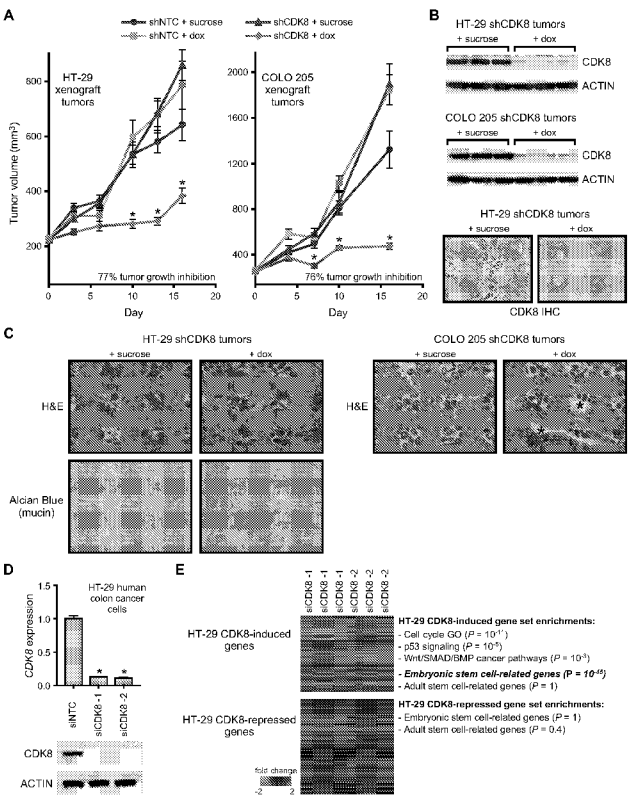
(54) Title: METHODS OF USING CDK8 ANTAGONISTS

Figure 1



(57) Abstract: Provided herein are CDK8 antagonists and methods of using the same, including methods of inducing differentiation and treating cancer.

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METHODS OF USING CDK8 ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] None.

FIELD

[0002] The present invention relates to methods of inducing differentiation, particularly differentiation of tumor cells, by inhibition of CDK8.

BACKGROUND

[0003] Recent studies have highlighted the ability of tumors to employ genetic programs normally found active in the embryonic state. Young, R. A., *Cell* 144, 940-954 (2011); Takebe, N. *et al.*, *Nat Rev Clin Oncol* 8, 97-106 (2011); Ben-Porath, I. *et al.*, *Nat Genet* 40, 499-507 (2008); Wong D.J. *et al.*, *Cell Stem Cell* 2:333-344 (2008). In embryonic stem cells, pluripotency-related gene signatures are often re-expressed in multiple cancer types, and expression of these stem cell-related genes strongly correlate with poor clinical outcome. Ben-Porath, I. *et al.*, *Nat Genet* 40, 499-507 (2008); Wong D.J. *et al.*, *Cell Stem Cell* 2:333-344 (2008). Identifying new druggable targets that are critical to the stem cell-like properties of tumors offers a new avenue of therapeutic intervention. The MYC oncogene is a critical transcriptional regulator in many tumor types (Meyer N. & Penn L.Z. *Nat Rev Cancer* 8:976-90 (2008)) and has also been demonstrated to play an essential role in ES cell proliferation and pluripotency but has been an intractable therapeutic target. Young, R. A., *Cell* 144, 940-954 (2011); Cartwright P. *et al.*, *Development* 132:885-96 (2005).

[0004] CDK8 is a cyclin dependent kinase that has a conserved function in transcription as part of the Mediator complex. Taatjes, D. J., *Trends Biochem Sci* 35, 315-322 (2010); Conaway, R. C. and Conaway, J. W., *Curr Opin Genet Dev* 21, 225-230 (2011). More recently, CDK8 has been reported to as an oncogene in both colon cancer (Firestein R. *et al.*, *Nature* 455:547-51 (2008); Morris E.J. *et al.*, *Nature* 455:552-6 (2008); Starr T.K. *et al.*, *Science* 323:1747-50 (2009)) and melanoma (Kapoor A. *et al.*, *Nature* 468:1105-9 (2010)). CDK8 is upregulated and amplified in a subset of human colon tumors. CDK8 transforms immortalized cells and is required for colon cancer proliferation in vitro. Firestein, R. *et al.*, *Nature* 455, 547-551 (2008). CDK8 has also been found to be overexpressed and essential for proliferation in melanoma. Kapoor, A. *et al.*, *Nature* 468, 1105-1109 (2010). CDK8 has been shown to regulate several signaling pathways that are key regulators of both ES pluripotency and cancer. CDK8 activates the Wnt pathway by promoting expression of β-Catenin target genes (Firestein, R. *et al.*, *Nature* 455, 547-551 (2008)) or by inhibiting E2F1, a potent inhibitor of β-Catenin transcriptional activity. Morris, E. J. *et al.*, *Nature* 455, 552-556 (2008). CDK8 promotes Notch target gene expression by phosphorylating the Notch intracellular domain, activating Notch enhancer complexes at target genes. Fryer C.J. *et al.*, *Mol Cell* 16:509-20 (2004). Lastly, CDK8 phosphorylation of SMAD proteins leads to activation of TGF-β/BMP target genes followed by degradation of the SMAD proteins to limit the target gene expression. Alarcon, C. *et al.*, *Cell* 139, 757-769 (2009). Many

of these studies, however, were conducted in vitro, in cell based assays that miss certain aspects of tumor growth in vivo.

[0005] There is a need to understand the functional and molecular consequences of CDK8 loss in both fully formed tumors and ES cells and better predict clinical outcome and differentiation status in colon cancer patients.

SUMMARY

[0006] The invention provides CDK8 antagonist and methods of using the same. Provided herein methods of screening for and/or identifying a CDK8 antagonist which promotes cell differentiation said method comprising: contacting a reference cell, wherein the reference cell is a stem cell and/or a cancer stem cell, with a CDK8 candidate antagonist, wherein the CDK8 candidate antagonist binds CDK8, and whereby differentiation of the reference cell into a differentiated cell identifies the CDK8 candidate antagonist as a CDK8 antagonist which promotes cell differentiation. In some embodiments, the reference cell is a cancer stem cell. In some embodiments, the differentiated cell is a goblet cell and/or enterocyte cell. In some embodiments, the CDK8 candidate antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide.

[0007] In anther aspect, provided herein are methods of inducing differentiation comprising contacting the cell with an effective amount of CDK8 antagonist. In some embodiments, the cell is a stem cell. In some embodiments, the cell is a cancer stem cell.

[0008] Provided herein are methods of treating a cancer cell, wherein the cancer cell differentially expresses one or more biomarkers of a CDK8 gene signature (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)), the method comprising providing an effective amount of a CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0009] Further provided herein are methods of treating cancer in an individual comprising administering to the individual an effective amount of a CDK8 antagonist, wherein treatment is based upon the cancer comprising cancer stem cell-like properties. In some embodiments, the cancer stem cell-like properties comprise differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)). In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated

expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0010] Further provided herein are methods of treating a disease or disorder in an individual comprising administering to the individual an effective amount of a CDK8 antagonist, wherein treatment is based upon differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)). In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0011] Provided herein are methods of treating a disease or disorder in an individual comprising administering to the individual an effective amount of a CDK8 antagonist, wherein treatment is continued based upon differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)). In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is reduced expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature.

[0012] Further provided herein are methods for treating a disease or disorder in an individual, the method comprising: determining that a sample obtained from the individual comprises differential expression levels of one or more biomarkers of a CDK8 gene signature (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)), and administering an effective amount of a CDK8 antagonist to the individual, whereby the disease or disorder is treated. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0013] Provided herein are methods of treating disease or disorder in an individual, comprising: (a) selecting an individual having differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)); and (b) administering to the individual thus selected an effective amount of a CDK8 antagonist, whereby the disease or disorder is treated. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0014] Also provided herein are methods of identifying an individual with a disease or disorder who is more or less likely to exhibit benefit from treatment with a therapy comprising a CDK8 antagonist, the method comprising: determining the expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, wherein differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is more likely to exhibit benefit from treatment with the therapy comprising the CDK8 antagonist and/or non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is less likely to exhibit benefit from treatment with the therapy comprising the CDK8 antagonist. In some embodiments, the method further comprises administering an effective amount of a therapy comprising a CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0015] Provided herein are methods for predicting whether an individual with a disease or disorder is more or less likely to respond effectively to treatment with a therapy comprising a CDK8 antagonist, the method comprising assessing expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, whereby differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is more likely to respond effectively to treatment with the CDK8 antagonist and/or non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is less likely to respond effectively to treatment with the CDK8 antagonist. In some embodiments, the method further comprises administering an effective amount of a therapy comprising a CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0016] Provided herein are methods of predicting the response or lack of response of an individual with a disease or disorder to a therapy comprising a CDK8 antagonist comprising measuring expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, wherein differential

expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) is predictive of response of the individual to the therapy comprising the CDK8 antagonist and non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) is predictive of lack of response of the individual to the therapy comprising the CDK8 antagonist. In some embodiments, the method further comprises administering an effective amount of a therapy comprising a CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0017] Further provided herein are methods of determining whether an individual having a disease or disorder is more or less likely responding to therapy, wherein therapy comprises a CDK8 antagonist, based upon levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, wherein differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) identifies the individual as more likely responding to therapy comprising the CDK8 antagonist and non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) identifies the individual as less likely responding to therapy comprising the CDK8 antagonist. In some embodiments, the method further comprises administering an effective amount of a therapy comprising a CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is reduced expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature.

[0018] In some embodiments of any of the methods, the one or more biomarkers of the CDK8 gene signature comprises one or more biomarkers of the CDK8 cancer cell gene signature. In some embodiments, the one or more biomarkers of the CDK8 cancer cell gene signature comprises one or more genes listed in Table 2. In some embodiments, the one or more genes listed in Table 2 comprises one or more ES cell-related genes, MYC ES target genes, p53 signalling genes, cell cycle genes, Wnt signalling genes, and/or SMAD/BMP signalling genes.

[0019] In some embodiments of any of the methods, the one or more biomarkers of the CDK8 gene signature comprises one or more biomarkers of the CDK8 embryonic stem cell gene signature. In some

embodiments, the one or more biomarkers of the CDK8 embryonic stem cell gene signature comprises one or more genes listed in Table 3.

[0020] In some embodiments of any of the methods, the disease or disorder is cancer.

[0021] In some embodiments of any of the methods, the CDK8 antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the CDK8 antagonist is an antibody. In some embodiments, the CDK8 antagonist is a small molecule. In some embodiments, the small molecule is a small molecule kinase inhibitor. In some embodiments, the small molecule kinase inhibitor is selected from the group consisting of flavopiridol, ABT-869, AST-487, BMS-387032/SNS032, BIRB-796, sorafenib, staurosporine, cortistatin, cortistatin A, and/or a steroidal alkaloid or derivative thereof. In some embodiments, the CDK8 antagonist induces cell cycle arrest or is capable of promoting differentiation. In some embodiments, wherein the CDK8 antagonist is capable of promoting a change in cell fate and promoting differentiation is indicated by reduced expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or elevated expression of one or more CDK8-reduced biomarkers of the CDK8 gene signature.

BRIEF DESCRIPTION OF THE FIGURES

[0022] Figure 1 | CDK8 was required for tumor growth and maintenance of a de-differentiated state *in vivo*. **A** Xenograft tumor volume measurements over time (n = 10 mice per group). The tumor growth inhibition values were determined by an area under the curve calculation. Mean ± s.e.m. is shown *, P=0.001 compared to all other groups, Student's t-test. **B** Western blot of CDK8 protein levels in shCDK8 xenograft tumors at Day 8 (HT-29) or Day 12 (COLO 205) (top). Immunohistochemistry of CDK8 protein in HT-29 shCDK8 tumors from the end of the study (bottom). **C** Images of hematoxylin and eosin (H&E) stained tumors from the end of the study. HT-29 shCDK8 tumors were stained with alcian blue that stains secreted mucin. Asterisks indicate the lumen of well-formed glands seen in COLO 205 shCDK8 tumors. **D** Quantitative RT-PCR and Western blot analysis of CDK8 three days after siRNA transfection in HT-29 human colon cancer cells. Mean ± s.d. is shown *, $P = 10^{-5}$, Student's t-test. **E** The top 1500 genes that change after CDK8 knockdown in HT-29 cells relative to siNTC (P<0.001, Student's t-test between siNTC and siCDK8 -1/-2). GO, gene ontology.

[0023] Figure 2 | CDK8 maintained ES cells in an undifferentiated state. **A,** Images of alkaline phosphatase stained R1 mouse ES cells before and after induced differentiation. Positive staining (red) indicates undifferentiated stem cells. **B, C,** Quantitative RT-PCR and Western blot detection of NANOG (**B**) and CDK8 (**C**) at the indicated times after ES cell differentiation. CDK8 protein levels were quantified relative to ACTIN and normalized to Day 0. Mean ± s.d. is shown. *, $P = 10^{-5}$, Student's t-test. **D,** Alkaline phosphatase staining and phase contrast images of ES cells at the indicated times following shRNA infection. The

staining in shNTC samples was representative of all subsequent time points. The requirement for CDK8 to maintain ES cells in an undifferentiated state was observed in at least three independent knockdown experiments. The number of alkaline phosphatase stained ES cell colonies observed per 24 mm^2 field is shown to the right. *, $P = 0.001$ compared to shNTC, Student's *t*-test. **E,** Western blot of shRNA infected ES cells at Day 13 after infection. **F,** Alkaline phosphatase staining and phase contrast images of ES cells at Day 11 after exogenous expression of CDK8 or empty vector in the presence of the indicated shRNA. **G,** Quantitation of alkaline phosphatase stained ES cell colonies observed per 24 mm^2 field. Mean ± s.d. is shown. $P = 10^{-5}$ between shCdk8 + vector and shCdk8 + CDK8, Student's *t*-test. **H,** Western blot of CDK8-rescued ES cells at Day 11. Exogenously expressed human CDK8 protein was shifted slightly higher on the gel due to it being FLAG-tagged.

[0024] Figure 3 | CDK8 regulated MYC target gene and protein levels. **A,** Shown are the top 1500 genes that change after CDK8 knockdown in R1 ES cells at Day 8 relative to shNTC control ($P = 0.003$, Student's *t*-test between shNTC and two independent CDK8 shRNAs). The expression of these same genes at Day 13 is shown. **B,** Quantitative RT-PCR analysis of two representative ES cell genes (*H2afx* and *Tcl1*) at the indicated times after shCDK8 treatment. Mean ± s.d. is shown. *, $P = 0.05$, Student's *t*-test. **C,** Western blot of infected ES cells at the indicated time after shRNA infection. A schematic of common MYC phosphorylation modifications is on the left. **D,** OCT4, NANOG, and MYC proteins levels were quantified relative to ACTIN, and then normalized to their respective shNTC for each time point. **E,** For each time point MYC-pS62 and MYC-pT58 protein levels were quantified relative to total MYC and then normalized to their respective shNTC.

[0025] Figure 4 | CDK8 partially regulated ES cell pluripotency through MYC. **A** Western blot of ES cells stably expressing MYC, MYC^{T58A}, MYC^{S62A}, or GFP in the presence of the indicated shRNA at Day 11. Total MYC protein was quantified relative to ACTIN and normalized to their respective shNTC. The anti-MYC antibody detects mouse and human MYC. **B,** Alkaline phosphatase staining and phase contrast images of ES cells at Day 11 after expression of MYC, MYC^{T58A}, MYC^{S62A}, or GFP control in the presence of the indicated shRNA. The number of alkaline phosphatase stained ES cell colonies observed per 24 mm^2 field is shown to the right of each group. The dashed gray line indicated the number of colonies observed in shNTC + GFP control cells. Mean ± s.d. is shown *, $P = 0.005$ compared to the respective GFP expression control, Student's *t*-test.

[0026] Figure 5 | Coordinated expression of CDK8-regulated MYC targets in primary human colon cancer. **A,** Gene set enrichments in HT-29 CDK8-induced and CDK8-repressed genes. **B,** Quantitative RT-PCR of four MYC-driven ES cell target genes in HT-29 cells. Mean ± s.d. is shown. *, $P = 0.01$, Student's *t*-test. **C,** The $\log_2$ mean centered expression of CDK8-induced MYC ES cell target genes (from Fig. 5A) was shown for 227 primary and metastatic human colon tumors (from Gene Logic). The tumors were sorted based on

high to low average expression of the CDK8-induced MYC ES cell targets and split in two at the mean expression level. Bar graph depicted average ± s.e.m. $\log_2$ expression of *CDK8* in the two groups ($P = 0.002$, Student's *t*-test). **D,** Western blot analysis of normal colon, primary colon tumors, and metastatic colon tumors. CDK8 and MYC levels were quantified relative to ACTIN then normalized to their average in normal colon. Phospho-specific MYC (S62 and T58) levels were quantified relative to MYC, then the ratio was normalized to their average ratio in normal colon. *P*-values for Pearson correlations are one-tailed *t*-tests. **E,** The average $\log_2$ expression of the CDK8-induced MYC ES cell targets was sorted high to low for 213 primary human colon tumors with known tumor differentiation status (Smith JJ. *et al.*, *Gastroenterology* 138:958-68 (2010)). Hash marks indicated poorly differentiated tumors; the remaining tumors are either well or moderately differentiated. *P*-values were calculated with a fisher exact test using a 2x2 contingency table. **F,** The average $\log_2$ expression of the CDK8-induced MYC ES cell targets for 50 primary human colon tumors that underwent recurrence (Jorissen R.N. *et al.*, *Colorectal Cancer. Clin Cancer Res* 15:7642-51 (2009).); time to recurrence was indicated below each tumor. The average time to recur ± s.e.m. for each group is shown ($P = 0.02$, Student's *t*-test).

[0027] Figure 6 | Gene expression analysis of ES cell-related genes in HT-29 siCDK8 cells. Quantitative RT-PCR of multiple ES cell-related genes three days after CDK8 siRNA transfection in HT-29 human colon cancer cells. Expression was normalized to siNTC treated cells. Mean +/- s.d. is shown. *, $P = 0.01$, Student's *t*-test).

[0028] Figure 7 | CDK8 maintained multiple ES cell lines in an undifferentiated state. **A**, Western blot of the indicated shRNA infected ES cell lines at Day 7 after infection. **B**, Alkaline phosphatase staining and phase contrast images at Day 7. The number of alkaline phosphatase stained ES cell colonies observed per 24 mm^2 filed is shown below. *, $P = 10^{-4}$, Student's *t*-test).

[0029] Figure 8 | CDK8 and MED12 regulated distinct gene expression programs in ES cells. **A**, Quantitative RT-PCR of Med12 levels at Day 13 after MED12 shRNA infection in R1 ES cells. Mean +/- s.d. is shown. *, $P = 10^{-6}$, Student's *t*-test). **B**, Alkaline phosphatase staining and phase contrast images of ES cells at Day 13 after MED12 shRNA treatment. **C**, Shown are the top 1500 genes that changed after CDK8 knockdown at Day 8 in R1 ES cells relative to shNTC control. The expression of these same genes following MED12 knockdown at Day 13 is shown. **D**, Shown are a set of genes found to be regulated by MED12 in mouse ES cells (Kagey *et al.*, *Nature* (2010)). Expression data of these genes from the previous study is sorted low to high. Next to this is expression of the same genes from this study in mouse ES cells and from mouse ES cells that have undergone forced differentiation through three different chemical methods or mouse ES cells that have differentiated following siNanog or siOct4 treatment (data from Gene Expression Omnibus accession GSE4189; Loh *et al.*, *Nature Genetics* (2006)). The fold change scale for each data set relative to shNTC or siNTC controls is indicated on the right. **E**, The bar graph shows the Pearson

correlations of the gene expression pattern for each indicated data set with the shMed12 expression pattern from Kagey *et al.* *P*-values of various Pearson correlations were calculated with one-tailed *t*-tests.

[0030] Figure 9 | **A, B**, Loss of CDK8 leads to decreased MYC protein level but does not alter its subcellular localization. A, Immunofluorescence images of MYC and CDK8 in R1 ES cells at Day 8 after shRNA infection. Cell nuclei are indicated by Hoechst staining. B, Immunofluorescence images of MYC and phosphor-specific MYC proteins in ES cells at Day 13 after shRNA infection. **C**, Myc expression weakly changes upon CDK8 loss in ES cells. Quantitative RT-PCR analysis of Myc at Day 8 and Day 13 of shCdk8 treatment in R1 ES cells. Mean +/- s.d. is shown. *, $P = 0.002$, Student's *t*-test).

[0031] Figure 10 | Gene expression analysis of MYC ES cell targets in HT-29 siCDK8 cells. Quantitative RT-PCR of multiple MYC ES cell targets (previously identified through chromatin IP experiments in mouse ES cells; Kim *et al.*, *Cell* (2008)) three days after CDK8 siRNA transfection in HT-29 human colon cancer cells. Expression is normalized to siNTC treated cells. Mean +/- s.d. is shown. *, $P = 0.01$, Student's *t*-test).

[0032] Figure 11 | *MYC* is co-expressed with the HT-29 CDK8-regulated gene signature in human colon cancer. **A**, Bar graph shows Pearson correlations of the indicated transcription factor and pathway genes with expression of the CDK8-regulated HT-29 signature (from Fig. 1E) in human tumors (n=230 total). Genes with a positive Pearson correlation indicate that the gene is co-expressed with the CDK8 signature. Dashed lines specify *P*-value cut-offs for low and high correlations (*P*-values calculated with one-tailed *t*-test). **B**, Correlation of high *MYC* expression with increased expression of the HT-29 CDK8-regulated signature. Bar graph depicts $\log_2$ mean centered *MYC* expression for individual human colon tumor samples. Tumors were sorted from high to low based on expression of the CDK8 signature (the dark bar on the left indicates CDK8-induced genes; the grey bar indicates CDK8-repressed genes). Higher *MYC* expression was seen in tumors that express the CDK8-regulated signature, while low *MYC* expression is seen in tumors with the opposite pattern of the CDK8 signature (Pearson = 0.57, $P = 10^{-12}$, Student's *t*-test).

DETAILED DESCRIPTION

I. Definitions

[0033] The terms "CDK8" and "cyclin-dependent kinase 8" refer herein to a native CDK8 from any vertebrate source, including mammals such as primates (*e.g.,* humans) and rodents (*e.g.,* mice and rats), unless otherwise indicated. The term encompasses "full-length," unprocessed CDK8 as well as any form of CDK8 that results from processing in the cell. The term also encompasses naturally occurring variants of CDK8, *e.g.,* splice variants or allelic variants. The sequence of an exemplary human CDK8 nucleic acid sequence is NM_001260 (gi:4502744) or an exemplary human CDK8 is amino acid sequence of CDK8 NP_001251.1, UniProtKB/Swiss-Prot:P49336, P49336.2, and/or P49336.1.

[0034] "CDK8 variant" or variations thereof, means a CDK8 polypeptide or polynucleotide, generally being or encoding an active CDK8 polypeptide, as defined herein having at least about 80% amino acid sequence

identity with any of the native sequence CDK8 polypeptide sequences as disclosed herein. Such CDK8 variants include, for instance, CDK8 wherein one or more nucleic acid or amino acid residues are added or deleted. Ordinarily, a CDK8 variant will have at least about 80% sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity, to CDK8 as disclosed herein. Ordinarily, CDK8 variant are at least about 10 residues in length, alternatively at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 in length, or more. Optionally, CDK8 variant will have or encode a sequence having no more than one conservative amino acid substitution as compared to CDK8, alternatively no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitution as compared to CDK8.

[0035] The term "CDK8 antagonist" as defined herein is any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity mediated by a native sequence CDK8. In certain embodiments such antagonist binds to CDK8. According to one embodiment, the antagonist is a polypeptide. According to another embodiment, the antagonist is an anti-CDK8 antibody. According to another embodiment, the antagonist is a small molecule antagonist. According to another embodiment, the antagonist is a polynucleotide antagonist.

[0036] "Polynucleotide," or "nucleic acid," as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase, or by a synthetic reaction. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after synthesis, such as by conjugation with a label. Other types of modifications include, for example, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.) and with charged linkages (*e.g.*, phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (*e.g.*, nucleases, toxins, antibodies, signal peptides, ply-L-lysine, etc.), those with intercalators (*e.g.*, acridine, psoralen, etc.), those containing chelators (*e.g.*, metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (*e.g.*, alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to

prepare additional linkages to additional nucleotides, or may be conjugated to solid or semi-solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, α-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S("thioate"), P(S)S ("dithioate"), "(O)NR_2 ("amidate"), P(O)R, P(O)OR', CO or CH_2 ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

[0037] "Oligonucleotide," as used herein, generally refers to short, single stranded, polynucleotides that are, but not necessarily, less than about 250 nucleotides in length. Oligonucleotides may be synthetic. The terms "oligonucleotide" and "polynucleotide" are not mutually exclusive. The description above for polynucleotides is equally and fully applicable to oligonucleotides.

[0038] The term “primer” refers to a single stranded polynucleotide that is capable of hybridizing to a nucleic acid and following polymerization of a complementary nucleic acid, generally by providing a free 3’-OH group.

[0039] The term "small molecule" refers to any molecule with a molecular weight of about 2000 daltons or less, preferably of about 500 daltons or less.

[0040] The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[0041] The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors."

[0042] An "isolated" antibody is one which has been separated from a component of its natural environment. In some embodiments, an antibody is purified to greater than 95% or 99% purity as determined by, for example, electrophoretic (*e.g.*, SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatographic (*e.g.*, ion exchange or reverse phase HPLC). For review of methods for assessment of antibody purity, *see, e.g.*, Flatman *et al.*, *J. Chromatogr. B* 848:79-87 (2007).

[0043] An "isolated" nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0044] The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

[0045] The terms “anti-CDK8 antibody” and “an antibody that binds to CDK8” refer to an antibody that is capable of binding CDK8 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting CDK8. In one embodiment, the extent of binding of an anti-CDK8 antibody to an unrelated, non-CDK8 protein is less than about 10% of the binding of the antibody to CDK8 as measured, *e.g.*, by a radioimmunoassay (RIA). In certain embodiments, an anti-CDK8 antibody binds to an epitope of CDK8 that is conserved among CDK8 from different species.

[0046] A “blocking” antibody or an “antagonist” antibody is one which inhibits or reduces biological activity of the antigen it binds. Preferred blocking antibodies or antagonist antibodies substantially or completely inhibit the biological activity of the antigen.

[0047] “Affinity” refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

[0048] An “affinity matured” antibody refers to an antibody with one or more alterations in one or more hypervariable regions (HVRs), compared to a parent antibody which does not possess such alterations, such alterations resulting in an improvement in the affinity of the antibody for antigen.

[0049] An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments

include but are not limited to Fv, Fab, Fab', Fab'-SH, $F(ab')_2$; diabodies; linear antibodies; single-chain antibody molecules (*e.g.,* scFv); and multispecific antibodies formed from antibody fragments.

[0050] An "antibody that binds to the same epitope" as a reference antibody refers to an antibody that blocks binding of the reference antibody to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. An exemplary competition assay is provided herein.

[0051] The term "chimeric" antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0052] The "class" of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively.

[0053] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0054] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, *e.g.*, containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

[0055] A "human antibody" is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human

antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues.

[0056] A "humanized" antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (*e.g.*, CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of an antibody, *e.g.*, a non-human antibody, refers to an antibody that has undergone humanization.

[0057] An "immunoconjugate" is an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.

[0058] "Percent (%) amino acid sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, California, or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0059] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0060] The term "detection" includes any means of detecting, including direct and indirect detection.

[0061] The terms "cancer stem cell-like properties" and "cancer stem cell" as used herein refers to a population of cells from a tumor that: (1) have extensive proliferative capacity; (2) are capable of asymmetric cell division to generate one or more kinds of differentiated progeny with reduced proliferative or developmental potential; (3) are capable of symmetric cell divisions for self-renewal or self-maintenance; and/or, (4) are capable of forming palpable tumors upon serial transplantation in a xenograft model. In some embodiments, the properties of enhanced proliferative capacity and asymmetric and symmetric cell division of "cancer stem cells" confer on those cancer stem cells the ability to form palpable tumors upon serial transplantation into an immuno-compromised mouse compared to the majority of tumor cells that fail to generate tumors.

[0062] The term "biomarker" as used herein refers to an indicator, *e.g.*, predictive, diagnostic, and/or prognostic, which can be detected in a sample. The biomarker may serve as an indicator of a particular subtype of a disease or disorder (*e.g.*, cancer) characterized by certain, molecular, pathological, histological, and/or clinical features. In some embodiments, a biomarker is a gene. Biomarkers include, but are not limited to, polynucleotides (*e.g.*, DNA, and/or RNA), polypeptides, polypeptide and polynucleotide modifications (*e.g.* posttranslational modifications), carbohydrates, and/or glycolipid-based molecular markers.

[0063] The terms "biomarker signature," "signature," "biomarker expression signature," or "expression signature" are used interchangeably herein and refer to one or a combination of biomarkers whose expression is an indicator, *e.g.*, predictive, diagnostic, and/or prognostic. The biomarker signature may serve as an indictor of a particular subtype of a disease or disorder (*e.g.*, cancer) characterized by certain molecular, pathological, histological, and/or clinical features. In some embodiments, the biomarker signature is a "gene signature." The term "gene signature" is used interchangeably with "gene expression signature" and refers to one or a combination of polynucleotides whose expression is an indicator, *e.g.*, predictive, diagnostic, and/or prognostic. In some embodiments, the biomarker signature is a "protein signature." The term "protein signature" is used interchangeably with "protein expression signature" and refers to one or a combination of polypeptides whose expression is an indicator, *e.g.*, predictive, diagnostic, and/or prognostic.

[0064] The "amount" or "level" of a biomarker associated with an increased clinical benefit to an individual is a detectable level in a biological sample. These can be measured by methods known to one skilled in the art and also disclosed herein. The expression level or amount of biomarker assessed can be used to determine the response to the treatment.

[0065] The terms "level of expression" or "expression level" in general are used interchangeably and generally refer to the amount of a biomarker in a biological sample. "Expression" generally refers to the process by which information (*e.g.*, gene-encoded and/or epigenetic) is converted into the structures present and operating in the cell. Therefore, as used herein, "expression" may refer to transcription into a polynucleotide, translation into a polypeptide, or even polynucleotide and/or polypeptide modifications (*e.g.*, posttranslational modification of a polypeptide). Fragments of the transcribed polynucleotide, the translated polypeptide, or polynucleotide and/or polypeptide modifications (*e.g.*, posttranslational modification of a polypeptide) shall also be regarded as expressed whether they originate from a transcript generated by alternative splicing or a degraded transcript, or from a post-translational processing of the polypeptide, *e.g.*, by proteolysis. "Expressed genes" include those that are transcribed into a polynucleotide as mRNA and then translated into a polypeptide, and also those that are transcribed into RNA but not translated into a polypeptide (for example, transfer and ribosomal RNAs).

[0066] “Elevated expression,” “elevated expression levels,” or “elevated levels” refers to an increased expression or increased levels of a biomarker in an individual relative to a control, such as an individual or individuals who are not suffering from the disease or disorder (*e.g.*, cancer) or an internal control (*e.g.*, housekeeping biomarker).

[0067] “Reduced expression,” “reduced expression levels,” or “reduced levels” refers to a decrease expression or decreased levels of a biomarker in an individual relative to a control, such as an individual or individuals who are not suffering from the disease or disorder (*e.g.*, cancer) or an internal control (*e.g.*, housekeeping biomarker).

[0068] The term “housekeeping biomarker” refers to a biomarker or group of biomarkers (*e.g.*, polynucleotides and/or polypeptides) which are typically similarly present in all cell types. In some embodiments, the housekeeping biomarker is a “housekeeping gene.” A “housekeeping gene” refers herein to a gene or group of genes which encode proteins whose activities are essential for the maintenance of cell function and which are typically similarly present in all cell types.

[0069] “Amplification,” as used herein generally refers to the process of producing multiple copies of a desired sequence. “Multiple copies” mean at least two copies. A “copy” does not necessarily mean perfect sequence complementarity or identity to the template sequence. For example, copies can include nucleotide analogs such as deoxyinosine, intentional sequence alterations (such as sequence alterations introduced

through a primer comprising a sequence that is hybridizable, but not complementary, to the template), and/or sequence errors that occur during amplification.

[0070] The term "multiplex-PCR" refers to a single PCR reaction carried out on nucleic acid obtained from a single source (*e.g.*, an individual) using more than one primer set for the purpose of amplifying two or more DNA sequences in a single reaction.

[0071] "Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel *et al.*, Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

[0072] "Stringent conditions" or "high stringency conditions", as defined herein, can be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) overnight hybridization in a solution that employs 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with a 10 minute wash at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) followed by a 10 minute high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

[0073] "Moderately stringent conditions" can be identified as described by Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (*e.g.*, temperature, ionic strength and %SDS) less stringent that those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

[0074] The term "diagnosis" is used herein to refer to the identification or classification of a molecular or pathological state, disease or condition (*e.g.*, cancer). For example, "diagnosis" may refer to identification of a particular type of cancer. "Diagnosis" may also refer to the classification of a particular subtype of cancer, *e.g.*, by histopathological criteria, or by molecular features (*e.g.*, a subtype characterized by expression of one or a combination of biomarkers (*e.g.*, particular genes or proteins encoded by said genes)).

[0075] The term "aiding diagnosis" is used herein to refer to methods that assist in making a clinical determination regarding the presence, or nature, of a particular type of symptom or condition of a disease or disorder (*e.g.*, cancer). For example, a method of aiding diagnosis of a disease or condition (*e.g.*, cancer) can comprise measuring certain biomarkers in a biological sample from an individual.

[0076] The term "sample," as used herein, refers to a composition that is obtained or derived from a subject and/or individual of interest that contains a cellular and/or other molecular entity that is to be characterized and/or identified, for example based on physical, biochemical, chemical and/or physiological characteristics. For example, the phrase "disease sample" and variations thereof refers to any sample obtained from a subject of interest that would be expected or is known to contain the cellular and/or molecular entity that is to be characterized. Samples include, but are not limited to, primary or cultured cells or cell lines, cell supernatants, cell lysates, platelets, serum, plasma, vitreous fluid, lymph fluid, synovial fluid, follicular fluid, seminal fluid, amniotic fluid, milk, whole blood, blood-derived cells, urine, cerebro-spinal fluid, saliva, sputum, tears, perspiration, mucus, tumor lysates, and tissue culture medium, tissue extracts such as homogenized tissue, tumor tissue, cellular extracts, and combinations thereof.

[0077] By "tissue sample" or "cell sample" is meant a collection of similar cells obtained from a tissue of a subject or individual. The source of the tissue or cell sample may be solid tissue as from a fresh, frozen and/or preserved organ, tissue sample, biopsy, and/or aspirate; blood or any blood constituents such as plasma; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid, or interstitial fluid; cells from any time in gestation or development of the subject. The tissue sample may also be primary or cultured cells or cell lines. Optionally, the tissue or cell sample is obtained from a disease tissue/organ. The tissue sample may contain compounds which are not naturally intermixed with the tissue in nature such as preservatives, anticoagulants, buffers, fixatives, nutrients, antibiotics, or the like.

[0078] A "reference sample", "reference cell", "reference tissue", "control sample", "control cell", or "control tissue", as used herein, refers to a sample, cell, tissue, standard, or level that is used for comparison purposes. In one embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from a healthy and/or non-diseased part of the body (*e.g.*, tissue or cells) of the same subject or individual. For example, healthy and/or non-diseased cells or tissue adjacent to the diseased cells or tissue (*e.g.*, cells or tissue adjacent to a tumor). In another embodiment, a reference sample is obtained from an untreated tissue and/or cell of the body of the same subject or individual. In yet another

embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from a healthy and/or non-diseased part of the body (*e.g.*, tissues or cells) of an individual who is not the subject or individual. In even another embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from an untreated tissue and/or cell of the body of an individual who is not the subject or individual.

[0079] For the purposes herein a "section" of a tissue sample is meant a single part or piece of a tissue sample, *e.g.* a thin slice of tissue or cells cut from a tissue sample. It is understood that multiple sections of tissue samples may be taken and subjected to analysis, provided that it is understood that the same section of tissue sample may be analyzed at both morphological and molecular levels, or analyzed with respect to both polypeptides and polynucleotides.

[0080] By "correlate" or "correlating" is meant comparing, in any way, the performance and/or results of a first analysis or protocol with the performance and/or results of a second analysis or protocol. For example, one may use the results of a first analysis or protocol in carrying out a second protocols and/or one may use the results of a first analysis or protocol to determine whether a second analysis or protocol should be performed. With respect to the embodiment of polynucleotide analysis or protocol, one may use the results of the polynucleotide expression analysis or protocol to determine whether a specific therapeutic regimen should be performed.

[0081] "Individual response" or "response" can be assessed using any endpoint indicating a benefit to the individual, including, without limitation, (1) inhibition, to some extent, of disease progression (*e.g.*, cancer progression), including slowing down and complete arrest; (2) a reduction in tumor size; (3) inhibition (*i.e.*, reduction, slowing down or complete stopping) of cancer cell infiltration into adjacent peripheral organs and/or tissues; (4) inhibition (*i.e.* reduction, slowing down or complete stopping) of metasisis; (5) relief, to some extent, of one or more symptoms associated with the disease or disorder (*e.g.*, cancer); (6) increase in the length of progression free survival; and/or (9) decreased mortality at a given point of time following treatment.

[0082] The term "substantially the same" or "non-differential" as used herein, denotes a sufficiently high degree of similarity between two numeric values, such that one of skill in the art would consider the difference between the two values to be of little or no biological and/or statistical significance within the context of the biological characteristic measured by said values (*e.g.*, Kd values or expression). The difference between said two values is, for example, less than about 50%, less than about 40%, less than about 30%, less than about 20%, and/or less than about 10% as a function of the reference/comparator value.

[0083] The phrase "substantially different" or "differential" as used herein, denotes a sufficiently high degree of difference between two numeric values such that one of skill in the art would consider the difference between the two values to be of statistical significance within the context of the biological

characteristic measured by said values (*e.g.*, Kd values). The difference between said two values is, for example, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, and/or greater than about 50% as a function of the value for the reference/comparator molecule.

[0084] The word "label" when used herein refers to a detectable compound or composition. The label is typically conjugated or fused directly or indirectly to a reagent, such as a polynucleotide probe or an antibody, and facilitates detection of the reagent to which it is conjugated or fused. The label may itself be detectable (*e.g.*, radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which results in a detectable product.

[0085] An "effective amount" of an agent refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[0086] A “therapeutically effective amount” of a substance/molecule of the invention, agonist or antagonist may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the substance/molecule, agonist or antagonist to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the substance/molecule, agonist or antagonist are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically but not necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[0087] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[0088] A “pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject., A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0089] As used herein, “treatment” (and grammatical variations thereof such as “treat” or “treating”) refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, antibodies of the invention are used to delay development of a disease or to slow the progression of a disease.

[0090] The term "anti-cancer therapy" refers to a therapy useful in treating cancer. Examples of anti-cancer therapeutic agents include, but are limited to, *e.g.*, chemotherapeutic agents, growth inhibitory agents, cytotoxic agents, agents used in radiation therapy, anti-angiogenesis agents, apoptotic agents, anti-tubulin agents, and other agents to treat cancer , anti-CD20 antibodies, platelet derived growth factor inhibitors (*e.g.*, Gleevec™ (Imatinib Mesylate)), a COX-2 inhibitor (*e.g.*, celecoxib), interferons, cytokines, antagonists (*e.g.*, neutralizing antibodies) that bind to one or more of the following targets PDGFR-beta, BlyS, APRIL, BCMA receptor(s), TRAIL/Apo2, and other bioactive and organic chemical agents, etc. Combinations thereof are also included in the invention.

[0091] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (*e.g.*, At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32} and radioactive isotopes of Lu), chemotherapeutic agents *e.g.*, methotrexate, adriamicin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents, enzymes and fragments thereof such as nucleolytic enzymes, antibiotics, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof, and the various antitumor or anticancer agents disclosed below. Other cytotoxic agents are described below. A tumoricidal agent causes destruction of tumor cells.

[0092] A "chemotherapeutic agent" refers to a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopolectin, and 9-aminocamptothecin); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e. g., calicheamicin, especially calicheamicin gamma1I and calicheamicin omega1I (*see, e.g.*, Nicolaou *et al.*, *Angew. Chem Intl.*

Ed. Engl., 33: 183-186 (1994)); CDP323, an oral alpha-4 integrin inhibitor; dynemicin, including dynemicin A; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, doxorubicin HCl liposome injection (DOXIL®), liposomal doxorubicin TLC D-99 (MYOCET®), peglylated liposomal doxorubicin (CAELYX®), and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), an epothilone, and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2'-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine (ELDISINE®, FILDESIN®); dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoid, *e.g.*, paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANE^{TM}), and docetaxel (TAXOTERE®); chloranbucil; 6-thioguanine; mercaptopurine; methotrexate; platinum agents such as cisplatin, oxaliplatin (*e.g.*, ELOXATIN®), and carboplatin; vincas, which prevent tubulin polymerization from forming microtubules, including vinblastine (VELBAN®), vincristine (ONCOVIN®), vindesine (ELDISINE®, FILDESIN®), and vinorelbine (NAVELBINE®); etoposide (VP-16); ifosfamide; mitoxantrone; leucovorin; novantrone; edatrexate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid, including bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacitabine (a 1,3-dioxolane

nucleoside cytosine analog); antisense oligonucleotides, particularly those that inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Raf, H-Ras, and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (*e.g.*, LURTOTECAN®); rmRH (*e.g.*, ABARELIX®); BAY439006 (sorafenib; Bayer); SU-11248 (sunitinib, SUTENT®, Pfizer); perifosine, COX-2 inhibitor (*e.g.,* celecoxib or etoricoxib), proteosome inhibitor (*e.g.,* PS341); bortezomib (VELCADE®); CCI-779; tipifarnib (R11577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; EGFR inhibitors (see definition below); tyrosine kinase inhibitors (see definition below); serine-threonine kinase inhibitors such as rapamycin (sirolimus, RAPAMUNE®); farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASAR^{TM}); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATIN^{TM}) combined with 5-FU and leucovorin.

[0093] Chemotherapeutic agents as defined herein include "anti-hormonal agents" or "endocrine therapeutics" which act to regulate, reduce, block, or inhibit the effects of hormones that can promote the growth of cancer. They may be hormones themselves, including, but not limited to: anti-estrogens with mixed agonist/antagonist profile, including, tamoxifen (NOLVADEX®), 4-hydroxytamoxifen, toremifene (FARESTON®), idoxifene, droloxifene, raloxifene (EVISTA®), trioxifene, keoxifene, and selective estrogen receptor modulators (SERMs) such as SERM3; pure anti-estrogens without agonist properties, such as fulvestrant (FASLODEX®), and EM800 (such agents may block estrogen receptor (ER) dimerization, inhibit DNA binding, increase ER turnover, and/or suppress ER levels); aromatase inhibitors, including steroidal aromatase inhibitors such as formestane and exemestane (AROMASIN®), and nonsteroidal aromatase inhibitors such as anastrazole (ARIMIDEX®), letrozole (FEMARA®) and aminoglutethimide, and other aromatase inhibitors include vorozole (RIVISOR®), megestrol acetate (MEGASE®), fadrozole, and 4(5)-imidazoles; lutenizing hormone-releaseing hormone agonists, including leuprolide (LUPRON® and ELIGARD®), goserelin, buserelin, and tripterelin; sex steroids, including progestines such as megestrol acetate and medroxyprogesterone acetate, estrogens such as diethylstilbestrol and premarin, and androgens/retinoids such as fluoxymesterone, all transretionic acid and fenretinide; onapristone; anti-progesterones; estrogen receptor down-regulators (ERDs); anti-androgens such as flutamide, nilutamide and bicalutamide; and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above.

[0094] The term "prodrug" as used in this application refers to a precursor or derivative form of a pharmaceutically active substance that is less cytotoxic to tumor cells compared to the parent drug and is

capable of being enzymatically activated or converted into the more active parent form. *See, e.g.*, Wilman, "Prodrugs in Cancer Chemotherapy" *Biochemical Society Transactions*, 14, pp. 375-382, 615th Meeting Belfast (1986) and Stella *et al.*, "Prodrugs: A Chemical Approach to Targeted Drug Delivery," *Directed Drug Delivery*, Borchardt *et al.*, (ed.), pp. 247-267, Humana Press (1985). The prodrugs of this invention include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, β-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into the more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form for use in this invention include, but are not limited to, those chemotherapeutic agents described above.

[0095] A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell (*e.g.*, a cell whose growth is dependent upon CDK8 expression either *in vitro* or *in vivo*). Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami *et al.*, (WB Saunders: Philadelphia, 1995), especially p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTERE®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (TAXOL®, Bristol-Myers Squibb). Paclitaxel and docetaxel promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization, which results in the inhibition of mitosis in cells.

[0096] By "radiation therapy" is meant the use of directed gamma rays or beta rays to induce sufficient damage to a cell so as to limit its ability to function normally or to destroy the cell altogether. It will be appreciated that there will be many ways known in the art to determine the dosage and duration of treatment. Typical treatments are given as a one time administration and typical dosages range from 10 to 200 units (Grays) per day.

[0097] An "individual" or "subject" is a mammal. Mammals include, but are not limited to, domesticated animals (*e.g.*, cows, sheep, cats, dogs, and horses), primates (*e.g.*, humans and non-human primates such as monkeys), rabbits, and rodents (*e.g.*, mice and rats). In certain embodiments, the individual or subject is a human.

[0098] The term "concurrently" is used herein to refer to administration of two or more therapeutic agents, where at least part of the administration overlaps in time. Accordingly, concurrent administration includes a dosing regimen when the administration of one or more agent(s) continues after discontinuing the administration of one or more other agent(s).

[0099] By "reduce or inhibit" is meant the ability to cause an overall decrease of 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or greater. Reduce or inhibit can refer to the symptoms of the disorder being treated, the presence or size of metastases, or the size of the primary tumor.

[0100] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

[0101] An "article of manufacture" is any manufacture (*e.g.*, a package or container) or kit comprising at least one reagent, *e.g.*, a medicament for treatment of a disease or disorder (*e.g.*, cancer), or a probe for specifically detecting a biomarker described herein. In certain embodiments, the manufacture or kit is promoted, distributed, or sold as a unit for performing the methods described herein.

[0102] A "target audience" is a group of people or an institution to whom or to which a particular medicament is being promoted or intended to be promoted, as by marketing or advertising, especially for particular uses, treatments, or indications, such as individuals, populations, readers of newspapers, medical literature, and magazines, television or internet viewers, radio or internet listeners, physicians, drug companies, etc.

[0103] As is understood by one skilled in the art, reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

[0104] It is understood that aspect and embodiments of the invention described herein include "consisting" and/or "consisting essentially of" aspects and embodiments. As used herein, the singular form "a", "an", and "the" includes plural references unless indicated otherwise.

II. Methods and Uses

[0105] Provided herein are methods utilizing a CDK8 antagonist. For example, in some embodiments, provided herein are methods of treating a disease or disorder in an individual comprising administering to the individual an effective amount of a CDK8 antagonist, wherein treatment is based upon differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)). In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of

the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0106] Also provided herein are methods of treating a cancer cell, wherein the cancer cell differentially expresses one or more biomarkers of a CDK8 gene signature (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)), the method comprising providing an effective amount of a CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0107] Also provided are methods of treating a disease or disorder in an individual comprising administering to the individual an effective amount of a CDK8 antagonist, wherein treatment is continued based upon differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)). In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is reduced expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or elevated expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0108] Provided herein are methods for treating a disease or disorder in an individual, the method comprising: determining that a sample obtained from the individual comprises differential expression levels of one or more biomarkers of a CDK8 gene signature (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)), and administering an effective amount of a CDK8 antagonist to the individual, whereby the disease or disorder is treated. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-reduced biomarkers of the CDK8 gene signature.

[0109] Methods are also provided herein for treating disease or disorder in an individual, comprising: (a) selecting an individual having differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)); and (b) administering to the individual thus selected an effective amount of a CDK8 antagonist, whereby the disease or disorder is treated. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0110] Provided are methods of identifying an individual with a disease or disorder who is more or less likely to exhibit benefit from treatment with a therapy comprising a CDK8 antagonist, the method comprising: determining the expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, wherein differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is more likely to exhibit benefit from treatment with the therapy comprising the CDK8 antagonist and/or non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is less likely to exhibit benefit from treatment with the therapy comprising the CDK8 antagonist. In some embodiments, the method further comprises administering an effective amount of a therapy comprising a CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0111] Further provided herein are methods for predicting whether an individual with a disease or disorder is more or less likely to respond effectively to treatment with a therapy comprising a CDK8 antagonist, the method comprising assessing expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, whereby differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is more likely to respond effectively to treatment with the CDK8 antagonist and/or non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is less likely to respond effectively to treatment with the CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0112] Further provided are methods of predicting the response or lack of response of an individual with a disease or disorder to a therapy comprising a CDK8 antagonist comprising measuring expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, wherein differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from

the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) is predictive of response of the individual to the therapy comprising the CDK8 antagonist and non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) is predictive of lack of response of the individual to the therapy comprising the CDK8 antagonist. In some embodiments, the method further comprises administering an effective amount of a therapy comprising a CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

[0113] Provided herein are methods of determining whether an individual having a disease or disorder is more or less likely responding to therapy, wherein therapy comprises a CDK8 antagonist, based upon levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, wherein differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) identifies the individual as more likely responding to therapy comprising the CDK8 antagonist and non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) identifies the individual as less likely responding to therapy comprising the CDK8 antagonist. In some embodiments, differential expression of one or more biomarkers of the CDK8 gene signature is reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature and/or elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature.

[0114] Also provided herein are methods of promoting differentiation of a stem cell and/or a cancer stem cell comprising contacting the cell with an effective amount of CDK8 antagonist. Provided herein are methods of treating cancer, wherein the cancer comprises cancer stem cell-like properties comprising administering to an individual an effective amount of a therapy comprising a CDK8 antagonist. In some embodiments, the CDK8 antagonist promotes differentiation of the cancer stem cell. In some embodiments, the cancer stem cell differentiates into a goblet cell and/or enterocyte cell. In some embodiments, the CDK8 antagonist inhibits growth and/or proliferation of the cancer. In some embodiments, the cancer stem cell-like properties comprise differential expression of one or more gene of the CDK8 signature.

[0115] In some embodiments, the one or more biomarkers of the CDK8 gene signature comprises one or more biomarkers of a CDK8 cancer cell gene signature. In some embodiments, the cancer cell is a colorectal

cancer cell. In some embodiments, the cancer cell is a colon cancer cell. In some embodiments, the one or more biomarkers of a CDK8 cancer cell gene signature comprises one or more biomarkers of Table 2. In some embodiments, the one or more biomarkers listed in Table 2 comprises one or more ES cell-related genes. In some embodiments, the one or more biomarkers listed in Table 2 comprises one or more MYC ES target genes. In some embodiments, the one or more biomarkers listed in Table 2 comprises one or more p53 signalling genes, cell cycle genes, Wnt signalling genes, and/or SMAD/BMP signalling genes. In some embodiments, the one or more biomarkers listed in Table 2 does not comprise (*e.g.*, excludes) ES genes and/or MYC ES target genes. In some embodiments, the one or more biomarkers listed in Table 2 comprises one or more p53 signalling genes, cell cycle genes, Wnt signalling genes, and/or SMAD/BMP signalling genes, but is not a MYC ES target gene and/or ES genes. In some embodiments, the one or more biomarkers of the CDK8 gene signature comprises one or more biomarkers of a CDK8 embryonic stem cell gene signature. In some embodiments, the one or more biomarkers of a CDK8 embryonic stem cell gene signature comprises one or more biomarkers of Table 3. In some embodiments, the one or more biomarkers of the CDK8 gene signature comprises one or more genes selected from the group consisting of SABP5, LEAP2, SKP2, CDK6, DICER1, LYAR, RNF138, STIL, POLD3, JAG2, OBRC2A, PPARGCIB, TPD52L2, MRPL12, NUCKS1, and GEMIN5.

[0116] In some embodiments of any of the methods, the one or more biomarkers of the CDK8 gene signature in Tables 2 and/or 3 have a P-value of greater than about any of $1x10^{-2}$, $1x10^{-3}$, $1x10^{-4}$, $1x10^{-5}$, $1x10^{-6}$, $1x10^{-7}$, $1x10^{-8}$, $1x10^{-9}$, and/or $1x10^{-10}$.

[0117] In some embodiments of any of the methods, the one or more biomarkers of the CDK8 gene signature, one or more biomarkers of a CDK8 cancer cell gene signature, and/or one or more biomarkers of a CDK8 embryonic stem cell gene signature includes greater than about any of 5, 10, 25, 50, 100, 175, 250, 375, 500, 625, 750, 875, 1000, 1125, 1250, 1375 and/or 1500 biomarkers listed in Table 2 and/or 3. In some embodiments of any of the methods, the one or more biomarkers of the CDK8 gene signature, one or more biomarkers of a CDK8 cancer cell gene signature, and/or one or more biomarkers of a CDK8 embryonic stem cell gene signature includes all of the biomarkers listed in Table 2 and/or 3. In some embodiments of any of the methods, the one or more biomarkers of the CDK8 gene signature includes all of the biomarkers listed in Table 2 and 3.

[0118] In some embodiments of any of the methods, the disease or disorder is an angiogenesis disease or disorder, proliferative disease or disorder, and/or an angiogenic disease or disorder. In some embodiments, the disease or disorder is a tumor and/or cancer. Examples of cancers and cancer cells include, but are not limited to, carcinoma, lymphoma, blastoma (including medulloblastoma and retinoblastoma), sarcoma (including liposarcoma and synovial cell sarcoma), neuroendocrine tumors (including carcinoid tumors, gastrinoma, and islet cell cancer), mesothelioma, schwannoma (including acoustic neuroma), meningioma, adenocarcinoma, melanoma, and leukemia or lymphoid malignancies. More particular examples of such

cancers include squamous cell cancer (*e.g.*, epithelial squamous cell cancer), lung cancer including small-cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer (including metastatic breast cancer), colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophageal cancer, tumors of the biliary tract, as well as head and neck cancer. In some embodiments, the cancer is metastatic cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is colon cancer.

[0119] In some embodiments of any of the methods, differential expression levels of one or more biomarkers of a CDK8 gene signature is elevated expression. In some embodiments, elevated expression refers to an overall increase of about any of 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (*e.g.*, protein or nucleic acid (*e.g.*, gene or mRNA)), detected by standard art known methods such as those described herein, as compared to a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In certain embodiments, the elevated expression refers to the increase in expression level/amount of a biomarker in the sample wherein the increase is at least about any of 1.5X, 1.75X, 2X, 3X, 4X, 5X, 6X, 7X, 8X, 9X, 10X, 25X, 50X, 75X, or 100X the expression level/amount of the respective biomarker in a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In some embodiments, elevated expression refers to an overall increase of greater than about any of 1.05 fold, 1.1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, about 1.75 fold, about 2 fold, about 2.25 fold, about 2.5 fold, about 2.75 fold, about 3.0 fold, or about 3.25 fold as compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene).

[0120] In some embodiments of any of the methods, differential expression levels of one or more biomarkers of a CDK8 gene signature is reduced expression. In some embodiments, reduced expression refers to an overall reduction of about any of 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (*e.g.*, protein or nucleic acid (*e.g.*, gene or mRNA)), detected by standard art known methods such as those described herein, as compared to a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In certain embodiments, reduced expression refers to the decrease in expression level/amount of a biomarker in the sample wherein the decrease is at least about any of 0.9X, 0.8X, 0.7X, 0.6X, 0.5X, 0.4X, 0.3X, 0.2X, 0.1X, 0.05X, or 0.01X the expression level/amount of the respective biomarker in a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue.

[0121] Presence and/or expression levels/amount of a biomarker of the CDK8 gene signature can be determined qualitatively and/or quantitatively based on any suitable criterion known in the art, including but not limited to DNA, mRNA, cDNA, proteins, protein fragments and/or gene copy number. In certain embodiments, presence and/or expression levels/amount of a biomarker in a first sample is increased as compared to presence/absence and/or expression levels/amount in a second sample. In certain embodiments, presence/absence and/or expression levels/amount of a biomarker in a first sample is decreased as compared to presence and/or expression levels/amount in a second sample. In certain embodiments, the second sample is a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. Additional disclosures for determining presence/absence and/or expression levels/amount of a gene are described herein. In some embodiments, the reference gene is CD133 and/or CD44.

[0122] Presence and/or expression level/amount of various biomarkers in a sample can be analyzed by a number of methodologies, many of which are known in the art and understood by the skilled artisan, including, but not limited to, immunohistochemical ("IHC"), Western blot analysis, immunoprecipitation, molecular binding assays, ELISA, ELIFA, fluorescence activated cell sorting ("FACS"), MassARRAY, proteomics, quantitative blood based assays (as for example Serum ELISA), biochemical enzymatic activity assays, in situ hybridization, Southern analysis, Northern analysis, whole genome sequencing, polymerase chain reaction ("PCR") including quantitative real time PCR ("qRT-PCR") and other amplification type detection methods, such as, for example, branched DNA, SISBA, TMA and the like), RNA-Seq, FISH, microarray analysis, gene expression profiling, and/or serial analysis of gene expression ("SAGE"), as well as any one of the wide variety of assays that can be performed by protein, gene, and/or tissue array analysis. Typical protocols for evaluating the status of genes and gene products are found, for example in Ausubel *et al.*, eds., 1995, Current Protocols In Molecular Biology, Units 2 (Northern Blotting), 4 (Southern Blotting), 15 (Immunoblotting) and 18 (PCR Analysis). Multiplexed immunoassays such as those available from Rules Based Medicine or Meso Scale Discovery ("MSD") may also be used.

[0123] In some embodiments, presence and/or expression level/amount of a biomarker is determined using a method comprising: (a) performing gene expression profiling, PCR (such as rtPCR), RNA-seq, microarray analysis, SAGE, MassARRAY technique, or FISH on a sample (such as an subject cancer sample); and b) determining presence and/or expression level/amount of a biomarker in the sample. In some embodiments, the microarray method comprises the use of a microarray chip having one or more nucleic acid molecules that can hybridize under stringent conditions to a nucleic acid molecule encoding a gene mentioned above or having one or more polypeptides (such as peptides or antibodies) that can bind to one or more of the proteins encoded by the genes mentioned above. In one embodiment, the PCR method is qRT-PCR. In one embodiment, the PCR method is multiplex-PCR. In some embodiments, gene expression is measured by

microarray. In some embodiments, gene expression is measured by qRT-PCR. In some embodiments, expression is measured by multiplex-PCR.

[0124] Methods for the evaluation of mRNAs in cells are well known and include, for example, hybridization assays using complementary DNA probes (such as in situ hybridization using labeled riboprobes specific for the one or more genes, Northern blot and related techniques) and various nucleic acid amplification assays (such as RT-PCR using complementary primers specific for one or more of the genes, and other amplification type detection methods, such as, for example, branched DNA, SISBA, TMA and the like).

[0125] Samples from mammals can be conveniently assayed for mRNAs using Northern, dot blot or PCR analysis. In addition, such methods can include one or more steps that allow one to determine the levels of target mRNA in a biological sample (*e.g.,* by simultaneously examining the levels a comparative control mRNA sequence of a "housekeeping" gene such as an actin family member). Optionally, the sequence of the amplified target cDNA can be determined.

[0126] Optional methods of the invention include protocols which examine or detect mRNAs, such as target mRNAs, in a tissue or cell sample by microarray technologies. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes whose expression correlates with increased or reduced clinical benefit of anti-angiogenic therapy may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene.

[0127] According to some embodiments, presence and/or expression level/amount is measured by observing protein expression levels of an aforementioned gene. In certain embodiments, the method comprises contacting the biological sample with antibodies to a biomarker described herein under conditions permissive for binding of the biomarker, and detecting whether a complex is formed between the antibodies and biomarker. Such method may be an in vitro or in vivo method. In one embodiment, an antibody is used to select subjects eligible for therapy with CDK8 antagonist, *e.g.,* a biomarker for selection of individuals.

[0128] In certain embodiments, the presence and/or expression level/amount of biomarker proteins in a sample is examined using IHC and staining protocols. IHC staining of tissue sections has been shown to be a reliable method of determining or detecting presence of proteins in a sample. In one aspect, expression level of biomarker is determined using a method comprising: (a) performing IHC analysis of a sample (such as a subject cancer sample) with an antibody; and b) determining expression level of a biomarker in the sample. In some embodiments, IHC staining intensity is determined relative to a reference value.

[0129] IHC may be performed in combination with additional techniques such as morphological staining and/or fluorescence in-situ hybridization. Two general methods of IHC are available; direct and indirect assays. According to the first assay, binding of antibody to the target antigen is determined directly. This direct assay uses a labeled reagent, such as a fluorescent tag or an enzyme-labeled primary antibody, which can be visualized without further antibody interaction. In a typical indirect assay, unconjugated primary antibody binds to the antigen and then a labeled secondary antibody binds to the primary antibody. Where the secondary antibody is conjugated to an enzymatic label, a chromogenic or fluorogenic substrate is added to provide visualization of the antigen. Signal amplification occurs because several secondary antibodies may react with different epitopes on the primary antibody.

[0130] The primary and/or secondary antibody used for IHC typically will be labeled with a detectable moiety. Numerous labels are available which can be generally grouped into the following categories: (a) Radioisotopes, such as 35S, 14C, 125I, 3H, and 131I; (b) colloidal gold particles; (c) fluorescent labels including, but are not limited to, rare earth chelates (europium chelates), Texas Red, rhodamine, fluorescein, dansyl, Lissamine, umbelliferone, phycocrytherin, phycocyanin, or commercially available fluorophores such SPECTRUM ORANGE7 and SPECTRUM GREEN7 and/or derivatives of any one or more of the above; (d) various enzyme-substrate labels are available and U.S. Patent No. 4,275,149 provides a review of some of these. Examples of enzymatic labels include luciferases (*e.g.,* firefly luciferase and bacterial luciferase; U.S. Patent No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, malate dehydrogenase, urease, peroxidase such as horseradish peroxidase (HRPO), alkaline phosphatase, β-galactosidase, glucoamylase, lysozyme, saccharide oxidases (*e.g.,* glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase), heterocyclic oxidases (such as uricase and xanthine oxidase), lactoperoxidase, microperoxidase, and the like.

[0131] Examples of enzyme-substrate combinations include, for example, horseradish peroxidase (HRPO) with hydrogen peroxidase as a substrate; alkaline phosphatase (AP) with para-Nitrophenyl phosphate as chromogenic substrate; and β-D-galactosidase (β-D-Gal) with a chromogenic substrate (*e.g.,* p-nitrophenyl-β-D-galactosidase) or fluorogenic substrate (*e.g.,* 4-methylumbelliferyl-β-D-galactosidase). For a general review of these, *see* U.S. Patent Nos. 4,275,149 and 4,318,980.

[0132] Specimens thus prepared may be mounted and coverslipped. Slide evaluation is then determined, *e.g.,* using a microscope, and staining intensity criteria, routinely used in the art, may be employed. In some embodiments, a staining pattern score of about 1+ or higher is diagnostic and/or prognostic. In certain embodiments, a staining pattern score of about 2+ or higher in an IHC assay is diagnostic and/or prognostic. In other embodiments, a staining pattern score of about 3 or higher is diagnostic and/or prognostic. In one embodiment, it is understood that when cells and/or tissue from a tumor or colon adenoma are examined using IHC, staining is generally determined or assessed in tumor cell and/or tissue (as opposed to stromal or surrounding tissue that may be present in the sample).

[0133] In alternative methods, the sample may be contacted with an antibody specific for said biomarker under conditions sufficient for an antibody-biomarker complex to form, and then detecting said complex. The presence of the biomarker may be detected in a number of ways, such as by Western blotting and ELISA procedures for assaying a wide variety of tissues and samples, including plasma or serum. A wide range of immunoassay techniques using such an assay format are available, *see, e.g.,* U.S. Pat. Nos. 4,016,043, 4,424,279 and 4,018,653. These include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labeled antibody to a target biomarker.

[0134] Presence and/or expression level/amount of a selected biomarker in a tissue or cell sample may also be examined by way of functional or activity-based assays. For instance, if the biomarker is an enzyme, one may conduct assays known in the art to determine or detect the presence of the given enzymatic activity in the tissue or cell sample.

[0135] In certain embodiments, the samples are normalized for both differences in the amount of the biomarker assayed and variability in the quality of the samples used, and variability between assay runs. Such normalization may be accomplished by detecting and incorporating the expression of certain normalizing biomarkers, including well known housekeeping genes, such as ACTB. Alternatively, normalization can be based on the mean or median signal of all of the assayed genes or a large subset thereof (global normalization approach). On a gene-by-gene basis, measured normalized amount of a subject tumor mRNA or protein is compared to the amount found in a reference set. Normalized expression levels for each mRNA or protein per tested tumor per subject can be expressed as a percentage of the expression level measured in the reference set. The presence and/or expression level/amount measured in a particular subject sample to be analyzed will fall at some percentile within this range, which can be determined by methods well known in the art.

[0136] In certain embodiments, relative expression level of a gene is determined as follows:

Relative expression gene1 sample1 = 2 exp (Ct housekeeping gene – Ct gene1) with Ct determined in a sample.

Relative expression gene1 reference RNA = 2 exp (Ct housekeeping gene – Ct gene1) with Ct determined in the reference sample.

Normalized relative expression gene1 sample1 = (relative expression gene1 sample1 / relative expression gene1 reference RNA) x 100

Ct is the threshold cycle. The Ct is the cycle number at which the fluorescence generated within a reaction crosses the threshold line.

[0137] All experiments are normalized to a reference RNA, which is a comprehensive mix of RNA from various tissue sources (*e.g.,* reference RNA #636538 from Clontech, Mountain View, CA). Identical

reference RNA is included in each qRT-PCR run, allowing comparison of results between different experimental runs.

[0138] In one embodiment, the sample is a clinical sample. In another embodiment, the sample is used in a diagnostic assay. In some embodiments, the sample is obtained from a primary or metastatic tumor. Tissue biopsy is often used to obtain a representative piece of tumor tissue. Alternatively, tumor cells can be obtained indirectly in the form of tissues or fluids that are known or thought to contain the tumor cells of interest. For instance, samples of lung cancer lesions may be obtained by resection, bronchoscopy, fine needle aspiration, bronchial brushings, or from sputum, pleural fluid or blood. Genes or gene products can be detected from cancer or tumor tissue or from other body samples such as urine, sputum, serum or plasma. The same techniques discussed above for detection of target genes or gene products in cancerous samples can be applied to other body samples. Cancer cells may be sloughed off from cancer lesions and appear in such body samples. By screening such body samples, a simple early diagnosis can be achieved for these cancers. In addition, the progress of therapy can be monitored more easily by testing such body samples for target genes or gene products.

[0139] In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is a single sample or combined multiple samples from the same subject or individual that are obtained at one or more different time points than when the test sample is obtained. For example, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained at an earlier time point from the same subject or individual than when the test sample is obtained. Such reference sample, reference cell, reference tissue, control sample, control cell, or control tissue may be useful if the reference sample is obtained during initial diagnosis of cancer and the test sample is later obtained when the cancer becomes metastatic.

[0140] In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is a combined multiple samples from one or more healthy individuals who are not the subject or individual. In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is a combined multiple samples from one or more individuals with a disease or disorder (*e.g.,* cancer) who are not the subject or individual. In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is pooled RNA samples from normal tissues or pooled plasma or serum samples from one or more individuals who are not the subject or individual. In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is pooled RNA samples from tumor tissues or pooled plasma or serum samples from one or more individuals with a disease or disorder (*e.g.,* cancer) who are not the subject or individual.

[0141] In some embodiments of any of the methods, the CDK8 antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the CDK8 antagonist is an

antibody. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a human, humanized, or chimeric antibody. In some embodiments, the antibody is an antibody fragment and the antibody fragment binds CDK8. In some embodiments, the CDK8 antagonist is a small molecule. In some embodiments, the small molecule is a small molecule kinase inhibitor. In some embodiments, the small molecule kinase inhibitor is selected from the group consisting of flavopiridol, ABT-869, AST-487, BMS-387032/SNS032, BIRB-796, sorafenib, staurosporine, cortistatin, cortistatin A, and/or a steroidal alkaloid or derivative thereof. In some embodiments, the CDK8 antagonist induces cell cycle arrest or is capable of promoting differentiation. In some embodiments, the CDK8 antagonist is capable of promoting a change in cell fate and promoting differentiation is indicated by reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature and/or elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature.

[0142] In some embodiments of any of the methods, the individual according to any of the above embodiments may be a human.

[0143] In some embodiments of any of the methods, the method comprises administering to an individual having such cancer an effective amount of a CDK8 antagonist. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. In some embodiments, the individual may be a human.

[0144] The CDK8 antagonist described herein can be used either alone or in combination with other agents in a therapy. For instance, a CDK8 antagonist, described herein may be co-administered with at least one additional therapeutic agent including another CDK8 antagonist. In certain embodiments, an additional therapeutic agent is a chemotherapeutic agent.

[0145] Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of the CDK8 antagonist can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent and/or adjuvant. CDK8 antagonist can also be used in combination with radiation therapy.

[0146] A CDK8 antagonist (*e.g.,* an antibody, binding polypeptide, and/or small molecule) described herein (and any additional therapeutic agent) can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, *e.g.,* by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but

not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

[0147] CDK8 antagonist (*e.g.,* an antibody, binding polypeptide, and/or small molecule) described herein may be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The CDK8 antagonist, need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of the CDK8 antagonist, present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[0148] For the prevention or treatment of disease, the appropriate dosage of a CDK8 antagonist, described herein (when used alone or in combination with one or more other additional therapeutic agents) will depend on the type of disease to be treated, the severity and course of the disease, whether the CDK8 antagonist, is administered for preventive or therapeutic purposes, previous therapy, the subject's clinical history and response to the CDK8 antagonist, and the discretion of the attending physician. The CDK8 antagonist is suitably administered to the individual at one time or over a series of treatments. One typical daily dosage might range from about 1 μg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. Such doses may be administered intermittently, *e.g.,* every week or every three weeks (*e.g.,* such that the individual receives from about two to about twenty, or *e.g.,* about six doses of the CDK8 antagonist). An initial higher loading dose, followed by one or more lower doses may be administered. An exemplary dosing regimen comprises administering. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

[0149] It is understood that any of the above formulations or therapeutic methods may be carried out using an immunoconjugate of the invention in place of or in addition to the CDK8 antagonist.

III. Therapeutic Compositions

[0150] Provided herein are CDK8 antagonists useful in the methods described herein. In some embodiments, the CDK8 antagonists are an antibody, binding polypeptide, small molecule, and/or polynucleotide.

A. Antibodies

[0151] In one aspect, provided herein isolated antibodies that bind to CDK8. In any of the above embodiments, an antibody is humanized. In a further aspect of the invention, an anti-CDK8 antibody according to any of the above embodiments is a monoclonal antibody, including a chimeric, humanized or human antibody. In one embodiment, an anti-CDK8 antibody is an antibody fragment, *e.g.*, a Fv, Fab, Fab', scFv, diabody, or $F(ab')_2$ fragment. In another embodiment, the antibody is a full length antibody, *e.g.*, an intact IgG1" antibody or other antibody class or isotype as defined herein.

[0152] In a further aspect, an anti-CDK8 antibody according to any of the above embodiments may incorporate any of the features, singly or in combination, as described in Sections below:

1. Antibody Affinity

[0153] In certain embodiments, an antibody provided herein has a dissociation constant (Kd) of $\leq$ 1μM. In one embodiment, Kd is measured by a radiolabeled antigen binding assay (RIA) performed with the Fab version of an antibody of interest and its antigen as described by the following assay. Solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of (^{125}I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (*see, e.g.,* Chen *et al., J. Mol. Biol.* 293:865-881(1999)). To establish conditions for the assay, MICROTITER® multi-well plates (Thermo Scientific) are coated overnight with 5 μg/ml of a capturing anti-Fab antibody (Cappel Labs) in 50 mM sodium carbonate (pH 9.6), and subsequently blocked with 2% (w/v) bovine serum albumin in PBS for two to five hours at room temperature (approximately 23°C). In a non-adsorbent plate (Nunc #269620), 100 pM or 26 pM [^{125}I]-antigen are mixed with serial dilutions of a Fab of interest (*e.g.,* consistent with assessment of the anti-VEGF antibody, Fab-12, in Presta *et al.*, *Cancer Res.* 57:4593-4599 (1997)). The Fab of interest is then incubated overnight; however, the incubation may continue for a longer period (*e.g.,* about 65 hours) to ensure that equilibrium is reached. Thereafter, the mixtures are transferred to the capture plate for incubation at room temperature (*e.g.,* for one hour). The solution is then removed and the plate washed eight times with 0.1% polysorbate 20 (TWEEN-20®) in PBS. When the plates have dried, 150 μl/well of scintillant (MICROSCINT-20™; Packard) is added, and the plates are counted on a TOPCOUNT™ gamma counter (Packard) for ten minutes. Concentrations of each Fab that give less than or equal to 20% of maximal binding are chosen for use in competitive binding assays.

[0154] According to another embodiment, Kd is measured using surface plasmon resonance assays using a BIACORE®-2000 or a BIACORE®-3000 (BIAcore, Inc., Piscataway, NJ) at 25°C with immobilized antigen CM5 chips at ~10 response units (RU). Briefly, carboxymethylated dextran biosensor chips (CM5, BIACORE, Inc.) are activated with *N*-ethyl-*N'*- (3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide (NHS) according to the supplier's instructions. Antigen is diluted with 10 mM sodium acetate, pH 4.8, to 5 μg/ml (~0.2 μM) before injection at a flow rate of 5 μl/minute to achieve approximately 10 response units (RU) of coupled protein. Following the injection of antigen, 1 M

ethanolamine is injected to block unreacted groups. For kinetics measurements, two-fold serial dilutions of Fab (0.78 nM to 500 nM) are injected in PBS with 0.05% polysorbate 20 (TWEEN-20™) surfactant (PBST) at 25°C at a flow rate of approximately 25 µl/min. Association rates (k_{on}) and dissociation rates (k_{off}) are calculated using a simple one-to-one Langmuir binding model (BIACORE® Evaluation Software version 3.2) by simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant (Kd) is calculated as the ratio k_{off}/k_{on}. *See, e.g.,* Chen *et al., J. Mol. Biol.* 293:865-881 (1999). If the on-rate exceeds $10^6 M^{-1}s^{-1}$ by the surface plasmon resonance assay above, then the on-rate can be determined by using a fluorescent quenching technique that measures the increase or decrease in fluorescence emission intensity (excitation = 295 nm; emission = 340 nm, 16 nm band-pass) at 25°C of a 20 nM anti-antigen antibody (Fab form) in PBS, pH 7.2, in the presence of increasing concentrations of antigen as measured in a spectrometer, such as a stop-flow equipped spectrophometer (Aviv Instruments) or a 8000-series SLM-AMINCO™ spectrophotometer (ThermoSpectronic) with a stirred cuvette.

2. *Antibody Fragments*

[0155] In certain embodiments, an antibody provided herein is an antibody fragment. Antibody fragments include, but are not limited to, Fab, Fab', Fab'-SH, $F(ab')_2$, Fv, and scFv fragments, and other fragments described below. For a review of certain antibody fragments, *see* Hudson *et al., Nat. Med.* 9:129-134 (2003). For a review of scFv fragments, *see, e.g.,* Pluckthün, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., (Springer-Verlag, New York), pp. 269-315 (1994); *see* also WO 93/16185; and U.S. Patent Nos. 5,571,894 and 5,587,458. For discussion of Fab and $F(ab')_2$ fragments comprising salvage receptor binding epitope residues and having increased *in vivo* half-life, *see* U.S. Patent No. 5,869,046.

[0156] Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. *See,* for example, EP 404,097; WO 1993/01161; Hudson *et al., Nat. Med.* 9:129-134 (2003); and Hollinger *et al., Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson *et al., Nat. Med.* 9:129-134 (2003).

[0157] Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, MA; *see, e.g.,* U.S. Patent No. 6,248,516 B1).

[0158] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (*e.g., E. coli* or phage), as described herein.

3. *Chimeric and Humanized Antibodies*

[0159] In certain embodiments, an antibody provided herein is a chimeric antibody. Certain chimeric antibodies are described, *e.g.,* in U.S. Patent No. 4,816,567; and Morrison *et al., Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). In one example, a chimeric antibody comprises a non-human variable region (*e.g.,* a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) and a human constant region. In a further example, a chimeric antibody is a "class switched" antibody in which the class or subclass has been changed from that of the parent antibody. Chimeric antibodies include antigen-binding fragments thereof.

[0160] In certain embodiments, a chimeric antibody is a humanized antibody. Typically, a non-human antibody is humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Generally, a humanized antibody comprises one or more variable domains in which HVRs, *e.g.,* CDRs, (or portions thereof) are derived from a non-human antibody, and FRs (or portions thereof) are derived from human antibody sequences. A humanized antibody optionally will also comprise at least a portion of a human constant region. In some embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (*e.g.,* the antibody from which the HVR residues are derived), *e.g.,* to restore or improve antibody specificity or affinity.

[0161] Humanized antibodies and methods of making them are reviewed, *e.g.,* in Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008), and are further described, *e.g.,* in Riechmann *et al., Nature* 332:323-329 (1988); Queen *et al., Proc. Nat'l Acad. Sci. USA* 86:10029-10033 (1989); US Patent Nos. 5, 821,337, 7,527,791, 6,982,321, and 7,087,409; Kashmiri *et al., Methods* 36:25-34 (2005) (describing SDR (a-CDR) grafting); Padlan, *Mol. Immunol.* 28:489-498 (1991) (describing "resurfacing"); Dall'Acqua *et al., Methods* 36:43-60 (2005) (describing "FR shuffling"); and Osbourn *et al., Methods* 36:61-68 (2005) and Klimka *et al., Br. J. Cancer*, 83:252-260 (2000) (describing the "guided selection" approach to FR shuffling).

[0162] Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the "best-fit" method (*see, e.g.,* Sims *et al., J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (*see, e.g.,* Carter *et al., Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); and Presta *et al., J. Immunol.*, 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (*see, e.g.,* Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (*see, e.g.,* Baca *et al., J. Biol. Chem.* 272:10678-10684 (1997) and Rosok *et al., J. Biol. Chem.* 271:22611-22618 (1996)).

4. Human Antibodies

[0163] In certain embodiments, an antibody provided herein is a human antibody. Human antibodies can be produced using various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5: 368-74 (2001) and Lonberg, *Curr. Opin. Immunol.* 20:450-459 (2008).

[0164] Human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal's chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have generally been inactivated. For review of methods for obtaining human antibodies from transgenic animals, *see* Lonberg, Nat. Biotech. 23:1117-1125 (2005). *See also*, *e.g.,* U.S. Patent Nos. 6,075,181 and 6,150,584 describing XENOMOUSE™ technology; U.S. Patent No. 5,770,429 describing HuMab® technology; U.S. Patent No. 7,041,870 describing K-M MOUSE® technology, and U.S. Patent Application Publication No. US 2007/0061900, describing VelociMouse® technology). Human variable regions from intact antibodies generated by such animals may be further modified, *e.g.,* by combining with a different human constant region.

[0165] Human antibodies can also be made by hybridoma-based methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described. (*See, e.g.,* Kozbor *J. Immunol.*, 133: 3001 (1984); and Boerner *et al.*, J. Immunol., 147: 86 (1991).) Human antibodies generated via human B-cell hybridoma technology are also described in Li *et al.*, *Proc. Natl. Acad. Sci. USA*, 103:3557-3562 (2006). Additional methods include those described, for example, in U.S. Patent No. 7,189,826 (describing production of monoclonal human IgM antibodies from hybridoma cell lines) and Ni, *Xiandai Mianyixue*, 26(4):265-268 (2006) (describing human-human hybridomas). Human hybridoma technology (Trioma technology) is also described in Vollmers and Brandlein, *Histology and Histopathology*, 20(3):927-937 (2005) and Vollmers and Brandlein, *Methods and Findings in Experimental and Clin. Pharma.*, 27(3):185-91 (2005).

[0166] Human antibodies may also be generated by isolating Fv clone variable domain sequences selected from human-derived phage display libraries. Such variable domain sequences may then be combined with a desired human constant domain. Techniques for selecting human antibodies from antibody libraries are described below.

5. Library-Derived Antibodies

[0167] Antibodies of the invention may be isolated by screening combinatorial libraries for antibodies with the desired activity or activities. For example, a variety of methods are known in the art for generating phage

display libraries and screening such libraries for antibodies possessing the desired binding characteristics. Such methods are reviewed, *e.g.,* in Hoogenboom *et al.,* in METHODS IN MOL. BIOL. 178:1-37 (O'Brien *et al.*, ed., Human Press, Totowa, NJ, 2001) and further described, *e.g.,* in the McCafferty *et al.*, Nature 348:552-554; Clackson *et al.*, *Nature* 352: 624-628 (1991); Marks *et al.*, *J. Mol. Biol.* 222: 581-597 (1992); Marks and Bradbury, in METHODS IN MOL. BIOL. 248:161-175 (Lo, ed., Human Press, Totowa, NJ, 2003); Sidhu *et al.*, *J. Mol. Biol.* 338(2): 299-310 (2004); Lee *et al.*, J. Mol. Biol. 340(5): 1073-1093 (2004); Fellouse, *Proc. Natl. Acad. Sci. USA* 101(34): 12467-12472 (2004); and Lee *et al.*, *J. Immunol. Methods* 284(1-2): 119-132(2004).

[0168] In certain phage display methods, repertoires of VH and VL genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be screened for antigen-binding phage as described in Winter *et al.*, *Ann. Rev. Immunol.*, 12: 433-455 (1994). Phage typically display antibody fragments, either as single-chain Fv (scFv) fragments or as Fab fragments. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (*e.g.,* from human) to provide a single source of antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths *et al.*, *EMBO J*, 12: 725-734 (1993). Finally, naive libraries can also be made synthetically by cloning unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement in vitro, as described by Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381-388 (1992). Patent publications describing human antibody phage libraries include, for example: US Patent No. 5,750,373, and US Patent Publication Nos. 2005/0079574, 2005/0119455, 2005/0266000, 2007/0117126, 2007/0160598, 2007/0237764, 2007/0292936, and 2009/0002360.

[0169] Antibodies or antibody fragments isolated from human antibody libraries are considered human antibodies or human antibody fragments herein.

6. Multispecific Antibodies

[0170] In certain embodiments, an antibody provided herein is a multispecific antibody, *e.g.,* a bispecific antibody. Multispecific antibodies are monoclonal antibodies that have binding specificities for at least two different sites. In certain embodiments, one of the binding specificities is for CDK8 polypeptide and the other is for any other antigen. In certain embodiments, bispecific antibodies may bind to two different epitopes of CDK8 polypeptide. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express CDK8 polypeptide. Bispecific antibodies can be prepared as full length antibodies or antibody fragments.

[0171] Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two immunoglobulin heavy chain-light chain pairs having different specificities (*see* Milstein and Cuello, *Nature* 305: 537 (1983)), WO 93/08829, and Traunecker *et al.*, *EMBO J.* 10: 3655 (1991)), and

"knob-in-hole" engineering (*see, e.g.,* U.S. Patent No. 5,731,168). Multi-specific antibodies may also be made by engineering electrostatic steering effects for making antibody Fc-heterodimeric molecules (WO 2009/089004A1); cross-linking two or more antibodies or fragments (*see, e.g.,* US Patent No. 4,676,980, and Brennan *et al.*, *Science*, 229: 81 (1985)); using leucine zippers to produce bi-specific antibodies (*see, e.g.,* Kostelny *et al.*, *J. Immunol.*, 148(5):1547-1553 (1992)); using "diabody" technology for making bispecific antibody fragments (*see, e.g.,* Hollinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993)); and using single-chain Fv (sFv) dimers (*see, e.g.,* Gruber *et al.*, *J. Immunol.*, 152:5368 (1994)); and preparing trispecific antibodies as described, *e.g.,* in Tutt *et al.*, *J. Immunol.* 147: 60 (1991).

[0172] Engineered antibodies with three or more functional antigen binding sites, including "Octopus antibodies," are also included herein (*see, e.g.,* US 2006/0025576).

[0173] The antibody or fragment herein also includes a "Dual Acting FAb" or "DAF" comprising an antigen binding site that binds to a CDK8 polypeptide as well as another, different antigen (*see,* US 2008/0069820, for example).

7. Antibody Variants

a) Glycosylation variants

[0174] In certain embodiments, an antibody provided herein is altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[0175] Where the antibody comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. *See, e.g.,* Wright *et al.*, *TIBTECH* 15:26-32 (1997). The oligosaccharide may include various carbohydrates, *e.g.,* mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody variants with certain improved properties.

[0176] In one embodiment, antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (e. g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (Eu numbering of Fc region residues); however, Asn297 may also be located about ± 3 amino acids upstream or downstream of position 297, *i.e.*,

between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. *See, e.g.,* US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to "defucosylated" or "fucose-deficient" antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki *et al., J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki *et al., Biotech. Bioeng.* 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka *et al., Arch. Biochem. Biophys.* 249:533-545 (1986); US 2003/0157108, Presta, L; and WO 2004/056312, Adams *et al.*, especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (*see, e.g.,* Yamane-Ohnuki *et al., Biotech. Bioeng.* 87: 614 (2004); Kanda, Y. *et al., Biotechnol. Bioeng.*, 94(4):680-688 (2006); and WO2003/085107).

[0177] Antibodies variants are further provided with bisected oligosaccharides, *e.g.,* in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, *e.g.,* in WO 2003/011878 (Jean-Mairet *et al.*); US Patent No. 6,602,684 (Umana *et al.*); and US 2005/0123546 (Umana *et al.*). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, *e.g.,* in WO 1997/30087 (Patel *et al.*); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

b) Fc region variants

[0178] In certain embodiments, one or more amino acid modifications may be introduced into the Fc region of an antibody provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (*e.g.,* a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (*e.g.,* a substitution) at one or more amino acid positions.

[0179] In certain embodiments, the invention contemplates an antibody variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half life of the antibody *in vivo* is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. *In vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of

Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest is described in U.S. Patent No. 5,500,362 (*see, e.g.,* Hellstrom, I. *et al., Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I *et al., Proc. Nat'l Acad. Sci. USA* 82:1499-1502 (1985); 5,821,337 (*see* Bruggemann, M. *et al., J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (*see,* for example, ACTI™ non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, *e.g.,* in a animal model such as that disclosed in Clynes *et al., Proc. Natl. Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. *See, e.g.,* C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (*see,* for example, Gazzano-Santoro *et al., J. Immunol. Methods* 202:163 (1996); Cragg, M.S. *et al., Blood* 101:1045-1052 (2003); and Cragg, M.S. and M.J. Glennie, *Blood* 103:2738-2743 (2004)). FcRn binding and *in vivo* clearance/half life determinations can also be performed using methods known in the art (*see, e.g.,* Petkova, S.B. *et al., Int'l. Immunol.* 18(12):1759-1769 (2006)).

[0180] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Patent No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581).

[0181] Certain antibody variants with improved or diminished binding to FcRs are described. (*See, e.g.,* U.S. Patent No. 6,737,056; WO 2004/056312, and Shields *et al., J. Biol. Chem.* 9(2): 6591-6604 (2001).) In certain embodiments, an antibody variant comprises an Fc region with one or more amino acid substitutions which improve ADCC, *e.g.,* substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues). In some embodiments, alterations are made in the Fc region that result in altered (*i.e.*, either improved or diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), *e.g.,* as described in US Patent No. 6,194,551, WO 99/51642, and Idusogie *et al., J. Immunol.* 164: 4178-4184 (2000).

[0182] Antibodies with increased half lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer *et al., J. Immunol.* 117:587 (1976) and Kim *et al., J. Immunol.* 24:249 (1994)), are described in US2005/0014934A1 (Hinton *et al.*). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, *e.g.,* substitution of Fc region residue 434 (US Patent No. 7,371,826). *See also* Duncan & Winter, *Nature*

322:738-40 (1988); U.S. Patent No. 5,648,260; U.S. Patent No. 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

c) Cysteine engineered antibody variants

[0183] In certain embodiments, it may be desirable to create cysteine engineered antibodies, *e.g.*, "thioMAbs," in which one or more residues of an antibody are substituted with cysteine residues. In particular embodiments, the substituted residues occur at accessible sites of the antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, to create an immunoconjugate, as described further herein. In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, *e.g.*, in U.S. Patent No. 7,521,541.

B. Immunoconjugates

[0184] Further provided herein are immunoconjugates comprising an anti-CDK8 antibody conjugated to one or more cytotoxic agents, such as chemotherapeutic agents or drugs, growth inhibitory agents, toxins (*e.g.*, protein toxins, enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof), or radioactive isotopes.

[0185] In one embodiment, an immunoconjugate is an antibody-drug conjugate (ADC) in which an antibody is conjugated to one or more drugs, including but not limited to a maytansinoid (*see* U.S. Patent Nos. 5,208,020, 5,416,064 and European Patent EP 0 425 235 B1); an auristatin such as monomethylauristatin drug moieties DE and DF (MMAE and MMAF) (*see* U.S. Patent Nos. 5,635,483 and 5,780,588, and 7,498,298); a dolastatin; a calicheamicin or derivative thereof (*see* U.S. Patent Nos. 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, and 5,877,296; Hinman *et al.*, *Cancer Res.* 53:3336-3342 (1993); and Lode *et al.*, *Cancer Res.* 58:2925-2928 (1998)); an anthracycline such as daunomycin or doxorubicin (*see* Kratz *et al.*, *Current Med. Chem.* 13:477-523 (2006); Jeffrey *et al.*, *Bioorganic & Med. Chem. Letters* 16:358-362 (2006); Torgov *et al.*, *Bioconj. Chem.* 16:717-721 (2005); Nagy *et al.*, *Proc. Natl. Acad. Sci. USA* 97:829-834 (2000); Dubowchik *et al.*, *Bioorg. & Med. Chem. Letters* 12:1529-1532 (2002); King *et al.*, *J. Med. Chem.* 45:4336-4343 (2002); and U.S. Patent No. 6,630,579); methotrexate; vindesine; a taxane such as docetaxel, paclitaxel, larotaxel, tesetaxel, and ortataxel; a trichothecene; and CC1065.

[0186] In another embodiment, an immunoconjugate comprises an antibody as described herein conjugated to an enzymatically active toxin or fragment thereof, including but not limited to diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes.

[0187] In another embodiment, an immunoconjugate comprises an antibody as described herein conjugated to a radioactive atom to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugates. Examples include At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu. When the radioconjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example Tc^{99} or I^{123}, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, MRI), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

[0188] Conjugates of an antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, *Science* 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. *See* WO94/11026. The linker may be a "cleavable linker" facilitating release of a cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari *et al.*, *Cancer Res.* 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

[0189] The immunuoconjugates or ADCs herein expressly contemplate, but are not limited to such conjugates prepared with cross-linker reagents including, but not limited to, BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate) which are commercially available (*e.g.,* from Pierce Biotechnology, Inc., Rockford, IL., USA).

C. Binding Polypeptides

[0190] Binding polypeptides are polypeptides that bind, preferably specifically, to CDK8 as described herein. In some embodiments, the binding polypeptides are CDK8 antagonists.

[0191] Binding polypeptides may be chemically synthesized using known polypeptide synthesis methodology or may be prepared and purified using recombinant technology. Binding polypeptides are usually at least about 5 amino acids in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74,

75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length or more, wherein such binding polypeptides that are capable of binding, preferably specifically, to a target, CDK8, as described herein. Binding polypeptides may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening polypeptide libraries for binding polypeptides that are capable of specifically binding to a polypeptide target are well known in the art (*see, e.g.,* U.S. Patent Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/03564; Geysen *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 81:3998-4002 (1984); Geysen *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 82:178-182 (1985); Geysen *et al.*, in Synthetic Peptides as Antigens, 130-149 (1986); Geysen *et al.*, *J. Immunol. Meth.*, 102:259-274 (1987); Schoofs *et al.*, *J. Immunol.*, 140:611-616 (1988), Cwirla, S. E. *et al.,* (1990) *Proc. Natl. Acad. Sci. USA*, 87:6378; Lowman, H.B. *et al.,* (1991) *Biochemistry*, 30:10832; Clackson, T. *et al.,* (1991) *Nature*, 352: 624; Marks, J. D. *et al.,* (1991), *J. Mol. Biol.*, 222:581; Kang, A.S. *et al.,* (1991) *Proc. Natl. Acad. Sci. USA*, 88:8363, and Smith, G. P. (1991) *Current Opin. Biotechnol.*, 2:668).

[0192] In this regard, bacteriophage (phage) display is one well known technique which allows one to screen large polypeptide libraries to identify member(s) of those libraries which are capable of specifically binding to a target polypeptide, CDK8 polypeptide. Phage display is a technique by which variant polypeptides are displayed as fusion proteins to the coat protein on the surface of bacteriophage particles (Scott, J.K. and Smith, G. P. (1990) *Science*, 249: 386). The utility of phage display lies in the fact that large libraries of selectively randomized protein variants (or randomly cloned cDNAs) can be rapidly and efficiently sorted for those sequences that bind to a target molecule with high affinity. Display of peptide (Cwirla, S. E. *et al.,* (1990) *Proc. Natl. Acad. Sci. USA*, 87:6378) or protein (Lowman, H.B. *et al.,* (1991) *Biochemistry*, 30:10832; Clackson, T. *et al.,* (1991) *Nature*, 352: 624; Marks, J. D. *et al.,* (1991), *J. Mol. Biol.*, 222:581; Kang, A.S. *et al.,* (1991) *Proc. Natl. Acad. Sci. USA*, 88:8363) libraries on phage have been used for screening millions of polypeptides or oligopeptides for ones with specific binding properties (Smith, G. P. (1991) *Current Opin. Biotechnol.*, 2:668). Sorting phage libraries of random mutants requires a strategy for constructing and propagating a large number of variants, a procedure for affinity purification using the target receptor, and a means of evaluating the results of binding enrichments. U.S. Patent Nos. 5,223,409, 5,403,484, 5,571,689, and 5,663,143.

[0193] Although most phage display methods have used filamentous phage, lambdoid phage display systems (WO 95/34683; U.S. 5,627,024), T4 phage display systems (Ren *et al.*, *Gene*, 215: 439 (1998); Zhu *et al.*, *Cancer Research*, 58(15): 3209-3214 (1998); Jiang *et al.*, *Infection & Immunity*, 65(11): 4770-4777 (1997); Ren *et al.*, *Gene*, 195(2):303-311 (1997); Ren, *Protein Sci.*, 5: 1833 (1996); Efimov *et al.*, *Virus Genes*, 10: 173 (1995)) and T7 phage display systems (Smith and Scott, *Methods in Enzymology*, 217: 228-257 (1993); U.S. 5,766,905) are also known.

[0194] Additional improvements enhance the ability of display systems to screen peptide libraries for binding to selected target molecules and to display functional proteins with the potential of screening these proteins for desired properties. Combinatorial reaction devices for phage display reactions have been developed (WO 98/14277) and phage display libraries have been used to analyze and control bimolecular interactions (WO 98/20169; WO 98/20159) and properties of constrained helical peptides (WO 98/20036). WO 97/35196 describes a method of isolating an affinity ligand in which a phage display library is contacted with one solution in which the ligand will bind to a target molecule and a second solution in which the affinity ligand will not bind to the target molecule, to selectively isolate binding ligands. WO 97/46251 describes a method of biopanning a random phage display library with an affinity purified antibody and then isolating binding phage, followed by a micropanning process using microplate wells to isolate high affinity binding phage. The use of *Staphylococcus aureus* protein A as an affinity tag has also been reported (Li *et al.,* (1998) *Mol Biotech.*, 9:187). WO 97/47314 describes the use of substrate subtraction libraries to distinguish enzyme specificities using a combinatorial library which may be a phage display library. A method for selecting enzymes suitable for use in detergents using phage display is described in WO 97/09446. Additional methods of selecting specific binding proteins are described in U.S. Patent Nos. 5,498,538, 5,432,018, and WO 98/15833.

[0195] Methods of generating peptide libraries and screening these libraries are also disclosed in U.S. Patent Nos. 5,723,286, 5,432,018, 5,580,717, 5,427,908, 5,498,530, 5,770,434, 5,734,018, 5,698,426, 5,763,192, and 5,723,323.

D. Small molecules

[0196] Provided herein are small molecules for use as a CDK8 small molecule antagonist. In some embodiments, the CDK8 small molecule antagonist is flavopiridol or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is ABT-869 or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is AST-487 or derivative thereof. In some embodiments, the CDK8 small molecule BMS-387032/SNS032 or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is BIRB-796 or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is CP-724714 or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is sorafenib or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is staurosporine or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is cortistatin or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is cortistatin A or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is a steroidal alkaloid or derivative thereof. In some embodiments, the CDK8 small molecule antagonist is a small molecule kinase inhibitor disclosed in Karman M.W. *et al.*, *Nature Biotech.* 26(1):127-132 (2008), Schneider E.V. *et al.*, *J. Mol. Biol.* 412:251-266 (2011), Cee V.J. *et al.*, *Angew. Chem. Int. Ed.* 48:8952-8957 (2009), which are incorporated by reference in their entireties. Methods of screening for CDK8 small molecule antagonists are known in the art and

described in Karman M.W. *et al.*, *Nature Biotech.* 26(1):127-132 (2008), Schneider E.V. *et al.*, *J. Mol. Biol.* 412:251-266 (2011), Cee V.J. *et al.*, *Angew. Chem. Int. Ed.* 48:8952-8957 (2009), which are incorporated by reference in their entireties.

[0197] Small molecules are preferably organic molecules other than binding polypeptides or antibodies as defined herein that bind, preferably specifically, to CDK8 polypeptide as described herein. Organic small molecules may be identified and chemically synthesized using known methodology (*see, e.g.,* PCT Publication Nos. WO00/00823 and WO00/39585). Organic small molecules are usually less than about 2000 Daltons in size, alternatively less than about 1500, 750, 500, 250 or 200 Daltons in size, wherein such organic small molecules that are capable of binding, preferably specifically, to a polypeptide as described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic small molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (*see, e.g.,* PCT Publication Nos. WO00/00823 and WO00/39585). Organic small molecules may be, for example, aldehydes, ketones, oximes, hydrazones, semicarbazones, carbazides, primary amines, secondary amines, tertiary amines, N-substituted hydrazines, hydrazides, alcohols, ethers, thiols, thioethers, disulfides, carboxylic acids, esters, amides, ureas, carbamates, carbonates, ketals, thioketals, acetals, thioacetals, aryl halides, aryl sulfonates, alkyl halides, alkyl sulfonates, aromatic compounds, heterocyclic compounds, anilines, alkenes, alkynes, diols, amino alcohols, oxazolidines, oxazolines, thiazolidines, thiazolines, enamines, sulfonamides, epoxides, aziridines, isocyanates, sulfonyl chlorides, diazo compounds, acid chlorides, or the like.

E. Antagonist Polynucleotides

[0198] Provided are polynucleotide CDK8 antagonists for use in any of the methods described herein. In some embodiments, the polynucleotide CDK8 antagonists is AGCCAAGAGGAAAGAUGGG (SEQ ID NO:1), GCGAAUUACUCAGAACAG (SEQ ID NO:2), AGGUGUUUCUGUCUCAUGC (SEQ ID NO:3), UAGAAGGAACUGGGAUCUC (SEQ ID NO:4), GAATGGTGAAGTCACTATTAT (SEQ ID NO:5), CCCGATTATTTAATTCACCTT (SEQ ID NO:7), CAGGGATTTGAAACCTGCTAA (SEQ ID NO:8); shNanog, GCCAGTGATTTGGAGGTGAAT (SEQ ID NO:9), CAAAACTAGTAATCCTTATTT (SEQ ID NO:12), CCCTTACCCAAAACGAGAATT (SEQ ID NO:13), CCCATCTTTCCTCTTGGCTT (SEQ ID NO:14), CTGTTCTGAGGTAATTCGCT (SEQ ID NO:15), GCATGAGACAGAAACACCCTT (SEQ ID NO:16), GAGATCCCAGTTCCTTCTAT (SEQ ID NO:17), and/or GUUUUUFCCGGUUGUCAAA (SEQ ID NO:18). In some embodiments, the polynucleotide CDK8 antagonist is a polynucleotide CDK8 antagonist disclosed in US 2004/0180848.

[0199] The polynucleotide may be an antisense nucleic acid and/or a ribozyme. The antisense nucleic acids comprise a sequence complementary to at least a portion of an RNA transcript of a CDK8 gene. However, absolute complementarity, although preferred, is not required.

[0200] A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded CDK8 antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a CDK8 RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

[0201] Polynucleotides that are complementary to the 5' end of the message, *e.g.,* the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. *See generally*, Wagner, R., 1994, *Nature* 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'-non-translated, non-coding regions of the CDK8 gene, could be used in an antisense approach to inhibit translation of endogenous CDK8 mRNA. Polynucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense polynucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of CDK8 mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

[0202] In one embodiment, the CDK8 antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the CDK8 gene. Such a vector would contain a sequence encoding the CDK8 antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others know in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding CDK8, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature* 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, *Cell* 22:787-797 (1980), the herpes thymidine promoter (Wagner *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster *et al.*, *Nature* 296:39-42 (1982)), etc.

F. Antibody and Binding Polypeptide Variants

[0203] In certain embodiments, amino acid sequence variants of the antibodies and/or the binding polypeptides provided herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody and/or binding polypeptide. Amino acid sequence variants of an antibody and/or binding polypeptides may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody and/or binding polypeptide, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody and/or binding polypeptide. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, *e.g.*, target-binding.

[0204] In certain embodiments, antibody variants and/or binding polypeptide variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the HVRs and FRs. Conservative substitutions are shown in Table 1 under the heading of "conservative substitutions." More substantial changes are provided in Table 1 under the heading of "exemplary substitutions," and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into an antibody and/or binding polypeptide of interest and the products screened for a desired activity, *e.g.*, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

TABLE 1

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr

Original Residue	Exemplary Substitutions	Preferred Substitutions
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

[0205] Amino acids may be grouped according to common side-chain properties:

(1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;

(2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

(3) acidic: Asp, Glu;

(4) basic: His, Lys, Arg;

(5) residues that influence chain orientation: Gly, Pro;

(6) aromatic: Trp, Tyr, Phe.

[0206] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[0207] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (*e.g.,* a humanized or human antibody). Generally, the resulting variant(s) selected for further study will have modifications (*e.g.,* improvements) in certain biological properties (*e.g.,* increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, *e.g.,* using phage display-based affinity maturation techniques such as those described herein. Briefly, one or more HVR residues are mutated and the variant antibodies displayed on phage and screened for a particular biological activity (*e.g.,* binding affinity).

[0208] Alterations (*e.g.,* substitutions) may be made in HVRs, *e.g.,* to improve antibody affinity. Such alterations may be made in HVR "hotspots," *i.e.*, residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (*see, e.g.,* Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)), and/or SDRs (a-CDRs), with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, *e.g.,* in Hoogenboom *et al.,* in METHODS IN MOL. BIOL. 178:1-37 (O'Brien *et al.*, ed., Human Press, Totowa, NJ, (2001).) In some embodiments of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (*e.g.,* error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any

antibody variants with the desired affinity. Another method to introduce diversity involves HVR-directed approaches, in which several HVR residues (*e.g.,* 4-6 residues at a time) are randomized. HVR residues involved in antigen binding may be specifically identified, *e.g.,* using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

[0209] In certain embodiments, substitutions, insertions, or deletions may occur within one or more HVRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (*e.g.,* conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in HVRs. Such alterations may be outside of HVR "hotspots" or SDRs. In certain embodiments of the variant VH and VL sequences provided above, each HVR either is unaltered, or contains no more than one, two or three amino acid substitutions.

[0210] A useful method for identification of residues or regions of the antibody and/or the binding polypeptide that may be targeted for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells (1989) *Science*, 244:1081-1085. In this method, a residue or group of target residues (*e.g.,* charged residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (*e.g.,* alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

[0211] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (*e.g.,* for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

G. Antibody and Binding Polypeptide Derivatives

[0212] In certain embodiments, an antibody and/or binding polypeptide provided herein may be further modified to contain additional nonproteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody and/or binding polypeptide include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propropylene glycol homopolymers, prolypropylene oxide/ethylene

oxide co-polymers, polyoxyethylated polyols (*e.g.,* glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody and/or binding polypeptide may vary, and if more than one polymer is attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody and/or binding polypeptide to be improved, whether the antibody derivative and/or binding polypeptide derivative will be used in a therapy under defined conditions, etc.

[0213] In another embodiment, conjugates of an antibody and/or binding polypeptide to nonproteinaceous moiety that may be selectively heated by exposure to radiation are provided. In one embodiment, the nonproteinaceous moiety is a carbon nanotube (Kam *et al.*, *Proc. Natl. Acad. Sci. USA* 102: 11600-11605 (2005)). The radiation may be of any wavelength, and includes, but is not limited to, wavelengths that do not harm ordinary cells, but which heat the nonproteinaceous moiety to a temperature at which cells proximal to the antibody and/or binding polypeptide-nonproteinaceous moiety are killed.

H. Recombinant Methods and Compositions

[0214] Antibodies and/or binding polypeptides may be produced using recombinant methods and compositions, *e.g.*, as described in U.S. Patent No. 4,816,567. In one embodiment, isolated nucleic acid encoding an anti-CDK8 antibody. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (*e.g.*, the light and/or heavy chains of the antibody). In a further embodiment, one or more vectors (*e.g.*, expression vectors) comprising such nucleic acid encoding the antibody and/or binding polypeptide are provided. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a host cell comprises (*e.g.*, has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antibody. In one embodiment, the host cell is eukaryotic, *e.g.,* a Chinese Hamster Ovary (CHO) cell or lymphoid cell (*e.g.*, Y0, NS0, Sp20 cell). In one embodiment, a method of making an antibody such as an anti-CDK8 antibody and/or binding polypeptide is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody and/or binding polypeptide, as provided above, under conditions suitable for expression of the antibody and/or binding polypeptide, and optionally recovering the antibody and/or polypeptide from the host cell (or host cell culture medium).

[0215] For recombinant production of an antibody such as an anti-CDK8 antibody and/or a binding polypeptide, nucleic acid encoding the antibody and/or the binding polypeptide, *e.g.*, as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such

nucleic acid may be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0216] Suitable host cells for cloning or expression of vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, *see, e.g.,* U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523. (*See* also Charlton, METHODS IN MOL. BIOL., *Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli.*) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0217] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. *See* Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li *et al.*, *Nat. Biotech.* 24:210-215 (2006).

[0218] Suitable host cells for the expression of glycosylated antibody and/or glycosylated binding polypeptides are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[0219] Plant cell cultures can also be utilized as hosts. *See, e.g.,* US Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[0220] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, *e.g.*, in Graham *et al., J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, *e.g.,* in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, *e.g.,* in Mather *et al., Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including $DHFR^-$ CHO cells (Urlaub *et al., Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production and/or binding polypeptide production, *see, e.g.,* Yazaki and Wu, METHODS IN MOL. BIOL., *Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

[0221] While the description relates primarily to production of antibodies and/or binding polypeptides by culturing cells transformed or transfected with a vector containing antibody- and binding polypeptide-encoding nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare antibodies and/or binding polypeptides. For instance, the appropriate amino acid sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [*see, e.g.,* Stewart *et al.*, *Solid-Phase Peptide Synthesis*, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, *J. Am. Chem. Soc.*, 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the antibody and/or binding polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the desired antibody and/or binding polypeptide.

III. Methods of Screening and/or Identifying CDK8 Antagonists With Desired Function

[0222] Techniques for generating CDK8 antagonists such as antibodies, binding polypeptides, and/or small molecules have been described above. Additional CDK8 antagonists such as anti-CDK8 antibodies, binding polypeptides, and/or small molecules provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

[0223] Provided herein are methods of screening for and/or identifying a CDK8 antagonist which promotes cell differentiation said method comprising: contacting a reference cell, wherein the reference cell is a stem cell and/or a cancer stem cell, with a CDK8 candidate antagonist, wherein the CDK8 candidate antagonist binds CDK8, and whereby differentiation of the reference cell into a differentiated cell identifies the CDK8 candidate antagonist as promoting cell differentiation. In some embodiments, the reference cell is a cancer tem cell. In some embodiments, the differentiated cell is a goblet cell and/or enterocyte cell. In some embodiments, the CDK8 candidate antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the CDK8 candidate antagonist induces cancer cell cycle arrest, inhibits cancer cell proliferation, and/or promotes cancer cell death.

[0224] Provided herein are methods of screening for and/or identifying a CDK8 antagonist which alters a CDK8 gene signature said method comprising: (a) contacting a reference cell with a CDK8 candidate antagonist, wherein the CDK8 candidate antagonist binds CDK8, (b) determining expression levels of one or more biomarkers of a CDK8 gene signature at one time-point and a second time-point, wherein differential expression levels of one or more biomarkers of a CDK8 gene signature identifies the CDK8 candidate antagonist as a CDK8 antagonist In some embodiments, the CDK8 candidate antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the CDK8 candidate antagonist induces cancer cell cycle arrest, inhibits cancer cell proliferation, and/or promotes cancer cell death.

[0225] In some embodiments of any of the articles of manufacture, the one or more biomarkers of the CDK8 gene signature comprises one or more genes listed in Table 2 and/or Table 3. In some embodiments, the one or more genes listed in Table 2 and/or Table 3 comprises one or more ES cell-related genes. In some embodiments, the one or more genes listed in Table 2 and/or Table 3 comprises one or more MYC ES target genes. In some embodiments, the one or more genes listed in Table 2 and/or Table 3 comprises one or more p53 signalling genes, cell cycle genes, Wnt signalling genes, and/or SMAD/BMP signalling genes.

[0226] In some embodiments of any of the methods of screening for and/or identifying an CDK8 antagonist, the cancer cell, cancer tissue, or cancer sample is bladder cancer, pancreatic cancer, lung cancer, breast cancer, colon cancer, colorectal cancer, endometrial cancer, head & neck cancer, kidney cancer, ovarian cancer, hypopharyngeal, prostate cancer, esophageal, hepatocellular carcinoma, and/or urinary cancer. In some embodiments of any of the methods of screening for and/or identifying an CDK8 antagonist, the cancer cell, cancer tissue, or cancer sample is from a cancer selected from the group of bladder cancer, pancreatic cancer, lung cancer, breast cancer, colon cancer, colorectal cancer, endometrial cancer, head & neck cancer, kidney cancer, ovarian cancer, and/or urinary cancer. In some embodiments, the cancer cell, cancer tissue, or cancer sample is from a cancer selected from the group of bladder cancer, pancreatic cancer, endometrial cancer, head & neck cancer, kidney cancer, ovarian cancer, and/or urinary cancer.

[0227] In some embodiments of any of the methods of screening for and/or identifying an CDK8 antagonist, differential expression levels of one or more biomarkers of a CDK8 gene signature is elevated expression. In some embodiments, elevated expression refers to an overall increase of about any of 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (*e.g.*, protein or nucleic acid (*e.g.*, gene or mRNA)), detected by standard art known methods such as those described herein, as compared to a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In certain embodiments, the elevated expression refers to the increase in expression level/amount of a biomarker in the sample wherein the increase is at least about any of 1.5X, 1.75X, 2X, 3X, 4X, 5X, 6X, 7X, 8X, 9X, 10X, 25X, 50X, 75X, or 100X the expression level/amount of the respective biomarker in a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In some embodiments, elevated expression refers to an overall increase of greater than about 1.5 fold, about 1.75 fold, about 2 fold, about 2.25 fold, about 2.5 fold, about 2.75 fold, about 3.0 fold, or about 3.25 fold as compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene).

[0228] In some embodiments of any of the methods of screening for and/or identifying an CDK8 antagonist, differential expression levels of one or more biomarkers of a CDK8 gene signature is reduced expression. In some embodiments, reduced expression refers to an overall reduction of about any of 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (*e.g.*, protein or nucleic acid (*e.g.*, gene or mRNA)), detected by standard art known methods such as those

described herein, as compared to a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In certain embodiments, reduced expression refers to the decrease in expression level/amount of a biomarker in the sample wherein the decrease is at least about any of 0.9X, 0.8X, 0.7X, 0.6X, 0.5X, 0.4X, 0.3X, 0.2X, 0.1X, 0.05X, or 0.01X the expression level/amount of the respective biomarker in a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue.

[0229] The growth inhibitory effects of a CDK8 antagonist described herein may be assessed by methods known in the art, *e.g.*, using cells which express CDK8 either endogenously or following transfection with the respective gene(s). For example, appropriate tumor cell lines, and CDK8 polypeptide-transfected cells may be treated with a CDK8 antagonist described herein at various concentrations for a few days (*e.g.*, 2-7) days and stained with crystal violet or MTT or analyzed by some other colorimetric assay. Another method of measuring proliferation would be by comparing ^{3}H-thymidine uptake by the cells treated in the presence or absence an antibody, binding polypeptide or small molecule of the invention. After treatment, the cells are harvested and the amount of radioactivity incorporated into the DNA quantitated in a scintillation counter. Appropriate positive controls include treatment of a selected cell line with a growth inhibitory antibody known to inhibit growth of that cell line. Growth inhibition of tumor cells in vivo can be determined in various ways known in the art.

[0230] Methods of determining the distribution of cell cycle stage, level of cell proliferation, and/or level of cell death are known in the art and are described in the examples herein. In some embodiments, cancer cell cycle arrest is arrest in G1.

[0231] In some embodiments, the CDK8 antagonist will inhibit cancer cell proliferation of the cancer cell, cancer tissue, or cancer sample in vitro or in vivo by about 25-100% compared to the untreated cancer cell, cancer tissue, or cancer sample, more preferably, by about 30-100%, and even more preferably by about 50-100% or about 70-100%. For example, growth inhibition can be measured at a CDK8 antagonist concentration of about 0.5 to about 30 μg/ml or about 0.5 nM to about 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the CDK8 candidate antagonist. The CDK8 antagonist is growth inhibitory in vivo if administration of the CDK8 candidate antagonist at about 1 μg/kg to about 100 mg/kg body weight results in reduction in tumor size or reduction of tumor cell proliferation within about 5 days to 3 months from the first administration of the CDK8 candidate antagonist, preferably within about 5 to 30 days.

[0232] To select for a CDK8 antagonists which induces cancer cell death, loss of membrane integrity as indicated by, *e.g.*, propidium iodide (PI), trypan blue or 7AAD uptake may be assessed relative to a reference. A PI uptake assay can be performed in the absence of complement and immune effector cells. CDK8-expressing tumor cells are incubated with medium alone or medium containing the appropriate a CDK8 antagonist. The cells are incubated for a 3-day time period. Following each treatment, cells are

washed and aliquoted into 35 mm strainer-capped 12 x 75 tubes (1 ml per tube, 3 tubes per treatment group) for removal of cell clumps. Tubes then receive PI (10 μg/ml). Samples may be analyzed using a FACSCAN® flow cytometer and FACSCONVERT® CellQuest software (Becton Dickinson). Those CDK8 antagonists that induce statistically significant levels of cell death as determined by PI uptake may be selected as cell death-inducing antibodies, binding polypeptides or small molecules.

[0233] To screen for CDK8 antagonists which bind to an epitope on or interact with a polypeptide bound by an antibody of interest, a routine cross-blocking assay such as that described in Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. This assay can be used to determine if a candidate CDK8 antagonist binds the same site or epitope as a known antibody. Alternatively, or additionally, epitope mapping can be performed by methods known in the art. For example, the antibody and/or binding polypeptide sequence can be mutagenized such as by alanine scanning, to identify contact residues. The mutant antibody is initially tested for binding with polyclonal antibody and/or binding polypeptide to ensure proper folding. In a different method, peptides corresponding to different regions of a polypeptide can be used in competition assays with the candidate antibodies and/or polypeptides or with a candidate antibody and/or binding polypeptide and an antibody with a characterized or known epitope.

[0234] In some embodiments of any of the methods of screening and/or identifying, the CDK8 candidate antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the CDK8 candidate antagonist is an antibody. In some embodiments, the CDK8 antagonist is a small molecule.

[0235] In one aspect, a CDK8 antagonist is tested for its antigen binding activity, *e.g.*, by known methods such as ELISA, Western blot, etc.

K. Pharmaceutical Formulations

[0236] Pharmaceutical formulations of a CDK8 antagonist as described herein are prepared by mixing such antibody having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (REMINGTON'S PHARMA. SCI. 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. In some embodiments, the CDK8 antagonist is a small molecule, an antibody, binding polypeptide, and/or polynucleotide. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins;

chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.,* Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include insterstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

[0237] Exemplary lyophilized formulations are described in US Patent No. 6,267,958. Aqueous antibody formulations include those described in US Patent No. 6,171,586 and WO2006/044908, the latter formulations including a histidine-acetate buffer.

[0238] The formulation herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.

[0239] Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in REMINGTON'S PHARMA. SCI. 16th edition, Osol, A. Ed. (1980).

[0240] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the CDK8 antagonist, which matrices are in the form of shaped articles, *e.g.,* films, or microcapsules.

[0241] The formulations to be used for *in vivo* administration are generally sterile. Sterility may be readily accomplished, *e.g.*, by filtration through sterile filtration membranes.

L. Articles of Manufacture

[0242] In another aspect of the invention, an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a

CDK8 antagonist described herein. The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises a CDK8 antagonist; and (b) a second container with a composition contained therein, wherein the composition comprises a further cytotoxic or otherwise therapeutic agent.

[0243] In some embodiments, the article of manufacture comprises a container, a label on said container, and a composition contained within said container; wherein the composition includes one or more reagents (*e.g.,* primary antibodies that bind to one or more biomarkers or probes and/or primers to one or more of the biomarkers described herein), the label on the container indicating that the composition can be used to evaluate the presence of one or more biomarkers in a sample, and instructions for using the reagents for evaluating the presence of one or more biomarkers in a sample. The article of manufacture can further comprise a set of instructions and materials for preparing the sample and utilizing the reagents. In some embodiments, the article of manufacture may include reagents such as both a primary and secondary antibody, wherein the secondary antibody is conjugated to a label, *e.g.,* an enzymatic label. In some embodiments, the article of manufacture one or more probes and/or primers to one or more of the biomarkers of a CDK8 gene signature described herein.

[0244] In some embodiments of any of the articles of manufacture, the one or more biomarkers of the CDK8 gene signature comprises one or more genes listed in Table 2 and/or Table 3. In some embodiments, the one or more genes listed in Table 2 and/or Table 3 comprises one or more ES cell-related genes. In some embodiments, the one or more genes listed in Table 2 and/or Table 3 comprises one or more MYC ES target genes. In some embodiments, the one or more genes listed in Table 2 and/or Table 3 comprises one or more p53 signalling genes, cell cycle genes, Wnt signalling genes, and/or SMAD/BMP signalling genes.

[0245] In some embodiments of any of the articles of manufacture, the articles of manufacture comprise primers.

[0246] In some embodiments of any of the article of manufacture, the CDK8 antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the CDK8 antagonist is a small molecule. In some embodiments, the small molecule is a small molecule kinase inhibitor. In some embodiments, the small molecule kinase inhibitor is selected from the group consisting of flavopiridol, ABT-869, AST-487, BMS-387032/SNS032, BIRB-796, sorafenib, staurosporine, cortistatin, cortistatin A, and/or a steroidal alkaloid or derivative thereof. In some embodiments, the CDK8 antagonist is an antibody. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a human, humanized, or chimeric antibody. In some embodiments, the antibody is an antibody fragment and the antibody fragment binds CDK8.

[0247] The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0248] Other optional components in the article of manufacture include one or more buffers (*e.g.,* block buffer, wash buffer, substrate buffer, etc), other reagents such as substrate (*e.g.,* chromogen) which is chemically altered by an enzymatic label, epitope retrieval solution, control samples (positive and/or negative controls), control slide(s) etc.

[0249] It is understood that any of the above articles of manufacture may include an immunoconjugate described herein in place of or in addition to a CDK8 antagonist.

EXAMPLES

[0250] The following are examples of methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided above.

Materials and Methods for the Examples

Cell Lines

[0251] HT-29 and COLO 205 human colon cancer cells and 293T human embryonic kidney packaging cells were grown in DMEM (high glucose), 10% Fetal Bovine Serum (FBS), and 1% Penicillin-Streptomycin (Invitrogen). R1 mouse embryonic stem (ES) cells (courtesy of Merone Roose-Girma, Genentech) , which were derived from a (129X1/SvJ-129S1/SvImJ)F1 mouse embryo (Nagy A. *et al.*, *Proc Natl Acad Sci U S A* 90:8424-8 (1993)) were grown on 0.1% gelatin in the following media: Knockout DMEM (Invitrogen), 15% FBS, 1000 units/ml leukemia inhibitory factor (LIF; Millipore), 5 mM HEPES (MP Biomedicals), 1.4 mM L-Glutamine (MP Biomedicals), 0.05 mM 2-Mercaptoethanol (Sigma), 10 µg/ml Gentamicin (Quality Biological), and 1% Penicillin-Streptomycin (Invitrogen). TC1 ES cells, which were derived from 129S6/SvEvTac mice (Deng C. *et al.*, *Cell* 84:911-21(1996)), and GSI-1 ES cells, which were derived from 129X1/SvJ mice (Genome Systems), were grown on mitotically inactivated mouse embryonic fibroblast cells (MEFs) in the following media: Knockout DMEM, 15% FBS, 1000 units/ml LIF, 0.1 mM MEM Non-Essential Amino Acids (Gibco), 2 mM L-Glutamine, 0.1 mM 2-Mercaptoethanol, and 1% Penicillin-Streptomycin. To remove MEFs from downstream analyses, TC1 and GSI-1 ES cells were re-plated on 0.1% gelatin prior to analysis. To differentiate the R1 ES cells, LIF was removed from the media and 5 µM retinoic acid (Sigma) was added (Rohwedel, J. *et al.*, *Cells Tissues Organs* 165, 190-202 (1999)). All cell line stocks are maintained at Genentech and undergo genotyping to verify their identity every six months.

Infection/Transfection Procedures

[0252] Short hairpin RNAs (shRNAs) and cDNA expression plasmids were expressed in HT-29, COLO 205, and R1 cells using a lentiviral packaging system. Briefly, 293T cells were transfected with pLKO.1-shRNA vector, pHush-shRNA vector, pHush-cDNA vector, or pLenti6.2-cDNA vector, along with pCMV-VSVG and pCMV-dR8.9 to make replication-incompetent lentiviral particles. Viral particles were added to cells with 5-8 μg/ml polybrene and spin infected at room temperature (1800 rpm, 30-45 minutes). Stable integration of shRNAs was selected with 6-8 μg/ml puromycin (for pLKO.1 R1 knockdown experiments) or with 2 μg/ml puromycin (for pHush xenograft knockdown experiments). Stable integration of cDNAs was selected with 10 μg/ml blasticidin (for pLenti6.2 MYC rescue experiments) or by flow sorting for GFP-positive cells (for pHush CDK8 rescue experiments). HT-29 cells were transiently transfected with siRNAs using Lipofectamine RNAiMAX (Invitrogen).

Xenograft Tumor Models

[0253] HT-29 and COLO 205 cells were infected with doxycycline-inducible pHush-shRNAs targeting *CDK8* (or NTC control) and selected for stable integration with 2 μg/ml puromycin (Clontech). For each cell line, 5 x 10^6 cells were injected subcutaneously into the backs of 26 female NCr nude mice (Taconic) to initiate tumor growth. The size of each tumor was measured using a calliper. Once tumors reached 225 mm^3, the animals from each cell line were split into two groups. For each cell line, the first group of 13 mice was fed 5% sucrose in their water (control group) while the second group of 13 mice was fed 5% sucrose + 1 mg/ml doxycycline (Clontech) to induced hairpin expression. After 8 days (HT-29) or 12 days (COLO 205), three of the mice from each group were euthanized and the tumors were harvested for Western blot analysis. The remaining 10 mice per group were monitored until Day 16, and the tumor volume was measured every 3-4 days. In parallel, the weight of the mice was also measured and recorded. Tumor growth inhibition values were determined by an area under the curve calculation.

Human Colon Tissue Samples

[0254] Frozen normal human colon, colon tumors, and metastatic colon tumors were obtained from Asterand, Integrated Laboratory Services, Cooperative Human Tissue Network, or ProteoGenex. Prior to Western blot analysis, each tumor was verified by a board certified pathologist (R.F.) to contain a high percentage of tumor cells.

Plasmids and RNAi Constructs

[0255] Human *CDK8* cDNA (Origene) was cloned into pAcGP67 vector (BD Biosciences) that contained an N-terminal FLAG tag. FLAG-tagged *CDK8* was PCR amplified and cloned into pSHUTTLE-CMV-TO and then Gateway recombined (Invitrogen) into pHush-GFP expression vector (Gray, D. C. *et al.*, *BMC Biotechnol* 7, 61 (2007)). Human *MYC* cDNA (Invitrogen) was cloned into pLenti6.2 vector by Gateway recombination (Invitrogen). The T58A and S62A mutations were introduced by QuikChange site directed mutagenesis kit (Agilent/Stratagene) and verified by sequencing.

[0256] For the xenograft studies, a doxycycline-inducible pHush-shRNA system was utilized as described in Gray *et al.*, *BMC Biotechnol.* 7, 61 (2007). The pHush-shNTC control was obtained from David Davis (Genentech). The shCDK8 targeting sequence (GAATGGTGAAGTCACTATTAT (SEQ ID NO:5)) was first cloned into the pSHUTTLE-H1 vector. Then the pSHUTTLE-H1-shRNA was Gateway (Invitrogen) recombined into a puromycin-selectable pHush vector (Gray, D. C. *et al.*, *BMC Biotechnol* 7, 61 (2007)). For the R1 ES cell experiments, the following shRNA target sequences in pLKO.1 vector were utilized (from Open Biosystems unless otherwise stated): shNTC, CAACAAGATGAAGAGCACCAA (Sigma (SEQ ID NO:6); shCdk8 -1, CCCGATTATTTAATTCACCTT (SEQ ID NO:7); shCdk8 -2, CAGGGATTTGAAACCTGCTAA [mouse-specific] (SEQ ID NO:8); shNanog, GCCAGTGATTTGGAGGTGAAT (SEQ ID NO:9); shMed12 -1, CCTCTCCCTTTGATGATCCTA (SEQ ID NO:10); shMed12 -2, CCGTGCGATTACCAATGCAAA (SEQ ID NO:11). For the HT-29 colon cancer experiments, the following siRNA target sequences were utilized (from Ambion): siNTC (Negative Control #1); siCDK8 -1, CAAAACTAGTAATCCTTATTT (SEQ ID NO:12); siCDK8 -2, CCCTTACCCAAAACGAGAATT (SEQ ID NO:13).

Antibodies

[0257] The following antibodies were utilized: ACTIN (clone C4; MP Biomedicals), CDK8 (clone C-19; Santa Cruz Biotechnology), NANOG (Millipore), OCT4 (Abcam), c-MYC (clone D84C12; Cell Signaling Technology), c-MYC-pT58 (Sigma), c-MYC-pS62 (Abcam), c-MYC-pT58/S62 (Abcam), Alexa Fluor 488 donkey anti-rabbit IgG (Invitrogen), Alexa Fluor 568 donkey anti-goat IgG (Invitrogen), CD44-PE/Cy5 (Biolegend), and CD133-PE (Miltenyi Biotec).

Histological, Immunohistochemical, and FACS analyses

[0258] HT-29 xenograft tumors were stained for alcian blue as described in Sheehan, Dezna C. and Hrapchak, Barbara B., THEORY AND PRACTICE OF HISTOTECHNOLOGY, 2d ed. (Mosby, St. Louis, 1980). Hematoxylin and eosin stained xenograft tumors analysis were performed by a clinical pathologist (R.F.) to determine the differentiation status. Immunohistochemistry of CDK8 was performed as previously described in Firestein, R. *et al.*, *Nature* 455, 547-551 (2008). R1 ES cells were stained for alkaline phosphatase activity using an alkaline phosphatase detection kit (Millipore). To quantify the ES cell colonies, alkaline phosphatase positively stained colonies were manually counted under a low magnification microscope (each field was 24 mm^2). A minimum of four different fields were counted and then averaged. For immunofluorescence, cells were grown in 96-well, black-walled plates. Cells were fixed with 4% paraformaldehyde for 5 min. and permeabilized/blocked with PBS containing 10% normal horse serum, 0.1% Triton X-100. Primary antibody was added for 1 hour followed by secondary antibody for 30 minutes. Hoechst 33342 (Invitrogen) was added for 5 min. to stain nuclei. For FACS analysis, xenograft tumor cells were dissociated with collagenase for 30 minutes, washed in PBS + 2% FBS, stained 10 minutes for CD133,

CD44, and a mouse lineage antibody panel (BD Biosciences) to exclude mouse cells, and analyzed on a FACSCalibur flow cytometer (BD Biosciences).

Gene Expression Analysis

[0259] For quantitative RT-PCR, total RNA was isolated with the RNeasy mini kit (Qiagen). Reverse transcription followed by quantitative PCR was performed with the TaqMan one-step RT-PCR master mix using Taqman gene-specific probes (Applied Biosystems).

Microarray Hybridization

[0260] For microarray studies, total RNA was harvested from cells in triplicate using RNeasy mini kit with on-column DNase digestion (Qiagen). For HT-29 cells, RNA was harvested three days after siRNA transfection. For R1 cells, RNA was harvested at Day 8 or Day 13 after shRNA infection. RNA was quantified using UV-spec Nanodrop (Thermo Scientific) and then profiled on Agilent Bioanalyzer. RNA was amplified and hybridized to whole human or mouse genome 4x44K gene expression arrays according to manufacturer protocol (Agilent). Universal human or mouse reference RNA (Agilent/Stratagene) was used as reference control.

Microarray Data Analysis

CDK8-regulated genes in HT-29 cells

[0261] The microarray data output was a ratio of the sample RNA to the reference control RNA. Only genes with data in at least 70% of experiments were analyzed. Microarray data was $\log_2$-transformed, mean centered, then zero-transformed on the siNTC samples. Genes that significantly changed upon siCDK8 in HT-29 cells were identified by carrying out a Student's *t*-test between all siNTC controls and all replicates of siCDK8 -1/-2. The top 1500 induced or repressed genes/probes were selected (P=0.001, Student's *t*-test between siNTC and two independent CDK8 siRNAs).

CDK8-regulated genes in R1 ES cells

[0262] The microarray data was processed in the same way as the HT-29 cells described above. The top 1500 genes/probes significantly changing upon shCdk8 at Day 8 in R1 cells were identified as described above for HT-29 cells (P=0.003, Student's *t*-test between shNTC and two independent CDK8 shRNAs).

Gene set enrichment/pathway analysis

[0263] Gene set enrichment analysis was carried out using Genomica (http://genomica.weizmann.ac.il/) as described in Segal, E. *et al.*, *Nat Genet* 36, 1090-1098 (2004). *P*-values were determined by the hypergeometric distribution. The following gene sets were used: gene ontology (Ashburner, M. *et al.*, *Nat Genet* 25, 25-29 (2000)), chromatin immunoprecipitation-microarray target gene sets for mouse ES cell transcription factors (Kim, J. *et al.*, *Cell* 132, 1049-1061 (2008)); and mouse ES cell-related and adult stem cell-related gene signatures (Wong, D. J. *et al.*, *Cell Stem Cell* 2, 333-344 (2008)). Enrichment analysis for signalling pathways was carried out using Ingenuity Pathway Analysis (Ingenuity Systems, www.ingenuity.com). *P*-values were determined using a fisher exact test.

Comparison to MED12 knockdown data

[0264] Focusing on the mediator component MED12-regulated gene as defined by Kagey *et al.*, *Nature* 467, 430-435 (2010), the gene expression pattern was compared to data following CDK8 or MED12 knockdown in ES cells, as well as to data following forced differentiation of ES cells and NANOG or OCT4 knockdown in ES cells from Gene Expression Omnibus accession GSE4189; Loh, Y. H. *et al.*, *Nat Genet* 38, 431-440 (2006)). To determine the similarity of the expression patterns, a Pearson correlation was calculated between the shMed12 expression pattern from Kagey, M. H. *et al.*, *Nature* 467, 430-435 (2010) and the expression pattern from all other data sets.

Correlation of HT-29 CDK8-regulated signature to individual genes in colon cancer

[0265] The expression pattern of the top 1500 genes that change upon siCDK8 in HT-29 human colon cancer cells (the HT-29 CDK8-regulated signature) was collapsed into a single expression value for each gene by subtracting the average $\log_2$ expression value of each gene in siCDK8 samples from the average $\log_2$ expression value in siNTC samples. CDK8-induced genes were positive values and CDK8-repressed genes were negative values. Expression of this signature was then correlated to the expression of individual genes in two primary human colon cancer expression data sets: 100 tumors from Gene Expression Omnibus accession GSE5206 and 130 tumors from Gene Logic. First, a Pearson correlation was calculated between the collapsed HT-29 CDK8-regulated signature and the expression values for these genes in each tumor. This was essentially a score for the level of expression of the CDK8-regulated signature in each tumor, where a high correlation value indicates high expression of the CDK8-induced/repressed expression signature. Then a second Pearson correlation was calculated for each tumor between the Pearson value obtained in the first step and the expression of individual genes. High correlation values indicated a concordance between expression of the gene with expression of the CDK8-regulated signature.

CDK8-induced MYC ES cell target gene expression in colon tumors

[0266] For comparison to *CDK8* expression, CDK8-induced MYC ES cell target genes from HT-29 cells were selected out of microarray data from 227 primary human colon cancer tumors (Gene Logic). The average $\log_2$ expression of the CDK8-induced MYC ES targets was calculated for each tumor, and the tumors were sorted from high to low average target gene expression (for comparison, the average expression of all MYC ES cell targets (Kim, J. *et al.*, *Cell* 132, 1049-1061 (2008)) in each tumor was determined). The tumors were split into two groups by high versus low target gene expression, and *CDK8* expression levels in each group were averaged. For correlation to differentiation status, CDK8-induced MYC ES cell target genes were selected out of microarray data from 213 primary human colon tumors that had known differentiation status (Gene Expression Omnibus accession GSE17538; (Smith JJ. *et al.*, *Gastroenterology* 138:958-68 (2010)). The average expression of the targets was calculated for each tumor, and the tumors were sorted from high to low expression (the same procedure was also carried out for all MYC ES targets). The tumors were split into two groups by high versus low target gene expression, and the number of poorly differentiated

tumors in each group was counted. The enrichment of poorly differentiated tumors in one group over the other was calculated with a fisher exact test using a 2x2 contingency table. For correlation to clinical outcome, the same procedure described above was carried out on 50 tumors that had undergone recurrence (Gene Expression Omnibus accession GSE14333; Jorissen R.N. *et al.*, *Colorectal Cancer. Clin Cancer Res* 15:7642-51 (2009)). After splitting the tumors into high versus low expression of CDK8-induced MYC ES targets, the average time to recurrence was calculated for each group. For comparison, the same process was carried out for all MYC ES cell targets.

Example 1-Characterization of CDK8 Loss on Tumor Growth and Gene Expression

[0267] To characterize the effect of acute loss of CDK8 on tumor growth *in vivo*, an inducible short hairpin RNA (shRNA) system (Hoeflich, K. P. *et al.*, *Cancer Res* 66, 999-1006 (2006)) was used to deplete endogenous CDK8 in fully formed tumors. shRNAs to *CDK8* and a non-targeting control (shNTC) were introduced into two human colon cancer cell lines (HT-29 and COLO 205) and grown as xenograft tumors. These cell lines harbour genomic copy number gain and overexpression of CDK8 and were sensitive to CDK8 loss *in vitro*. Firestein, R. *et al.*, *Nature* 455, 547-551 (2008). Xenograft tumor volume was measured over time (n = 10 mice per group). The tumor growth inhibition values were determined by an area under the curve calculation. As shown in Fig. 1A, doxycycline-induced acute knockdown of CDK8 protein in fully formed tumors led to profound growth inhibition in both HT-29 and COLO 205 xenograft tumors when compared to either the shNTC controls and the non-doxycycline induced shCDK8 tumors. No significant weight changes were observed throughout the duration of the study for any of the treatment groups, consistent with the notion that loss of CDK8 in the tumor itself was causing growth inhibition (data not shown). Knockdown of CDK8 in the tumors after doxycycline treatment was confirmed by both Western blot and immunohistochemistry (Fig. 1B).

[0268] Initial immunohistochemical analyses revealed that HT-29 tumor cells with depleted CDK8 showed histological changes characterized by the formation of large cytoplasmic inclusions. Further morphological examination of these tumors showed that while the HT-29 and COLO 205 models normally grow as sheets of cells characteristic of poorly differentiated tumors, loss of CDK8 led to a well-differentiated tumor state in both tumor models (Fig. 1C). CDK8 depletion led to accumulation of mucin rich deposits in HT-29 xenografts, consistent with goblet cell differentiation, and led to well-formed glands with evidence of polarization in COLO 205 xenografts, consistent with enterocyte differentiation. In contrast, when CDK8 loss was induced in SW837 tumors, a colon cancer xenograft characterized by lack of CDK8 amplification and lower protein expression (Firestein R. *et al.*, *Nature* 455:547-51 (2008)), little effect on tumor growth and differentiation was seen (data not shown).

[0269] It has been proposed that colon tumor growth may be maintained by a small population of "cancer stem cells" (Clarke M.F. *et al.*, *Cell* 124:1111-5 (2006)). However, as shown herein, CDK8 was widely expressed in all xenograft tumor cells (Fig. 1B), mimicking the broad expression pattern of CDK8 in primary

colon tumors (Firestein R. *et al.*, *Int J Cancer* 126:2863-73 (2010)). Further, CDK8 inhibition in xenograft tumors and in culture had little effect on the levels of the proposed colon cancer stem cell makers CD133 and CD44 (O'Brien C.A. *et al.*, *Nature* 445:106-10 (2007); Ricci-Vitiani L. *et al.*, *Nature* 445:111-5 (2007); Dalerba P. *et al.*, *Proc Natl Acad Sci U S A* 104:10158-63(2007)) (data not shown). Together these observations demonstrate that CDK8 was required for tumor growth and maintenance of a de-differentiated state *in vivo*.

[0270] To gain insight into potential mechanisms for CDK8-mediated regulation of tumor growth and differentiation, the primary gene expression changes that occur after CDK8 knockdown in HT-29 cells was accessed using two independent small interfering RNAs (siRNAs) (Fig. 1D). The expression of 1500 genes were changed in CDK8 depleted cells compared to the siNTC control, which included genes that were enriched in pathways implicated in CDK8 biology (p53 signalling (Donner, A. J. *et al.*, *Mol Cell* 27, 121-133 (2007)), cell cycle, Wnt signalling (Firestein, R. *et al.*, *Nature* 455, 547-551 (2008); Morris, E. J. *et al.*, *Nature* 455, 552-556 (2008) and SMAD/BMP signalling (Alarcon, C. *et al.*, *Cell* 139, 757-769 (2009)); Fig. 1E and Table 2).

[0271] Given the effect of CDK8 loss on tumor differentiation (Fig. 1C), enrichment of defined embryonic stem cell-related and adult stem cell-related gene sets derived by integrating over 100 different expression profiles of a wide array of stem cells (Wong, D. J. *et al.*, *Cell Stem Cell* 2, 333-344 (2008)) was evaluated. CDK8-induced genes were specifically enriched for ES cell-related genes, but not for adult stem cell-related genes (Fig. 1E). This was unique to CDK8-induced genes, as CDK8-repressed genes showed no enrichment for ES or adult stem cell-related genes. Quantitative RT-PCR confirmed the reduced expression of multiple ES cell-related genes after CDK8 knockdown (Fig. 6). These observations indicated that CDK8 positively regulates an ES cell gene expression program in colon cancer cells and suggested a common role for CDK8 function in ES and cancer cells.

Example 2-Characterization of CDK8 in Embryonic Stem (ES) Cells

[0272] To directly test this hypothesis, CDK8 expression was characterized in murine ES cells subjected to forced differentiation by removal of leukaemia inhibitory factor (LIF) and addition of retinoic acid (Rohwedel, J. *et al.*, *Cells Tissues Organs* 165, 190-202 (1999)). Loss of ES pluripotency was marked by reduced alkaline phosphatase staining (Pease, S. *et al.*, *Dev Biol* 141, 344-352 (1990)) and loss of expression of the ES cell core regulator NANOG (Fig. 2A, B). Concomitant with ES cell differentiation, that CDK8 levels were reduced at both the mRNA and protein level (Fig. 2C). To determine whether CDK8 was directly required to maintain ES cells in an undifferentiated state, murine ES cells were treated with shCdk8 or positive (shNanog) and negative (shNTC) controls. Loss of CDK8 in ES cells led to a significant reduction in ES cell pluripotency as evidenced by reduced alkaline phosphatase staining, reduced ES cell colony formation, and reduced NANOG and OCT4 protein levels 11 days after shRNA treatment (Fig. 2D, E, and data not shown). CDK8 inhibition in two additional murine ES cell lines, TC1 and GSI-1, also significantly

reduced ES cell pluripotency (Fig. 7). All three ES cell lines analyzed had a normal karyotype (data not shown) and were disomic for Cdk8 copy number (data not shown). To determine whether the observed ES cell differentiation was mediated directly by CDK8 and not an off-target effect, we rescued the RNAi phenotype by simultaneously expressing human CDK8 in ES cells treated with mouse-specific shCdk8. Expression of CDK8 was sufficient to prevent the cells from undergoing shCdk8-induced differentiation (Fig. 2F-H). These data indicate that CDK8 is required to maintain ES cells in an undifferentiated state, and similar to the observation in the tumor models, reduced CDK8 expression promotes differentiation.

[0273] To determine which transcriptional pathways CDK8 regulates in ES cells, gene expression analysis was conducted following CDK8 loss in R1 mouse ES cells both prior to the onset of differentiation (Day 8) and after differentiation (Day 13). The top 1500 genes that significantly changed upon CDK8 loss prior to differentiation at Day 8 were indentified (Fig. 3A and Table 3). Consistent with its observed effects on ES cell pluripotency, both CDK8-induced and CDK8-repressed gene signatures identified at the onset of differentiation (Day 8) were enriched for genes involved in ES cell function (Fig. 3A). Reduced expression of a subset of these ES cell-related genes (Andang, M. *et al.*, *Nature* 451, 460-464 (2008); Glover, C. H. *et al.*, *PLoS Comput Biol* 2, e158 (2006)) after CDK8 knockdown was confirmed by quantitative RT-PCR (Fig. 3B). CDK8-regulated genes maintained a very similar expression pattern post differentiation at Day 13 (Fig. 3A), suggesting that the gene expression program introduced prior to differentiation remained present after differentiation occurred. In contrast, the expression pattern of ES cells depleted of the Mediator component MED12 was distinct from CDK8 knockdown cells (Fig. 8), suggesting that CDK8 and MED12 regulate ES cell pluripotency via distinct mechanisms.

[0274] In ES cells, a small number of core transcription factors (NANOG, OCT4, SOX2, and c-MYC) and their downstream target genes were essential for maintaining the proliferative capacity and pluripotent state of ES cells. Young RA. Cell 144:940-54 (2011); Cartwright, P. *et al.*, *Development* 132, 885-896 (2005); Chambers, I. & Smith, A., *Oncogene* 23, 7150-7160 (2004). Target genes for NANOG, OCT4, and SOX2, identified through genome-wide chromatin immunoprecipitation experiments in mouse ES cells (Kim, J. *et al.*, *Cell* 132, 1049-1061 (2008)), showed weak enrichment for CDK8-regulated genes in ES cells, while target genes for c-MYC (referred to as MYC from here on) were more strongly enriched (Fig. 3A). Specifically, MYC ES cell targets were strongly enriched in CDK8-induced genes but not in CDK8-repressed genes. This suggested that CDK8 may regulate target gene expression of core transcription factors in ES cells by promoting MYC target gene expression.

[0275] To dissect the temporal relationship between CDK8 loss and the transcriptional output from MYC, OCT4 and NANOG, the expression of these essential transcriptional factors was examined at multiple time points before, during, and after the ES cells underwent CDK8-loss induced differentiation. MYC levels were specifically reduced (Days 6, 8) well before either phenotypic changes of differentiation or changes in NANOG and OCT4 levels were observed (Fig. 3C, D). *Myc* mRNA levels were either weakly reduced (Day

8) or unchanged (Day 13) upon CDK8 loss (Fig. 9C), suggesting that MYC was regulated by post-transcriptional mechanisms. A critical step in regulating MYC activity involves priming the protein for degradation or transcriptional activation by phosphorylation on threonine 58 (T58) and serine 62 (S62), respectively (Sears, R. *et al.*, *Genes Dev* 14, 2501-2514 (2000); Sears, R. C., *Cell Cycle* 3, 1133-1137 (2004)). Using phospho-specific antibodies to both T58-MYC and S62-MYC, a relative increase in the proportion of the unstable T58-phospho-specific MYC was found and a decrease in the active S62-phospho-specific MYC after CDK8 depletion (Fig. 3C, E and Fig. 9A, B). Conversely, overexpression of CDK8 in either shNTC or shCdk8 treated ES cells increased MYC protein levels (Fig. 2H). These data suggest that CDK8 regulates ES pluripotency by maintaining sufficient levels of active MYC protein, which in turn can alter the expression levels of specific MYC target genes.

[0276] Next the sufficiency of MYC for CDK8-mediated ES cell pluripotency was examined. Wildtype MYC, degradation resistant MYC^{T58A}, or inactive MYC^{S62A} was expressed in conjunction with CDK8 knockdown, and the ability of MYC protein levels was able to restore and rescue the differentiation phenotype caused by loss of CDK8. Exogenous expression of either wildtype MYC or MYC^{T58A} in ES cells, which increased MYC levels to that seen in control shNTC cells, partially rescued the loss of ES cell pluripotency imparted by CDK8 depletion (Fig. 4A, B). In contrast, expression of MYC^{S62A}, which disrupts the active phosphorylation site, increased total MYC levels but was unable to rescue the defect in pluripotency. These data reveal that CDK8 regulation of ES cell pluripotency was mediated through MYC.

Example 3-Further Characterization of CDK8 Loss in Tumor Cells

[0277] To determine whether a common genetic circuitry underlies the ability of CDK8 to regulate both ES cell pluripotency and cancer, the effect of loss of CDK8 in human colon cancer cells on ES cell transcription factor related gene expression was evaluated. Similar to our findings in ES cells, CDK8-induced genes in colon cancer cells were more strongly enriched for MYC-mediated ES cell target genes than for OCT4, NANOG, and SOX2 ES cell targets (Fig. 5A). Quantitative RT-PCR confirmed the reduced expression of multiple MYC ES cell target genes after CDK8 knockdown in these colon cancer cells (Fig. 5B and Fig. 10). The data implied that CDK8 regulates a specific set of ES cell-related MYC target genes in both colon cancer and embryonic stem cells.

[0278] To characterize the interplay between CDK8 and MYC in human colon tumors, two independent cohorts of 100 and 130 human colon cancers were analyzed. Consistent with the observation that MYC targets were regulated by CDK8 in HT-29 colon cancer cells (Fig. 5A), increased *MYC* expression in both cohorts of human tumors was strongly associated with the presence of the HT-29 CDK8-regulated gene signature (Fig. 11). MYC overexpression can confer stem cell-like properties to epithelial cancer cells (Wong, D. J. *et al.*, *Cell Stem Cell* 2, 333-344 (2008)), and a MYC-centric gene expression program was found to be similarly expressed in both ES cells and multiple tumor types. Kim, J. *et al.*, *Cell* 143, 313-324 (2010). To determine whether CDK8 specifically regulates the subset of MYC target genes important for ES

cell pluripotency in human tumors, the expression of the CDK8-induced MYC ES cell target genes was evaluated (identified in Fig. 5A and listed in Table 2). High *CDK8* levels correlated with increased expression of the CDK8-induced MYC ES cell targets in colon tumors; in contrast, expression of the whole set of MYC ES target genes (Kim, J. *et al.*, *Cell* 132, 1049-1061 (2008)) was not associated with high *CDK8* levels (Fig. 5C). Consistent with this, high CDK8 protein expression in primary and metastatic colon tumors was characterized by increased total and active S62-phosphorylated MYC when compared to the unstable T58-phosphorylated MYC (Fig. 5D). These data implied that the ability of CDK8 to regulate MYC in ES cells extends to human tumors as well.

[0279] Genetic signatures related to ES cell pluripotency have been found to predict high tumor grade and poor clinical outcome in several cancer types. Ben-Porath, I. *et al.*, *Nat Genet* 40, 499-507 (2008); Wong, D. J. *et al.*, *Cell Stem Cell* 2, 333-344 (2008); Kim, J. *et al.*, *Cell* 143, 313-324 (2010). Consistent with these observations that CDK8 expression was important for maintaining tumors in a poorly differentiated state *in vivo* (Fig. 1C) and ES cells in an undifferentiated state (Fig. 2D), the CDK8-induced MYC ES cell signature was enriched in colon tumors characterized by both poor differentiation and poor patient outcome (Fig. 5E, F). Notably, this effect was CDK8 specific as signatures that include all MYC ES cell target genes were not found to be strongly associated with either tumor grade or patient survival (Fig. 5E, F). These data showed that CDK8 regulation of a MYC-centric ES cell signature was active and clinically defines a subset of colon cancers with poor differentiation and poor prognosis.

[0280] Here a novel role for the CDK8 oncogene in regulating tumor differentiation and stem cell Pluripotency has been found. Specifically, in xenograft tumor models CDK8 was required to promote rapid tumor growth as well as maintain the tumors in an undifferentiated state. Similarly, CDK8 was highly expressed in ES cells and was required to maintain ES cells in an undifferentiated, pluripotent state. CDK8 regulates MYC protein levels and MYC target gene expression to promote ES cell pluripotency, and expression of CDK8-regulated MYC target genes was predictive of tumor differentiation and clinical outcome of primary human colon tumors.

[0281] Recent studies have identified a role for Mediator components in regulating ES cell pluripotency. In ES cells, the Mediator component MED12 binds to the master ES cell regulator NANOG, and MED12 and NANOG were found to co-occupy and regulate the expression of specific NANOG target genes. Tutter, A. V. *et al.*, *J Biol Chem* 284, 3709-3718 (2009). And recently, multiple Mediator components, including MED12, were found to interact with cohesin at many target genes in ES cells to regulate their expression and modulate ES cell Pluripotency. Kagey, M. H. *et al.*, *Nature* 467, 430-435 (2010). The expression pattern of ES cells depleted of the Mediator component MED12 was found distinct from CDK8 knockdown cells. This implies that in ES cells, CDK8 and MED12 act divergently to regulate ES cell pluripotency through different mechanisms and the unique Mediator-independent functions of CDK8.

[0282] The finding that CDK8 regulates MYC at the protein levels raises an important distinction however been cancer and ES cell biology. Previous work in colon cancer cells revealed that CDK8 inhibition reduced both MYC mRNA and protein levels, suggesting that CDK8 regulates MYC on a transcriptional level. Firestein, R. *et al.*, *Nature* 455, 547-551 (2008). In stem cells, however, CDK8 inhibition had little effect on MYC transcript levels but strongly reduced MYC protein levels and altered the MYC post-translational modification landscape. Thus in cancer cells and in stem cells, CDK8 may regulate MYC through distinct mechanisms. MYC was known to undergo extensive post-translational modifications from a multitude of inputs, including other CDK proteins (Vervoorts J. *et al.*, *J Biol Chem* 281:34725-9 (2006); Hann SR. *Semin Cancer Biol* 16:288-302 (2006)). While the CDK8-MYC connection in stem cells was important to maintain pluripotency, it was unknown whether CDK8 was directly acting on MYC (such as through phosphorylation of S62 or other residues) or though indirect mechanisms on MYC or MYC target genes.

[0283] While the data imply that CDK8 regulates MYC activity, alternatively it is plausible that CDK8 and MYC may function convergently yet independently to regulate ES cell gene expression. For example, MYC regulation of RNA polymerase II pause release at ES cell target genes (Rahl P.B. *et al.*, *Cell* 141:432-45 (2010)) could act in tandem with CDK8-Mediator regulation of RNA polymerase II (Taatjes D.J. *Trends Biochem Sci* 35:315-22 (2010)). CDK9, another transcriptional CDK family member that has shared functions with CDK8 (Fryer C.J. *et al.*, *Mol Cell* 16:509-20 (2004); Alarcon C. *et al.*, *Cell* 139:757-69 (2009)), has also been shown to regulate ES cell pluripotency (Kaichi S. *et al.*, *J Cell Physiol* 226:248-54 (2011)). And since both CDK8 and CDK9 have been found to phosphorylate RNA polymerase II in similar ways (Pinhero R. *et al.*, *Eur J Biochem* 271:1004-14 (2004).), CDK8 and CDK9 may cooperate to modulate the transcription of ES cell-related genes, either in combination with or independently of MYC. Further, because MYC is not able to fully rescue the differentiation phenotype caused by CDK8 loss, further investigation is needed to identify MYC-independent mechanisms that CDK8 may be acting through to maintain tumors and stem cells in an undifferentiated state.

[0284] CDK8 inhibition in colon cancer cells leads to a significant decrease in the expression of ES cell-related genes, and these genes were particularly enriched for MYC target genes previously identified in ES cells. The subset of MYC target genes whose expression was CDK8 dependent was unique in its ability to predict tumor differentiation and clinical outcome. Specifically, increased expression of the CDK8-regulated MYC target genes singled out tumors that were poorly differentiated and were more prone to undergo rapid recurrence. This is in contrast to expression of the full set of MYC target genes, which were unable to identify these same tumors. These data suggest that the CDK8-regulated subset of MYC ES cell target genes are coordinately expressed in poorly differentiated, poor prognosis primary colon tumors. However it remains to be determined whether CDK8 is directly responsible for maintaining this coordinated expression.

[0285] In conclusion, convergent roles for CDK8 were defined regulating both tumor and ES cell differentiation states through regulating MYC. A CDK8-regulated MYC signature that was specifically

expressed in poor prognosis colon tumors that were poorly differentiated was identified. Together these observations raise the possibility that the stem cell-like properties of cancer cells may be specifically inhibited by therapeutically targeting CDK8.

[0286] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

Table 2: CDK8-regulated genes in human HT-29 colon cancer cells.
Provided are the top 1500 genes that significantly changed upon CDK8 loss in HT-29 cells. The fold change is relative to siNTC control. *P*-value is a Student's *t*-Test between siNTC and two independent CDK8 siRNAs. Genes that overlap the mouse ES cell-related gene signature (Wong et al., Cell Stem Cell, 2008) or MYC targets in ES cells (Kim et al., Cell, 2008) are indicated.

Human Entrez ID	Gene Symbol	CDK8-induced/ repressed	*P*-value	Fold change	ES cell-related gene	MYC ES cell target
1024	CDK8	CDK8-induced	4.03E-10	8.39	Yes	Yes
9441	CRSP7	CDK8-induced	5.72E-10	1.49		
2171	FABP5	CDK8-induced	6.05E-10	1.93		Yes
9221	NOLC1	CDK8-induced	1.46E-09	1.73	Yes	Yes
6158	RPL28	CDK8-induced	2.19E-09	1.32	Yes	Yes
159090	FAM122B	CDK8-induced	2.79E-08	1.75		
55622	TTC27	CDK8-induced	3.51E-08	1.48	Yes	Yes
7165	TPD52L2	CDK8-induced	3.72E-08	2.02		Yes
26502	NARF	CDK8-induced	3.86E-08	1.75		
10528	NOL5A	CDK8-induced	4.91E-08	1.42		Yes
2534	FYN	CDK8-induced	7.75E-08	1.51	Yes	
29803	REPIN1	CDK8-induced	8.74E-08	1.31		Yes
29980	DONSON	CDK8-induced	8.86E-08	1.46		
60386	SLC25A19	CDK8-induced	1.16E-07	1.57		
64710	NUCKS1	CDK8-induced	1.27E-07	1.84	Yes	Yes
131474	CHCHD4	CDK8-induced	1.40E-07	1.35		Yes
79000	C1orf135	CDK8-induced	1.69E-07	1.23		
90390	THRAP6	CDK8-induced	1.78E-07	1.29		
3985	LIMK2	CDK8-induced	1.80E-07	1.45		
84705	GTPBP3	CDK8-induced	1.82E-07	1.36	Yes	Yes
3491	CYR61	CDK8-induced	2.17E-07	1.78		
84916	CIRH1A	CDK8-induced	2.27E-07	1.29	Yes	
54997	TESC	CDK8-induced	2.34E-07	1.79		
7422	VEGF	CDK8-induced	3.47E-07	1.31		
8623	ASMTL	CDK8-induced	3.88E-07	1.69		
1111	CHEK1	CDK8-induced	3.97E-07	1.51	Yes	Yes
116842	LEAP-2	CDK8-induced	4.52E-07	1.89		Yes
6502	SKP2	CDK8-induced	4.55E-07	1.73		Yes
5111	PCNA	CDK8-induced	4.58E-07	1.48	Yes	Yes
338756	LOC338756	CDK8-induced	4.83E-07	1.44		
56655	POLE4	CDK8-induced	5.33E-07	1.19		
9943	OXSR1	CDK8-induced	5.35E-07	1.28		
3837	KPNB1	CDK8-induced	5.61E-07	1.27	Yes	Yes
440145	RP11-11C5.2	CDK8-induced	5.70E-07	1.44		
1122	CHML	CDK8-induced	5.82E-07	1.55		Yes
26973	CHORDC1	CDK8-induced	6.16E-07	1.56	Yes	
29078	C6orf66	CDK8-induced	6.53E-07	1.49	Yes	Yes
10914	PAPOLA	CDK8-induced	8.16E-07	1.40		
8318	CDC45L	CDK8-induced	8.18E-07	1.52	Yes	
9329	GTF3C4	CDK8-induced	8.86E-07	1.51		Yes
3008	HIST1H1E	CDK8-induced	9.74E-07	1.38		
8569	MKNK1	CDK8-induced	1.01E-06	1.55		
8358	HIST1H3B	CDK8-induced	1.04E-06	1.20		
56941	C3orf37	CDK8-induced	1.05E-06	1.75		
8438	RAD54L	CDK8-induced	1.07E-06	1.32	Yes	Yes
55055	ZWILCH	CDK8-induced	1.12E-06	1.56		Yes
9088	PKMYT1	CDK8-induced	1.19E-06	1.29		
9775	DDX48	CDK8-induced	1.36E-06	1.28	Yes	
55326	AGPAT5	CDK8-induced	1.42E-06	1.38	Yes	Yes
51406	NOL7	CDK8-induced	1.43E-06	1.33		YesT

10038	PARP2	CDK8-induced	1.51E-06	1.38	Yes	Yes
10189	THOC4	CDK8-induced	1.52E-06	1.35	Yes	Yes
6322	SCML1	CDK8-induced	1.53E-06	3.48		
204	AK2	CDK8-induced	1.58E-06	1.36	Yes	Yes
23650	TRIM29	CDK8-induced	1.82E-06	1.34		
152024	LOC152024	CDK8-induced	1.86E-06	1.48		
9255	SCYE1	CDK8-induced	2.10E-06	1.25		Yes
7170	TPM3	CDK8-induced	2.12E-06	1.30		
7167	TPI1	CDK8-induced	2.33E-06	1.31		
57213	C13orf1	CDK8-induced	2.37E-06	1.56		
55646	LYAR	CDK8-induced	2.46E-06	1.63	Yes	
57332	CBX8	CDK8-induced	2.57E-06	1.36		
25904	CNOT10	CDK8-induced	2.57E-06	1.20		Yes
90417	C15orf23	CDK8-induced	2.62E-06	1.50		
126789	PUSL1	CDK8-induced	2.86E-06	1.15		
221035	REEP3	CDK8-induced	2.89E-06	1.24		
56992	KIF15	CDK8-induced	2.90E-06	1.41		Yes
388886	LOC388886	CDK8-induced	2.93E-06	1.51		
2745	GLRX	CDK8-induced	3.06E-06	1.37		
1058	CENPA	CDK8-induced	3.18E-06	1.46		
8677	STX10	CDK8-induced	3.31E-06	1.19		
55839	CENPN	CDK8-induced	3.43E-06	1.50		Yes
51013	EXOSC1	CDK8-induced	3.78E-06	1.14	Yes	Yes
55132	LARP2	CDK8-induced	3.83E-06	1.34		
27335	EIF3S12	CDK8-induced	4.00E-06	1.34	Yes	Yes
10744	PTTG2	CDK8-induced	4.09E-06	1.31		
221823	PRPS1L1	CDK8-induced	4.35E-06	1.54		
79912	FLJ22028	CDK8-induced	4.58E-06	1.29		
51218	GLRX5	CDK8-induced	4.83E-06	1.36		Yes
890	CCNA2	CDK8-induced	4.83E-06	1.55	Yes	
6427	SFRS2	CDK8-induced	5.09E-06	1.15	Yes	Yes
10588	MTHFS	CDK8-induced	5.22E-06	1.29		
1021	CDK6	CDK8-induced	5.24E-06	1.91		Yes
5464	PPA1	CDK8-induced	5.55E-06	1.25	Yes	Yes
7088	TLE1	CDK8-induced	5.69E-06	1.41		Yes
23421	ITGB3BP	CDK8-induced	5.71E-06	1.33		Yes
708	C1QBP	CDK8-induced	5.77E-06	1.27		Yes
115106	CCDC5	CDK8-induced	6.39E-06	1.34	Yes	
8847	DLEU2	CDK8-induced	6.49E-06	2.03		
8367	HIST1H4E	CDK8-induced	6.77E-06	1.41		
3007	HIST1H1D	CDK8-induced	6.84E-06	1.65		
7486	WRN	CDK8-induced	7.89E-06	1.26		
5757	PTMA	CDK8-induced	7.96E-06	1.49		Yes
93081	RP11-484I6.3	CDK8-induced	8.01E-06	1.71		Yes
6947	TCN1	CDK8-induced	8.02E-06	3.62		
11200	CHEK2	CDK8-induced	8.24E-06	1.27	Yes	Yes
28977	MRPL42	CDK8-induced	8.91E-06	1.28		Yes
10920	COPS8	CDK8-induced	9.21E-06	1.30		Yes
5465	PPARA	CDK8-induced	9.33E-06	1.43		
11332	ACOT7	CDK8-induced	9.53E-06	1.52		
4678	NASP	CDK8-induced	9.74E-06	1.43	Yes	Yes
26127	FGFR1OP2	CDK8-induced	9.75E-06	1.36		
140809	SRXN1	CDK8-induced	9.98E-06	1.45		
7329	UBE2I	CDK8-induced	1.05E-05	1.14		Yes
84321	THOC3	CDK8-induced	1.10E-05	1.12	Yes	
3735	KARS	CDK8-induced	1.12E-05	1.49		Yes
9631	NUP155	CDK8-induced	1.14E-05	1.31		Yes
81624	DIAPH3	CDK8-induced	1.18E-05	1.62		Yes
348235	FAM33A	CDK8-induced	1.19E-05	1.54		Yes

4172	MCM3	CDK8-induced	1.21E-05	1.50	Yes	Yes
8883	APPBP1	CDK8-induced	1.24E-05	1.27	Yes	
2237	FEN1	CDK8-induced	1.25E-05	1.55	Yes	Yes
388965	LOC388965	CDK8-induced	1.31E-05	1.44		
4869	NPM1	CDK8-induced	1.31E-05	1.45	Yes	Yes
55559	UIP1	CDK8-induced	1.32E-05	1.31		
29902	C12orf24	CDK8-induced	1.34E-05	1.69		Yes
10460	TACC3	CDK8-induced	1.36E-05	1.25	Yes	Yes
6004	RGS16	CDK8-induced	1.36E-05	1.81		
1062	CENPE	CDK8-induced	1.38E-05	1.24		
51444	RNF138	CDK8-induced	1.44E-05	1.79	Yes	
216	ALDH1A1	CDK8-induced	1.47E-05	1.33		
64425	POLR1E	CDK8-induced	1.53E-05	1.51	Yes	Yes
10901	DHRS4	CDK8-induced	1.55E-05	1.37		
284427	MGC34725	CDK8-induced	1.57E-05	1.58		
221710	LOC221710	CDK8-induced	1.64E-05	1.58		
9882	TBC1D4	CDK8-induced	1.68E-05	1.40		
4698	NDUFA5	CDK8-induced	1.69E-05	1.17		Yes
25948	KBTBD2	CDK8-induced	1.71E-05	1.18		
1841	DTYMK	CDK8-induced	1.72E-05	1.22	Yes	Yes
9854	TMEM24	CDK8-induced	1.76E-05	1.25		Yes
9093	DNAJA3	CDK8-induced	1.89E-05	1.35		
57405	SPBC25	CDK8-induced	1.89E-05	1.43	Yes	
9442	CRSP8	CDK8-induced	1.90E-05	1.38		
55573	CDV3	CDK8-induced	1.93E-05	1.21	Yes	Yes
2147	F2	CDK8-induced	1.93E-05	1.26		
10162	MBOAT5	CDK8-induced	1.99E-05	1.42		
1515	CTSL2	CDK8-induced	2.01E-05	1.52		
3070	HELLS	CDK8-induced	2.04E-05	1.62	Yes	
6832	SUPV3L1	CDK8-induced	2.07E-05	1.35	Yes	Yes
26084	SGEF	CDK8-induced	2.08E-05	1.44		
84920	ALG10	CDK8-induced	2.09E-05	1.40		
4234	METTL1	CDK8-induced	2.10E-05	1.22		Yes
6625	SNRP70	CDK8-induced	2.14E-05	1.21		Yes
27309	ZNF330	CDK8-induced	2.14E-05	1.40		Yes
51678	MPP6	CDK8-induced	2.19E-05	1.89		
54819	ZCCHC10	CDK8-induced	2.21E-05	1.19		
2958	GTF2A2	CDK8-induced	2.21E-05	1.18		
64793	CCDC21	CDK8-induced	2.22E-05	1.42		
440577	LOC440577	CDK8-induced	2.22E-05	1.48		
7320	UBE2B	CDK8-induced	2.22E-05	1.41		Yes
79929	MAP6D1	CDK8-induced	2.25E-05	1.23		
84138	SLC7A6OS	CDK8-induced	2.30E-05	1.16		Yes
79172	CENPO	CDK8-induced	2.38E-05	1.31		Yes
2023	ENO1	CDK8-induced	2.38E-05	1.29	Yes	Yes
23137	SMC5	CDK8-induced	2.38E-05	1.45		
387103	C6orf173	CDK8-induced	2.42E-05	1.18		
80324	PUS1	CDK8-induced	2.43E-05	1.34	Yes	Yes
55604	LRRC16	CDK8-induced	2.43E-05	1.33		
81034	SLC25A32	CDK8-induced	2.46E-05	1.31		Yes
55840	EAF2	CDK8-induced	2.46E-05	1.31		
580	BARD1	CDK8-induced	2.46E-05	1.25		Yes
132001	C3orf31	CDK8-induced	2.50E-05	1.11	Yes	
151987	PPP4R2	CDK8-induced	2.51E-05	1.29		
79084	WDR77	CDK8-induced	2.55E-05	1.33	Yes	Yes
9657	IQCB1	CDK8-induced	2.59E-05	1.29		
54955	C1orf109	CDK8-induced	2.61E-05	1.34		
5091	PC	CDK8-induced	2.72E-05	1.33		
4257	MGST1	CDK8-induced	2.81E-05	1.12		

84706	GPT2	CDK8-induced	2.81E-05	1.31		
79731	NARS2	CDK8-induced	2.82E-05	1.23		Yes
9933	KIAA0020	CDK8-induced	2.85E-05	1.27		
27338	UBE2S	CDK8-induced	2.86E-05	1.16		
5359	PLSCR1	CDK8-induced	2.88E-05	1.31		
259266	ASPM	CDK8-induced	2.89E-05	1.42	Yes	Yes
8882	ZNF259	CDK8-induced	2.92E-05	1.28		Yes
26519	TIMM10	CDK8-induced	2.93E-05	1.27		Yes
133522	PPARGC1B	CDK8-induced	2.94E-05	1.95		Yes
25929	GEMIN5	CDK8-induced	2.95E-05	1.99		Yes
3009	HIST1H1B	CDK8-induced	2.95E-05	1.74		
79621	DLEU8	CDK8-induced	2.95E-05	1.17	Yes	
231	AKR1B1	CDK8-induced	3.02E-05	1.42		Yes
3796	KIF2	CDK8-induced	3.03E-05	1.32		
55227	LRRC1	CDK8-induced	3.07E-05	1.58		
6636	SNRPF	CDK8-induced	3.07E-05	1.20		
131076	CCDC58	CDK8-induced	3.10E-05	1.30	Yes	Yes
384	ARG2	CDK8-induced	3.16E-05	1.65		
7444	VRK2	CDK8-induced	3.16E-05	1.16		
84287	ZDHHC16	CDK8-induced	3.20E-05	1.30		Yes
57129	MRPL47	CDK8-induced	3.29E-05	1.15		Yes
55254	TMEM39A	CDK8-induced	3.36E-05	1.21		Yes
494514	C18orf56	CDK8-induced	3.37E-05	1.65		
6390	SDHB	CDK8-induced	3.38E-05	1.32		
252983	STXBP4	CDK8-induced	3.41E-05	1.52		
57185	NPAL3	CDK8-induced	3.46E-05	1.43		
2920	CXCL2	CDK8-induced	3.53E-05	1.72		
26018	LRIG1	CDK8-induced	3.54E-05	1.48		
348926	LOC348926	CDK8-induced	3.64E-05	1.22		
1302	COL11A2	CDK8-induced	3.65E-05	1.34		
10885	WDR3	CDK8-induced	3.72E-05	1.23		Yes
10714	POLD3	CDK8-induced	3.80E-05	1.79	Yes	
56942	C16orf61	CDK8-induced	3.83E-05	1.15		
9491	PSMF1	CDK8-induced	3.88E-05	1.14		
7533	YWHAH	CDK8-induced	3.92E-05	1.22		
51018	CGI-115	CDK8-induced	3.93E-05	1.36		Yes
83903	GSG2	CDK8-induced	3.97E-05	1.40	Yes	
11130	ZWINT	CDK8-induced	4.06E-05	1.40		
2288	FKBP4	CDK8-induced	4.13E-05	1.43		
7430	VIL2	CDK8-induced	4.19E-05	1.24		Yes
9295	SFRS11	CDK8-induced	4.37E-05	1.21		
83608	C18orf21	CDK8-induced	4.42E-05	1.20		
84289	ING5	CDK8-induced	4.45E-05	1.18		Yes
55034	MOCOS	CDK8-induced	4.56E-05	1.35		
79682	MLF1IP	CDK8-induced	4.61E-05	1.71		Yes
9824	ARHGAP11A	CDK8-induced	4.61E-05	1.21		Yes
51053	GMNN	CDK8-induced	4.74E-05	1.20	Yes	Yes
26092	TOR1AIP1	CDK8-induced	4.84E-05	1.21		
701	BUB1B	CDK8-induced	4.89E-05	1.22	Yes	Yes
26986	PABPC1	CDK8-induced	4.98E-05	1.66	Yes	Yes
7520	XRCC5	CDK8-induced	4.99E-05	1.15	Yes	Yes
10113	PREB	CDK8-induced	5.00E-05	1.30		
148789	B3GALNT2	CDK8-induced	5.04E-05	1.54		
23062	GGA2	CDK8-induced	5.08E-05	1.13	Yes	Yes
9213	XPR1	CDK8-induced	5.14E-05	1.58		
4043	LRPAP1	CDK8-induced	5.14E-05	1.53		
29107	NXT1	CDK8-induced	5.21E-05	1.29	Yes	
26255	PTTG3	CDK8-induced	5.31E-05	1.33		
11212	PROSC	CDK8-induced	5.42E-05	1.35		Yes

25764	HYPK	CDK8-induced	5.50E-05	1.20		Yes
650	BMP2	CDK8-induced	5.51E-05	2.63		
5289	PIK3C3	CDK8-induced	5.52E-05	1.22		
205	AK3L1	CDK8-induced	5.53E-05	1.27	Yes	
55127	HEATR1	CDK8-induced	5.58E-05	1.38		
148304	C1orf74	CDK8-induced	5.59E-05	1.28		
7913	DEK	CDK8-induced	5.60E-05	1.44	Yes	
85025	TMEM60	CDK8-induced	5.61E-05	1.39		
1176	AP3S1	CDK8-induced	5.66E-05	1.23	Yes	
27161	EIF2C2	CDK8-induced	5.73E-05	1.18		
51654	CDK5RAP1	CDK8-induced	5.76E-05	1.25		Yes
11072	DUSP14	CDK8-induced	5.84E-05	1.34		
993	CDC25A	CDK8-induced	5.85E-05	1.87		
9020	MAP3K14	CDK8-induced	5.89E-05	1.31		
29080	CCDC59	CDK8-induced	5.94E-05	1.27		Yes
286016	LOC286016	CDK8-induced	5.95E-05	1.29		
91298	C12orf29	CDK8-induced	5.99E-05	1.33		
23405	DICER1	CDK8-induced	6.00E-05	1.72	Yes	
4999	ORC2L	CDK8-induced	6.02E-05	1.34		
29116	MYLIP	CDK8-induced	6.03E-05	1.29		
3622	ING2	CDK8-induced	6.07E-05	1.30		
26574	AATF	CDK8-induced	6.07E-05	1.15	Yes	Yes
2030	SLC29A1	CDK8-induced	6.22E-05	1.25		Yes
664727	LOC664727	CDK8-induced	6.35E-05	1.54		
84128	WDR75	CDK8-induced	6.35E-05	1.21		Yes
10939	AFG3L2	CDK8-induced	6.38E-05	1.34		Yes
386757	SLC6A10P	CDK8-induced	6.46E-05	1.46		
27346	TMEM97	CDK8-induced	6.51E-05	1.19	Yes	Yes
64151	HCAP-G	CDK8-induced	6.61E-05	1.48		
64318	NOC3L	CDK8-induced	6.69E-05	1.15		Yes
168620	BHLHB8	CDK8-induced	6.75E-05	1.33		
192111	PGAM5	CDK8-induced	6.79E-05	1.38		
58495	OVOL2	CDK8-induced	7.02E-05	1.42		
116254	C6orf72	CDK8-induced	7.15E-05	1.46		
8896	BUD31	CDK8-induced	7.16E-05	1.11		
57621	ZBTB2	CDK8-induced	7.24E-05	1.31		Yes
122704	MRPL52	CDK8-induced	7.31E-05	1.14		
6418	SET	CDK8-induced	7.36E-05	1.37	Yes	Yes
79145	CHCHD7	CDK8-induced	7.41E-05	1.30		
85002	FAM86B1	CDK8-induced	7.54E-05	1.16		Yes
10606	PAICS	CDK8-induced	7.57E-05	1.55		
494143	CHAC2	CDK8-induced	7.57E-05	1.34		
84328	LZIC	CDK8-induced	7.76E-05	1.24		
53371	NUP54	CDK8-induced	7.79E-05	1.53		Yes
1786	DNMT1	CDK8-induced	7.92E-05	1.33	Yes	
26156	RSL1D1	CDK8-induced	7.98E-05	1.59	Yes	Yes
55825	PECR	CDK8-induced	8.18E-05	1.52		
1019	CDK4	CDK8-induced	8.25E-05	1.55	Yes	Yes
55234	SMU1	CDK8-induced	8.30E-05	1.22		
81929	SEH1L	CDK8-induced	8.31E-05	1.32		Yes
7919	BAT1	CDK8-induced	8.42E-05	1.18		
91942	mimitin	CDK8-induced	8.50E-05	1.42		
6584	SLC22A5	CDK8-induced	8.53E-05	1.31		
4552	MTRR	CDK8-induced	8.60E-05	1.52		Yes
84798	C19orf48	CDK8-induced	8.68E-05	1.30		
150468	CKAP2L	CDK8-induced	8.85E-05	1.33		Yes
83540	CDCA1	CDK8-induced	8.91E-05	1.23		Yes
6491	STIL	CDK8-induced	8.93E-05	1.81	Yes	
6182	MRPL12	CDK8-induced	9.05E-05	1.21	Yes	Yes

92140	MTDH	CDK8-induced	9.19E-05	1.44		Yes
79657	FLJ21908	CDK8-induced	9.26E-05	1.24		
54478	FAM64A	CDK8-induced	9.34E-05	1.28	Yes	
9747	KIAA0738	CDK8-induced	9.37E-05	1.89		
58515	SELK	CDK8-induced	9.37E-05	1.17		Yes
387851	AK3L2	CDK8-induced	9.38E-05	1.47		
478	ATP1A3	CDK8-induced	9.41E-05	1.34		
9791	PTDSS1	CDK8-induced	9.51E-05	1.39		
147804	LOC147804	CDK8-induced	9.62E-05	1.37		
10419	PRMT5	CDK8-induced	9.63E-05	1.28		Yes
646200	LOC646200	CDK8-induced	9.91E-05	1.13		
10988	METAP2	CDK8-induced	9.95E-05	1.24		Yes
8533	COPS3	CDK8-induced	9.95E-05	1.26	Yes	
7579	ZNF31	CDK8-induced	1.03E-04	1.18		
6232	RPS27	CDK8-induced	1.03E-04	1.17	Yes	
7322	UBE2D2	CDK8-induced	1.03E-04	1.15	Yes	
788	SLC25A20	CDK8-induced	1.03E-04	1.58		
29028	ATAD2	CDK8-induced	1.04E-04	1.78		Yes
23246	BOP1	CDK8-induced	1.04E-04	1.26		Yes
3987	LIMS1	CDK8-induced	1.04E-04	1.78		
5306	PITPNA	CDK8-induced	1.05E-04	1.32		
4927	NUP88	CDK8-induced	1.05E-04	1.39		Yes
284349	ZNF283	CDK8-induced	1.05E-04	1.28		
51514	DTL	CDK8-induced	1.05E-04	1.63	Yes	Yes
274	BIN1	CDK8-induced	1.06E-04	1.27		
3327	HSP90AB3P	CDK8-induced	1.09E-04	1.67		
55844	PPP2R2D	CDK8-induced	1.09E-04	1.18		
55872	PBK	CDK8-induced	1.09E-04	1.14		
54442	KCTD5	CDK8-induced	1.13E-04	1.26		Yes
11073	TOPBP1	CDK8-induced	1.14E-04	1.69	Yes	
11157	LSM6	CDK8-induced	1.14E-04	1.38		
23082	PPRC1	CDK8-induced	1.16E-04	1.25	Yes	
1104	RCC1	CDK8-induced	1.17E-04	1.27	Yes	Yes
55835	CENPJ	CDK8-induced	1.17E-04	1.37		
1514	CTSL	CDK8-induced	1.18E-04	1.26		
10884	MRPS30	CDK8-induced	1.19E-04	1.29	Yes	Yes
7846	TUBA3	CDK8-induced	1.20E-04	1.43		
51497	TH1L	CDK8-induced	1.20E-04	1.39		
10514	MYBBP1A	CDK8-induced	1.20E-04	1.25		Yes
9270	ITGB1BP1	CDK8-induced	1.22E-04	1.26		Yes
262	AMD1	CDK8-induced	1.22E-04	1.31	Yes	Yes
6256	RXRA	CDK8-induced	1.24E-04	1.33		
5542	PRB1	CDK8-induced	1.24E-04	3.35		
5074	PAWR	CDK8-induced	1.25E-04	1.68	Yes	Yes
3308	HSPA4	CDK8-induced	1.26E-04	1.15	Yes	Yes
1075	CTSC	CDK8-induced	1.26E-04	1.23	Yes	
27101	CACYBP	CDK8-induced	1.26E-04	1.32	Yes	
22824	HSPA4L	CDK8-induced	1.27E-04	1.60		
23016	EXOSC7	CDK8-induced	1.28E-04	1.23	Yes	
2332	FMR1	CDK8-induced	1.30E-04	1.26		
11277	TREX1	CDK8-induced	1.32E-04	1.14		
134266	GRPEL2	CDK8-induced	1.33E-04	1.15		Yes
55854	LEREPO4	CDK8-induced	1.34E-04	1.27		Yes
147968	CAPN12	CDK8-induced	1.34E-04	1.70		
6932	TCF7	CDK8-induced	1.35E-04	1.31		
22995	CEP152	CDK8-induced	1.37E-04	1.68		
10549	PRDX4	CDK8-induced	1.38E-04	1.28		
8338	HIST2H2AC	CDK8-induced	1.38E-04	1.26		
5911	RAP2A	CDK8-induced	1.40E-04	1.41		Yes

84817	TXNL5	CDK8-induced	1.40E-04	1.20		
27342	RABGEF1	CDK8-induced	1.40E-04	1.21		
5610	EIF2AK2	CDK8-induced	1.40E-04	1.30		
85028	C1orf79	CDK8-induced	1.40E-04	1.32		
23404	EXOSC2	CDK8-induced	1.41E-04	1.36		Yes
140462	ASB9	CDK8-induced	1.41E-04	1.89		
6632	SNRPD1	CDK8-induced	1.42E-04	1.22	Yes	Yes
4085	MAD2L1	CDK8-induced	1.43E-04	1.28	Yes	
10966	RAB40B	CDK8-induced	1.44E-04	1.56		
5496	PPM1G	CDK8-induced	1.46E-04	1.17	Yes	
6478	SIAH2	CDK8-induced	1.48E-04	1.39		
152137	CCDC50	CDK8-induced	1.51E-04	1.12		
55787	CXorf15	CDK8-induced	1.51E-04	1.30		
55746	NUP133	CDK8-induced	1.51E-04	1.18		Yes
7443	VRK1	CDK8-induced	1.52E-04	1.42	Yes	
9555	H2AFY	CDK8-induced	1.58E-04	1.47		
79080	CCDC86	CDK8-induced	1.59E-04	1.35	Yes	Yes
10622	POLR3G	CDK8-induced	1.60E-04	1.72		
11252	PACSIN2	CDK8-induced	1.60E-04	1.34		
123811	C16orf63	CDK8-induced	1.68E-04	1.17		
317781	DDX51	CDK8-induced	1.68E-04	1.33		Yes
4590	MUC8	CDK8-induced	1.68E-04	1.15		
6392	SDHD	CDK8-induced	1.69E-04	1.15	Yes	Yes
6510	SLC1A5	CDK8-induced	1.70E-04	1.27		
23034	SAMD4A	CDK8-induced	1.70E-04	1.48		
140460	ASB7	CDK8-induced	1.71E-04	1.29		
7371	UCK2	CDK8-induced	1.72E-04	1.35	Yes	Yes
23483	TGDS	CDK8-induced	1.74E-04	1.23		
26249	KLHL3	CDK8-induced	1.74E-04	1.37		
57602	USP36	CDK8-induced	1.75E-04	1.58		
595	CCND1	CDK8-induced	1.77E-04	1.38	Yes	Yes
10403	KNTC2	CDK8-induced	1.78E-04	1.30	Yes	
27348	TOR1B	CDK8-induced	1.82E-04	1.22		
1353	COX11	CDK8-induced	1.85E-04	1.25		
9377	COX5A	CDK8-induced	1.86E-04	1.12		Yes
2280	FKBP1A	CDK8-induced	1.86E-04	1.23		
7083	TK1	CDK8-induced	1.87E-04	1.18	Yes	Yes
1506	CTRL	CDK8-induced	1.87E-04	1.36		Yes
9984	THOC1	CDK8-induced	1.88E-04	1.54		Yes
79848	CSPP1	CDK8-induced	1.89E-04	1.79		
8802	SUCLG1	CDK8-induced	1.90E-04	1.15		
8634	RTCD1	CDK8-induced	1.93E-04	1.17		Yes
646197	LOC646197	CDK8-induced	1.93E-04	1.21		
23468	CBX5	CDK8-induced	1.93E-04	1.64	Yes	Yes
8726	EED	CDK8-induced	1.94E-04	1.32	Yes	Yes
3326	HSP90AB1	CDK8-induced	1.94E-04	1.37		Yes
9100	USP10	CDK8-induced	1.94E-04	1.55	Yes	
1032	CDKN2D	CDK8-induced	1.96E-04	1.55		Yes
11232	POLG2	CDK8-induced	1.98E-04	1.18		Yes
23047	APRIN	CDK8-induced	1.99E-04	1.29		
2935	GSPT1	CDK8-induced	2.00E-04	1.51		Yes
2932	GSK3B	CDK8-induced	2.01E-04	1.26		
56548	CHST7	CDK8-induced	2.03E-04	1.31		
30850	CDR2L	CDK8-induced	2.04E-04	1.19		
8405	SPOP	CDK8-induced	2.04E-04	1.19		
509	ATP5C1	CDK8-induced	2.05E-04	1.23		Yes
55723	ASF1B	CDK8-induced	2.06E-04	1.61	Yes	Yes
121053	C12orf45	CDK8-induced	2.09E-04	1.14		
159013	CXorf38	CDK8-induced	2.10E-04	1.19		

622	BDH1	CDK8-induced	2.17E-04	1.23	Yes	
25799	ZNF324	CDK8-induced	2.23E-04	1.12		
4645	MYO5B	CDK8-induced	2.24E-04	1.15		
55119	PRPF38B	CDK8-induced	2.27E-04	1.19		Yes
205564	SENP5	CDK8-induced	2.28E-04	1.42		Yes
9527	GOSR1	CDK8-induced	2.29E-04	1.30		
2091	FBL	CDK8-induced	2.30E-04	1.51	Yes	Yes
9801	MRPL19	CDK8-induced	2.32E-04	1.18		
51495	PTPLAD1	CDK8-induced	2.32E-04	1.32		
79960	PHF17	CDK8-induced	2.36E-04	1.61		
8208	CHAF1B	CDK8-induced	2.38E-04	1.35	Yes	
81610	FAM83D	CDK8-induced	2.39E-04	1.40		
7874	USP7	CDK8-induced	2.40E-04	1.21		
10036	CHAF1A	CDK8-induced	2.40E-04	1.14	Yes	
51184	ATPBD1C	CDK8-induced	2.40E-04	1.29		Yes
10813	UTP14A	CDK8-induced	2.41E-04	1.35		Yes
56255	TXNDC13	CDK8-induced	2.42E-04	1.48		
7268	TTC4	CDK8-induced	2.43E-04	1.15		
129787	TMEM18	CDK8-induced	2.43E-04	1.21		
55274	PHF10	CDK8-induced	2.47E-04	1.27		
10084	PQBP1	CDK8-induced	2.48E-04	1.22		
4735	2-Sep	CDK8-induced	2.49E-04	1.34		Yes
3833	KIFC1	CDK8-induced	2.49E-04	1.13		Yes
642480	LOC642480	CDK8-induced	2.50E-04	1.53		
84154	BXDC1	CDK8-induced	2.56E-04	1.35	Yes	Yes
9126	SMC3	CDK8-induced	2.56E-04	1.15	Yes	
9015	TAF1A	CDK8-induced	2.60E-04	1.35		
3192	HNRPU	CDK8-induced	2.63E-04	1.24		
55355	DKFZp762E1312	CDK8-induced	2.68E-04	1.40		Yes
51065	RPS27L	CDK8-induced	2.70E-04	1.16		Yes
4946	OAZ1	CDK8-induced	2.72E-04	1.38		
81689	HBLD2	CDK8-induced	2.74E-04	1.24		Yes
11325	DDX42	CDK8-induced	2.74E-04	1.35		
81853	TMEM14B	CDK8-induced	2.75E-04	1.15		
23097	CDC2L6	CDK8-induced	2.78E-04	1.29		
55353	LAPTM4B	CDK8-induced	2.80E-04	1.15		
4839	NOL1	CDK8-induced	2.81E-04	1.19	Yes	Yes
3306	HSPA2	CDK8-induced	2.81E-04	1.45		
6749	SSRP1	CDK8-induced	2.82E-04	1.26	Yes	
4998	ORC1L	CDK8-induced	2.83E-04	1.47	Yes	Yes
4841	NONO	CDK8-induced	2.86E-04	1.35	Yes	Yes
7171	TPM4	CDK8-induced	2.86E-04	1.11	Yes	
1207	CLNS1A	CDK8-induced	2.87E-04	1.12		Yes
7464	CORO2A	CDK8-induced	2.88E-04	1.54		
388817	LOC388817	CDK8-induced	2.89E-04	1.17		
3601	IL15RA	CDK8-induced	2.90E-04	1.18		
10465	PPIH	CDK8-induced	2.96E-04	1.29		
6929	TCF3	CDK8-induced	2.97E-04	1.46		
8607	RUVBL1	CDK8-induced	2.97E-04	1.20	Yes	Yes
291	SLC25A4	CDK8-induced	3.00E-04	1.30		
9232	PTTG1	CDK8-induced	3.01E-04	1.26		
5036	PA2G4	CDK8-induced	3.01E-04	1.66	Yes	Yes
55388	MCM10	CDK8-induced	3.02E-04	1.67	Yes	
4928	NUP98	CDK8-induced	3.05E-04	1.26		
1723	DHODH	CDK8-induced	3.05E-04	1.12		Yes
54984	PINX1	CDK8-induced	3.06E-04	1.61		
344967	LOC344967	CDK8-induced	3.07E-04	1.29		
4189	DNAJB9	CDK8-induced	3.07E-04	1.10		Yes
79944	L2HGDH	CDK8-induced	3.08E-04	1.53		

55178	RNMTL1	CDK8-induced	3.13E-04	1.30		Yes
63875	MRPL17	CDK8-induced	3.15E-04	1.17	Yes	Yes
1105	CHD1	CDK8-induced	3.16E-04	1.39	Yes	
26010	DNAPTP6	CDK8-induced	3.18E-04	1.16		
4953	ODC1	CDK8-induced	3.21E-04	1.55	Yes	Yes
23647	ARFIP2	CDK8-induced	3.22E-04	1.22		
8504	PEX3	CDK8-induced	3.24E-04	1.26		Yes
89927	C16orf45	CDK8-induced	3.29E-04	1.20		
94056	SYAP1	CDK8-induced	3.29E-04	1.94		
57157	PHTF2	CDK8-induced	3.29E-04	1.36	Yes	
129401	NUP35	CDK8-induced	3.31E-04	1.24	Yes	Yes
9319	TRIP13	CDK8-induced	3.36E-04	1.37	Yes	Yes
5434	POLR2E	CDK8-induced	3.37E-04	1.12		
51605	CGI-09	CDK8-induced	3.38E-04	1.37		Yes
5290	PIK3CA	CDK8-induced	3.40E-04	1.15		
25996	REXO2	CDK8-induced	3.41E-04	1.11	Yes	Yes
11143	MYST2	CDK8-induced	3.43E-04	1.20		Yes
55973	BCAP29	CDK8-induced	3.45E-04	1.38	Yes	Yes
23299	BICD2	CDK8-induced	3.46E-04	1.34		Yes
84196	USP48	CDK8-induced	3.48E-04	1.17		Yes
55251	PCMTD2	CDK8-induced	3.49E-04	1.26		
64928	MRPL14	CDK8-induced	3.51E-04	1.15		
3927	LASP1	CDK8-induced	3.53E-04	1.18		
10283	SDCCAG10	CDK8-induced	3.55E-04	1.15		
29128	UHRF1	CDK8-induced	3.57E-04	1.78	Yes	Yes
23517	SKIV2L2	CDK8-induced	3.58E-04	1.15		
28990	ASTE1	CDK8-induced	3.61E-04	1.39		
7247	TSN	CDK8-induced	3.62E-04	1.11		
23196	FAM120A	CDK8-induced	3.69E-04	1.36		
2992	GYG1	CDK8-induced	3.69E-04	1.23		
57062	DDX24	CDK8-induced	3.70E-04	1.28		Yes
96764	NCOA6IP	CDK8-induced	3.71E-04	1.57		
79709	GLT25D1	CDK8-induced	3.71E-04	1.30		Yes
84515	MCM8	CDK8-induced	3.73E-04	1.19		Yes
4691	NCL	CDK8-induced	3.74E-04	1.33	Yes	Yes
9585	MPHOSPH1	CDK8-induced	3.76E-04	1.43		
4174	MCM5	CDK8-induced	3.76E-04	1.19	Yes	Yes
9816	KIAA0133	CDK8-induced	3.77E-04	1.37		
55720	TSR1	CDK8-induced	3.80E-04	1.21	Yes	Yes
29093	MRPL22	CDK8-induced	3.82E-04	1.16		Yes
2909	GRLF1	CDK8-induced	3.83E-04	1.24		
5042	PABPC3	CDK8-induced	3.84E-04	1.55		
355	FAS	CDK8-induced	3.91E-04	1.44		
8560	DEGS1	CDK8-induced	3.92E-04	1.36		Yes
23174	ZCCHC14	CDK8-induced	3.92E-04	1.16		
5202	PFDN2	CDK8-induced	4.00E-04	1.22	Yes	Yes
8428	STK24	CDK8-induced	4.02E-04	1.17		
2921	CXCL3	CDK8-induced	4.04E-04	1.63		
29066	ZC3H7A	CDK8-induced	4.08E-04	1.61		Yes
10452	TOMM40	CDK8-induced	4.09E-04	1.38	Yes	Yes
480	ATP1A4	CDK8-induced	4.12E-04	1.29		
8364	HIST1H4C	CDK8-induced	4.14E-04	2.16		
27000	ZRF1	CDK8-induced	4.14E-04	1.21		Yes
4092	SMAD7	CDK8-induced	4.16E-04	1.19		
722	C4BPA	CDK8-induced	4.17E-04	1.15		
10313	RTN3	CDK8-induced	4.19E-04	1.09		
58478	MASA	CDK8-induced	4.21E-04	1.22	Yes	
4602	MYB	CDK8-induced	4.21E-04	1.45	Yes	
5393	EXOSC9	CDK8-induced	4.25E-04	1.42		

28982	FLVCR	CDK8-induced	4.26E-04	1.09		
7325	UBE2E2	CDK8-induced	4.27E-04	1.31		
220042	FLJ25416	CDK8-induced	4.27E-04	1.39		
79863	C18orf22	CDK8-induced	4.30E-04	1.50		
3842	TNPO1	CDK8-induced	4.30E-04	1.41		Yes
7174	TPP2	CDK8-induced	4.37E-04	1.17	Yes	Yes
157570	ESCO2	CDK8-induced	4.42E-04	1.44		
23133	PHF8	CDK8-induced	4.45E-04	1.35		
10575	CCT4	CDK8-induced	4.50E-04	1.25	Yes	Yes
87178	PNPT1	CDK8-induced	4.54E-04	1.27		Yes
7419	VDAC3	CDK8-induced	4.56E-04	1.11		
64969	MRPS5	CDK8-induced	4.59E-04	1.22		Yes
86	ACTL6A	CDK8-induced	4.61E-04	1.20		
7004	TEAD4	CDK8-induced	4.66E-04	1.20		
84081	CCDC55	CDK8-induced	4.70E-04	1.30		
84522	JAGN1	CDK8-induced	4.75E-04	1.09	Yes	Yes
7706	TRIM25	CDK8-induced	4.81E-04	1.20		Yes
2653	GCSH	CDK8-induced	4.85E-04	1.19	Yes	Yes
80304	FLJ21945	CDK8-induced	4.85E-04	1.28		
9531	BAG3	CDK8-induced	4.90E-04	1.31		
2395	FXN	CDK8-induced	4.90E-04	1.51		
56952	PRTFDC1	CDK8-induced	4.92E-04	1.25		
8833	GMPS	CDK8-induced	4.92E-04	1.28		Yes
3954	LETM1	CDK8-induced	4.93E-04	1.33		
2919	CXCL1	CDK8-induced	4.94E-04	1.92		
51073	MRPL4	CDK8-induced	4.96E-04	1.24	Yes	Yes
64794	DDX31	CDK8-induced	4.98E-04	1.52		Yes
5427	POLE2	CDK8-induced	5.00E-04	1.36	Yes	
284339	TMEM145	CDK8-induced	5.00E-04	1.19		
56997	CABC1	CDK8-induced	5.01E-04	1.47		Yes
55802	DCP1A	CDK8-induced	5.10E-04	1.54		
5033	P4HA1	CDK8-induced	5.18E-04	1.25		
128178	EDARADD	CDK8-induced	5.18E-04	1.21		
4176	MCM7	CDK8-induced	5.18E-04	1.42	Yes	Yes
839	CASP6	CDK8-induced	5.20E-04	1.36		
23367	LARP1	CDK8-induced	5.22E-04	1.20		
51660	BRP44L	CDK8-induced	5.30E-04	1.61		
401397	LOC401397	CDK8-induced	5.30E-04	1.26		
9262	STK17B	CDK8-induced	5.31E-04	1.58		
29889	GNL2	CDK8-induced	5.40E-04	1.12	Yes	Yes
93621	MRFAP1	CDK8-induced	5.42E-04	1.27		
113174	SAAL1	CDK8-induced	5.48E-04	1.19		
902	CCNH	CDK8-induced	5.48E-04	1.63		
51307	FAM53C	CDK8-induced	5.51E-04	1.26		
51537	MTP18	CDK8-induced	5.55E-04	1.22		Yes
55775	TDP1	CDK8-induced	5.56E-04	1.17	Yes	Yes
29105	GTL3	CDK8-induced	5.57E-04	1.22		
5631	PRPS1	CDK8-induced	5.60E-04	1.43	Yes	Yes
26155	NOC2L	CDK8-induced	5.62E-04	1.17		
5162	PDHB	CDK8-induced	5.66E-04	1.16		
9690	UBE3C	CDK8-induced	5.72E-04	1.71		Yes
55968	NSFL1C	CDK8-induced	5.77E-04	1.15		Yes
154807	VKORC1L1	CDK8-induced	5.82E-04	1.27		
113691	MGC16703	CDK8-induced	5.88E-04	1.30		
2519	FUCA2	CDK8-induced	5.93E-04	1.19		
84790	TUBA6	CDK8-induced	5.94E-04	1.42		
399655	ZNF539	CDK8-induced	5.97E-04	1.27		
85365	ALG2	CDK8-induced	5.98E-04	1.23		Yes
4621	MYH3	CDK8-induced	5.99E-04	1.51		

6599	SMARCC1	CDK8-induced	6.02E-04	1.92		
9183	ZW10	CDK8-induced	6.03E-04	1.23		
7752	ZNF200	CDK8-induced	6.10E-04	1.16		
51270	TFDP3	CDK8-induced	6.15E-04	3.58		
55722	CEP72	CDK8-induced	6.24E-04	1.24		
10412	TINP1	CDK8-induced	6.28E-04	1.10	Yes	Yes
3182	HNRPAB	CDK8-induced	6.30E-04	1.40	Yes	Yes
6523	SLC5A1	CDK8-induced	6.32E-04	1.89		
55142	CEP27	CDK8-induced	6.32E-04	1.35		Yes
3945	LDHB	CDK8-induced	6.36E-04	1.31		
51069	MRPL2	CDK8-induced	6.36E-04	1.12		Yes
64919	BCL11B	CDK8-induced	6.41E-04	1.42		Yes
3315	HSPB1	CDK8-induced	6.44E-04	1.16		
7511	XPNPEP1	CDK8-induced	6.58E-04	1.24	Yes	Yes
9043	SPAG9	CDK8-induced	6.59E-04	1.53		
9212	AURKB	CDK8-induced	6.61E-04	1.46	Yes	Yes
10199	MPHOSPH10	CDK8-induced	6.68E-04	1.34	Yes	Yes
64795	RMND5A	CDK8-induced	6.71E-04	1.51		Yes
645013	LOC645013	CDK8-induced	6.76E-04	1.15		
8140	SLC7A5	CDK8-induced	6.78E-04	1.28	Yes	Yes
58477	SRPRB	CDK8-induced	6.79E-04	1.19		
55341	LSG1	CDK8-induced	6.85E-04	1.23		Yes
1478	CSTF2	CDK8-induced	6.87E-04	1.25	Yes	
64859	OBFC2A	CDK8-induced	6.91E-04	1.84		Yes
92086	GGTLA4	CDK8-induced	6.94E-04	1.19		
27292	HSA9761	CDK8-induced	6.96E-04	1.31		Yes
84246	MED10	CDK8-induced	7.04E-04	1.12		
55540	IL17RB	CDK8-induced	7.09E-04	2.08		
5982	RFC2	CDK8-induced	7.10E-04	1.31		
10056	FARSLB	CDK8-induced	7.15E-04	1.14		Yes
2553	GABPB2	CDK8-induced	7.17E-04	1.46		
3265	HRAS	CDK8-induced	7.20E-04	1.17		
348825	TPRXL	CDK8-induced	7.21E-04	1.33		
26148	C10orf12	CDK8-induced	7.32E-04	1.39		
92703	C1orf37	CDK8-induced	7.37E-04	1.17		
55758	RCOR3	CDK8-induced	7.46E-04	1.19		
8602	C4orf9	CDK8-induced	7.48E-04	1.38		Yes
51491	HSPC111	CDK8-induced	7.48E-04	1.40		Yes
79598	LRRIQ2	CDK8-induced	7.53E-04	1.57		
51659	GINS2	CDK8-induced	7.62E-04	1.83		
11007	CCDC85B	CDK8-induced	7.66E-04	1.37		Yes
9833	MELK	CDK8-induced	7.71E-04	1.29	Yes	
29841	GRHL1	CDK8-induced	7.72E-04	1.32		
83461	CDCA3	CDK8-induced	7.73E-04	1.32	Yes	Yes
6187	RPS2	CDK8-induced	7.78E-04	1.14		Yes
9694	KIAA0103	CDK8-induced	8.00E-04	1.27		
8360	HIST1H4D	CDK8-induced	8.00E-04	1.86		
3714	JAG2	CDK8-induced	8.02E-04	1.67		Yes
2802	GOLGA3	CDK8-induced	8.02E-04	1.52		
51122	COMMD2	CDK8-induced	8.10E-04	1.39		
10592	SMC2	CDK8-induced	8.12E-04	1.40	Yes	
203068	TUBB	CDK8-induced	8.15E-04	1.25		
29089	UBE2T	CDK8-induced	8.17E-04	1.14	Yes	Yes
2888	GRB14	CDK8-induced	8.20E-04	1.42		
54499	TMCO1	CDK8-induced	8.23E-04	1.10		Yes
79135	FAM121B	CDK8-induced	8.24E-04	1.32		
317786	C14orf62	CDK8-induced	8.24E-04	1.35		
5001	ORC5L	CDK8-induced	8.24E-04	1.23		Yes
23310	hCAP-D3	CDK8-induced	8.25E-04	1.46		

476	ATP1A1	CDK8-induced	8.27E-04	1.22		
5813	PURA	CDK8-induced	8.29E-04	1.35		
51072	C2orf4	CDK8-induced	8.35E-04	1.17		
7982	ST7	CDK8-induced	8.43E-04	1.31		
1039	CDR2	CDK8-induced	8.44E-04	1.22	Yes	
23519	ANP32D	CDK8-induced	8.49E-04	1.73		
10915	TCERG1	CDK8-induced	8.56E-04	1.32		Yes
23683	PRKD3	CDK8-induced	8.61E-04	1.52		
3835	KIF22	CDK8-induced	8.64E-04	1.13	Yes	Yes
54822	TRPM7	CDK8-induced	8.68E-04	1.19		
11104	KATNA1	CDK8-induced	8.75E-04	1.40		
206426	MGC26597	CDK8-induced	8.75E-04	1.32		
374393	FAM111B	CDK8-induced	8.77E-04	1.71		
51538	ZCCHC17	CDK8-induced	8.77E-04	1.46		
644063	LOC644063	CDK8-induced	8.77E-04	1.28		
57695	USP37	CDK8-induced	8.79E-04	1.47		
58492	ZNF77	CDK8-induced	8.82E-04	1.54		
8050	PDHX	CDK8-induced	8.94E-04	1.28		
25896	INTS7	CDK8-induced	9.01E-04	1.23		Yes
339287	LOC339287	CDK8-induced	9.14E-04	1.33		
6574	SLC20A1	CDK8-induced	9.14E-04	1.38		Yes
51132	RNF12	CDK8-induced	9.17E-04	1.29		
11080	DNAJB4	CDK8-induced	9.22E-04	1.21		Yes
388272	LOC388272	CDK8-induced	9.30E-04	1.26		
6696	SPP1	CDK8-induced	9.31E-04	1.88		
6272	SORT1	CDK8-induced	9.37E-04	1.15		
26470	SEZ6L2	CDK8-repressed	2.47E-10	2.10		
8337	HIST2H2AA3	CDK8-repressed	4.88E-10	1.91		
332	BIRC5	CDK8-repressed	6.31E-10	1.75	Yes	
55194	C1orf78	CDK8-repressed	4.43E-09	2.31		
51571	FAM49B	CDK8-repressed	1.28E-08	2.22		
9948	WDR1	CDK8-repressed	1.79E-08	1.88		
1398	CRK	CDK8-repressed	2.76E-08	1.73		
55624	POMGNT1	CDK8-repressed	3.39E-08	1.68		
29058	C20orf30	CDK8-repressed	3.74E-08	1.29		Yes
3133	HLA-E	CDK8-repressed	4.48E-08	1.39		
65990	C16orf24	CDK8-repressed	4.61E-08	1.62		
93487	C14orf32	CDK8-repressed	5.07E-08	1.46		
400	ARL1	CDK8-repressed	5.29E-08	1.76	Yes	
56925	LXN	CDK8-repressed	5.69E-08	1.56		
219902	TMEM136	CDK8-repressed	5.79E-08	4.53		
4128	MAOA	CDK8-repressed	6.05E-08	1.73	Yes	Yes
10519	CIB1	CDK8-repressed	6.60E-08	1.23		
2817	GPC1	CDK8-repressed	7.31E-08	1.92		
1020	CDK5	CDK8-repressed	7.46E-08	1.38		
373156	GSTK1	CDK8-repressed	7.70E-08	1.61		
8631	SCAP1	CDK8-repressed	8.10E-08	1.62		
2073	ERCC5	CDK8-repressed	8.28E-08	2.27		
6416	MAP2K4	CDK8-repressed	9.95E-08	2.33		
474343	SPIN-2	CDK8-repressed	1.04E-07	1.58		
2274	FHL2	CDK8-repressed	1.04E-07	1.73		
6924	TCEB3	CDK8-repressed	1.05E-07	1.58		
10099	TSPAN3	CDK8-repressed	1.11E-07	1.38		
149345	TMEM58	CDK8-repressed	1.13E-07	1.72		
79109	MAPKAP1	CDK8-repressed	1.15E-07	2.01		
124220	LOC124220	CDK8-repressed	1.30E-07	1.99		
360	AQP3	CDK8-repressed	1.33E-07	3.61		
55268	ECHDC2	CDK8-repressed	1.38E-07	2.02		

56950	SMYD2	CDK8-repressed	1.45E-07	1.40		
10581	IFITM2	CDK8-repressed	1.46E-07	1.45		Yes
122970	ACOT4	CDK8-repressed	1.55E-07	2.05		
51282	SCAND1	CDK8-repressed	1.59E-07	1.51		
217	ALDH2	CDK8-repressed	1.75E-07	1.17		
738	C11orf2	CDK8-repressed	1.81E-07	1.54		
9804	TOMM20	CDK8-repressed	1.91E-07	1.63		Yes
51222	ZNF219	CDK8-repressed	2.07E-07	1.42		
130576	OC130576/LYPD6	CDK8-repressed	2.17E-07	6.13		
1793	DOCK1	CDK8-repressed	2.44E-07	1.62		Yes
83982	FAM14A	CDK8-repressed	2.54E-07	1.89		
5880	RAC2	CDK8-repressed	2.88E-07	1.47		
84727	SPSB2	CDK8-repressed	2.95E-07	1.69		
51015	ISOC1	CDK8-repressed	2.97E-07	1.77		
59277	NTN4	CDK8-repressed	3.01E-07	1.98		
54974	ICF45	CDK8-repressed	3.09E-07	1.32		
65056	GPBP1	CDK8-repressed	3.27E-07	1.35		
84627	ZNF469	CDK8-repressed	3.48E-07	2.64		
3108	HLA-DMA	CDK8-repressed	3.89E-07	1.95		
131601	GPR175	CDK8-repressed	4.10E-07	1.18		
8644	AKR1C3	CDK8-repressed	4.13E-07	1.65		
84514	LGP1	CDK8-repressed	4.39E-07	2.08		
8099	CDK2AP1	CDK8-repressed	4.53E-07	1.70	Yes	
113655	MFSD3	CDK8-repressed	4.78E-07	1.63		
1307	COL16A1	CDK8-repressed	4.95E-07	1.59		
55062	WIPI1	CDK8-repressed	5.00E-07	1.40		
84248	FYTTD1	CDK8-repressed	5.11E-07	1.59		
64219	PJA1	CDK8-repressed	5.80E-07	1.51		
26118	WSB1	CDK8-repressed	5.87E-07	2.22		
57176	VARSL	CDK8-repressed	5.94E-07	1.61		
285613	C5orf16	CDK8-repressed	6.46E-07	1.49		Yes
63027	C6orf85	CDK8-repressed	6.83E-07	1.26		
81621	KAZALD1	CDK8-repressed	7.18E-07	2.47		
8738	CRADD	CDK8-repressed	7.24E-07	1.71		
55625	ZDHHC7	CDK8-repressed	7.39E-07	1.33		
29982	NRBF2	CDK8-repressed	7.61E-07	2.23		
57491	AHRR	CDK8-repressed	7.72E-07	2.05		
8815	BANF1	CDK8-repressed	8.34E-07	2.05	Yes	Yes
2629	GBA	CDK8-repressed	8.35E-07	2.17		
5281	PIGF	CDK8-repressed	8.41E-07	1.58		
84000	TMPRSS13	CDK8-repressed	8.86E-07	1.63		
441964	LOC441964	CDK8-repressed	9.09E-07	1.63		
27352	RUTBC3	CDK8-repressed	9.18E-07	1.65		
400684	LOC400684	CDK8-repressed	9.49E-07	2.37		
27258	LSM3	CDK8-repressed	9.98E-07	1.29	Yes	
57521	KIAA1303	CDK8-repressed	1.04E-06	1.62		Yes
7162	TPBG	CDK8-repressed	1.08E-06	1.57		
79639	TMEM53	CDK8-repressed	1.11E-06	1.38		
25898	RCHY1	CDK8-repressed	1.17E-06	1.53		
113452	TMEM54	CDK8-repressed	1.24E-06	1.39		
84878	ZNF499	CDK8-repressed	1.27E-06	1.45		
4111	MAGEA12	CDK8-repressed	1.32E-06	1.25		
254170	FBXO33	CDK8-repressed	1.35E-06	1.36		
92305	TMEM129	CDK8-repressed	1.35E-06	1.98		Yes
91523	FAM113B	CDK8-repressed	1.36E-06	1.41		
85455	DISP2	CDK8-repressed	1.36E-06	2.39		
10524	HTATIP	CDK8-repressed	1.43E-06	1.55		Yes
9454	HOMER3	CDK8-repressed	1.44E-06	2.22		
51646	YPEL5	CDK8-repressed	1.47E-06	1.45		

9403	15-Sep	CDK8-repressed	1.48E-06	1.13		Yes
203054	ADCK5	CDK8-repressed	1.49E-06	1.51		
29984	RHOD	CDK8-repressed	1.51E-06	1.63		
9518	GDF15	CDK8-repressed	1.68E-06	2.15		
5358	PLS3	CDK8-repressed	1.70E-06	1.75		
79102	RNF26	CDK8-repressed	1.77E-06	1.22	Yes	
2067	ERCC1	CDK8-repressed	1.77E-06	1.47		Yes
79258	MMEL1	CDK8-repressed	1.80E-06	2.38		
5696	PSMB8	CDK8-repressed	1.82E-06	1.20		
3106	HLA-B	CDK8-repressed	1.85E-06	1.38		
5863	RGL2	CDK8-repressed	1.92E-06	1.48		
6888	TALDO1	CDK8-repressed	1.95E-06	1.37		Yes
23231	KIAA0746	CDK8-repressed	2.02E-06	1.38		
6817	SULT1A1	CDK8-repressed	2.08E-06	1.40		
64780	MICAL1	CDK8-repressed	2.12E-06	1.71		
644	BLVRA	CDK8-repressed	2.14E-06	2.48		Yes
3020	H3F3A	CDK8-repressed	2.15E-06	1.97		
284185	C17orf55	CDK8-repressed	2.16E-06	1.18		
60682	SMAP1	CDK8-repressed	2.16E-06	1.71		
6609	SMPD1	CDK8-repressed	2.21E-06	2.71		
113263	GLCCI1	CDK8-repressed	2.36E-06	1.65		
1509	CTSD	CDK8-repressed	2.40E-06	1.53		Yes
157567	ANKRD46	CDK8-repressed	2.60E-06	1.90		
114790	STK11IP	CDK8-repressed	2.63E-06	1.54		
5682	PSMA1	CDK8-repressed	2.71E-06	1.19	Yes	
9205	ZMYM5	CDK8-repressed	2.71E-06	1.34		
65983	GRAMD3	CDK8-repressed	2.76E-06	2.18		
6799	SULT1A2	CDK8-repressed	2.83E-06	1.37		
51035	LOC51035	CDK8-repressed	2.90E-06	1.15		
55206	SBNO1	CDK8-repressed	2.95E-06	1.31		
23564	DDAH2	CDK8-repressed	2.99E-06	1.94		
7423	VEGFB	CDK8-repressed	3.10E-06	1.50		
132299	OCIAD2	CDK8-repressed	3.25E-06	1.46		
54938	SARS2	CDK8-repressed	3.27E-06	1.27		Yes
64847	SPATA20	CDK8-repressed	3.34E-06	1.45		
896	CCND3	CDK8-repressed	3.35E-06	2.00		
2752	GLUL	CDK8-repressed	3.44E-06	2.01		Yes
9267	PSCD1	CDK8-repressed	3.47E-06	1.46		
93082	LINCR	CDK8-repressed	3.62E-06	5.20		
6734	SRPR	CDK8-repressed	3.64E-06	2.06		Yes
5570	PKIB	CDK8-repressed	3.73E-06	2.30		
2819	GPD1	CDK8-repressed	3.78E-06	1.27		
150737	TTC30B	CDK8-repressed	3.92E-06	2.19		
56981	PRDM11	CDK8-repressed	3.99E-06	1.31		
221908	MGC22793	CDK8-repressed	4.23E-06	1.59		Yes
11244	ZHX1	CDK8-repressed	4.34E-06	1.38		
3134	HLA-F	CDK8-repressed	4.45E-06	1.40		
8537	BCAS1	CDK8-repressed	4.49E-06	1.45		
55699	IARS2	CDK8-repressed	4.83E-06	1.40		
10058	ABCB6	CDK8-repressed	5.05E-06	1.54	Yes	Yes
29970	SCHIP1	CDK8-repressed	5.08E-06	2.37		
257054	D2HGDH	CDK8-repressed	5.47E-06	1.28		
57701	KIAA1602	CDK8-repressed	5.82E-06	1.22		Yes
5002	SLC22A18	CDK8-repressed	5.90E-06	1.47		
51329	ARL6IP4	CDK8-repressed	5.96E-06	1.54		
23271	CAMSAP1L1	CDK8-repressed	6.01E-06	1.67		
90835	LOC90835	CDK8-repressed	6.19E-06	1.56		
79778	MICAL-L2	CDK8-repressed	6.23E-06	1.29		
81669	CCNL2	CDK8-repressed	6.24E-06	1.35		Yes

30815	ST6GALNAC6	CDK8-repressed	6.34E-06	1.31		
57120	GOPC	CDK8-repressed	6.63E-06	1.34		
23484	LEPROTL1	CDK8-repressed	6.66E-06	1.58		Yes
51079	NDUFA13	CDK8-repressed	6.72E-06	1.30		Yes
8991	SELENBP1	CDK8-repressed	6.74E-06	1.86		
784	CACNB3	CDK8-repressed	6.89E-06	1.45		
8718	TNFRSF25	CDK8-repressed	7.08E-06	1.51		
55902	ACSS2	CDK8-repressed	7.18E-06	2.16		
79176	FBXL15	CDK8-repressed	7.20E-06	1.54		
79086	C19orf42	CDK8-repressed	7.25E-06	1.32		
3156	HMGCR	CDK8-repressed	7.36E-06	1.33		
55231	CCDC87	CDK8-repressed	7.57E-06	3.11		Yes
116540	MRPL53	CDK8-repressed	7.60E-06	1.21		
55565	LOC55565	CDK8-repressed	7.67E-06	1.29		
6164	RPL34	CDK8-repressed	7.81E-06	1.24		Yes
222699	LOC222699	CDK8-repressed	7.95E-06	1.28		
79095	C9orf16	CDK8-repressed	8.01E-06	1.31		
9961	MVP	CDK8-repressed	8.11E-06	1.45		
90843	TCEAL8	CDK8-repressed	8.27E-06	1.23		
4052	LTBP1	CDK8-repressed	8.49E-06	2.38		
90780	PYGO2	CDK8-repressed	8.63E-06	1.49		
119032	C10orf32	CDK8-repressed	8.67E-06	1.75		Yes
3091	HIF1A	CDK8-repressed	8.68E-06	1.37		
284346	ZNF575	CDK8-repressed	8.68E-06	1.42		
84078	KBTBD7	CDK8-repressed	8.79E-06	1.73		Yes
11264	PXMP4	CDK8-repressed	8.86E-06	1.46		
5287	PIK3C2B	CDK8-repressed	8.89E-06	1.55		
4718	NDUFC2	CDK8-repressed	9.07E-06	1.56		
9064	MAP3K6	CDK8-repressed	9.15E-06	1.35		Yes
56288	PARD3	CDK8-repressed	9.20E-06	1.53		
128	ADH5	CDK8-repressed	9.33E-06	1.72	Yes	Yes
2064	ERBB2	CDK8-repressed	9.36E-06	1.36		
55520	ELAC1	CDK8-repressed	9.57E-06	1.35		
27345	KCNMB4	CDK8-repressed	9.65E-06	2.14		
25824	PRDX5	CDK8-repressed	9.65E-06	1.42		Yes
90993	CREB3L1	CDK8-repressed	9.79E-06	1.58		
51608	C7orf20	CDK8-repressed	1.00E-05	1.21		
219402	MTIF3	CDK8-repressed	1.01E-05	1.48		
81627	C1orf25	CDK8-repressed	1.09E-05	1.53		Yes
10712	C1orf2	CDK8-repressed	1.11E-05	1.31		
284018	C17orf58	CDK8-repressed	1.12E-05	1.58		
25950	RWDD3	CDK8-repressed	1.17E-05	1.60		
8764	TNFRSF14	CDK8-repressed	1.17E-05	1.30		
23536	ADAT1	CDK8-repressed	1.18E-05	1.40		Yes
54469	ZFAND6	CDK8-repressed	1.18E-05	1.41		
3384	ICAM2	CDK8-repressed	1.20E-05	1.36		
5783	PTPN13	CDK8-repressed	1.21E-05	2.84		
51635	DHRS7	CDK8-repressed	1.22E-05	1.34		
51324	SPG21	CDK8-repressed	1.25E-05	1.72		Yes
23138	N4BP3	CDK8-repressed	1.28E-05	1.60		
3107	HLA-C	CDK8-repressed	1.31E-05	1.38		
92922	CCDC102A	CDK8-repressed	1.32E-05	1.38		
4192	MDK	CDK8-repressed	1.34E-05	1.39		
54843	SYTL2	CDK8-repressed	1.35E-05	2.42		
10481	HOXB13	CDK8-repressed	1.35E-05	1.32		
389432	RP5-875H10.1	CDK8-repressed	1.36E-05	3.15		
26297	SERGEF	CDK8-repressed	1.37E-05	1.40		
23132	RAD54L2	CDK8-repressed	1.40E-05	1.52		
113246	C12orf57	CDK8-repressed	1.42E-05	1.83		

81628	TSC22D4	CDK8-repressed	1.42E-05	1.33		Yes
5645	PRSS2	CDK8-repressed	1.44E-05	1.23		
25897	RNF19	CDK8-repressed	1.47E-05	1.46		
642649	DKFZP779L1068	CDK8-repressed	1.48E-05	1.73		
4938	OAS1	CDK8-repressed	1.50E-05	1.56		
10123	ARL4C	CDK8-repressed	1.50E-05	1.77		
284266	CD33L3	CDK8-repressed	1.50E-05	1.52		
9399	STOML1	CDK8-repressed	1.53E-05	1.30		
348093	RBPMS2	CDK8-repressed	1.53E-05	4.98		
10567	RABAC1	CDK8-repressed	1.54E-05	1.47		
57666	KIAA1545	CDK8-repressed	1.57E-05	1.34		
441320	LOC441320	CDK8-repressed	1.61E-05	1.48		
643155	DKFZP686E2158	CDK8-repressed	1.61E-05	1.32		
64787	EPS8L2	CDK8-repressed	1.62E-05	1.24		
54620	FBXL19	CDK8-repressed	1.62E-05	1.18		Yes
9158	FIBP	CDK8-repressed	1.66E-05	1.28		Yes
50619	DEF6	CDK8-repressed	1.67E-05	1.46		Yes
9552	SPAG7	CDK8-repressed	1.68E-05	1.42	Yes	
3136	HLA-H	CDK8-repressed	1.70E-05	1.42		
55611	OTUB1	CDK8-repressed	1.71E-05	1.28		Yes
4521	NUDT1	CDK8-repressed	1.72E-05	1.23	Yes	
5193	PEX12	CDK8-repressed	1.72E-05	1.74		Yes
203328	SUSD3	CDK8-repressed	1.74E-05	1.45		
23673	STX12	CDK8-repressed	1.75E-05	1.90		Yes
5777	PTPN6	CDK8-repressed	1.75E-05	1.36		
8350	HIST1H3A	CDK8-repressed	1.77E-05	1.85		
4105	MAGEA6	CDK8-repressed	1.83E-05	1.21		
400451	LOC400451	CDK8-repressed	1.84E-05	1.72		
51596	CUTA	CDK8-repressed	1.85E-05	1.44		
22920	KIFAP3	CDK8-repressed	1.88E-05	1.14		
7844	RNF103	CDK8-repressed	1.91E-05	1.43		
221749	C6orf145	CDK8-repressed	1.94E-05	1.35		
404217	CTXN1	CDK8-repressed	1.95E-05	1.26		
114926	C8orf40	CDK8-repressed	1.95E-05	1.32		
79154	MGC4172	CDK8-repressed	1.98E-05	1.31		Yes
8742	TNFSF12	CDK8-repressed	2.03E-05	2.07		
29883	CNOT7	CDK8-repressed	2.05E-05	1.68		
7866	IFRD2	CDK8-repressed	2.05E-05	1.33	Yes	Yes
257236	CCDC96	CDK8-repressed	2.10E-05	1.81		
200185	KRTCAP2	CDK8-repressed	2.12E-05	1.13		Yes
51093	C1orf66	CDK8-repressed	2.15E-05	1.41		
51291	GMIP	CDK8-repressed	2.16E-05	1.71		
115399	LRRC56	CDK8-repressed	2.17E-05	1.52		
151146	LOC151146	CDK8-repressed	2.18E-05	1.29		
83480	PUS3	CDK8-repressed	2.22E-05	1.13		Yes
55160	ARHGEF10L	CDK8-repressed	2.24E-05	1.48		
9545	RAB3D	CDK8-repressed	2.31E-05	1.54		Yes
79792	GSDMDC1	CDK8-repressed	2.34E-05	1.48		
64420	SUSD1	CDK8-repressed	2.35E-05	2.23		
5501	PPP1CC	CDK8-repressed	2.38E-05	1.18		
161882	ZFPM1	CDK8-repressed	2.39E-05	1.24		
196383	MGC7036	CDK8-repressed	2.39E-05	1.91		Yes
64839	FBXL17	CDK8-repressed	2.41E-05	1.87		
55898	UNC45A	CDK8-repressed	2.43E-05	1.22		
84269	CHCHD5	CDK8-repressed	2.44E-05	1.16		Yes
2887	GRB10	CDK8-repressed	2.47E-05	1.56		
170463	SSBP4	CDK8-repressed	2.59E-05	1.39		Yes
8563	THOC5	CDK8-repressed	2.59E-05	1.39		
90864	SPSB3	CDK8-repressed	2.60E-05	1.25		Yes

4494	MT1F	CDK8-repressed	2.63E-05	2.97		
64771	C6orf106	CDK8-repressed	2.71E-05	1.11		
64946	CENPH	CDK8-repressed	2.83E-05	1.50	Yes	
26017	FAM32A	CDK8-repressed	2.88E-05	1.55		
5305	PIP5K2A	CDK8-repressed	3.01E-05	1.83		
1774	DNASE1L1	CDK8-repressed	3.05E-05	1.17		
55317	C20orf29	CDK8-repressed	3.09E-05	1.52		
3105	HLA-A	CDK8-repressed	3.13E-05	1.41		
79767	ELMO3	CDK8-repressed	3.19E-05	1.35		Yes
54344	DPM3	CDK8-repressed	3.19E-05	1.21		
27092	CACNG4	CDK8-repressed	3.20E-05	1.21		
129303	TMEM150	CDK8-repressed	3.22E-05	1.47		
2302	FOXJ1	CDK8-repressed	3.23E-05	1.51		
78999	LRFN4	CDK8-repressed	3.23E-05	1.43		
445329	SULT1A4	CDK8-repressed	3.25E-05	1.27		
285313	IGSF10	CDK8-repressed	3.32E-05	3.81		
2535	FZD2	CDK8-repressed	3.38E-05	1.52	Yes	Yes
28956	MAPBPIP	CDK8-repressed	3.38E-05	1.25		Yes
79874	RABEP2	CDK8-repressed	3.44E-05	1.38		
27243	CHMP2A	CDK8-repressed	3.48E-05	1.44		
3109	HLA-DMB	CDK8-repressed	3.50E-05	2.29		
222229	DKFZp434K1815	CDK8-repressed	3.50E-05	1.22	Yes	
57410	SCYL1	CDK8-repressed	3.53E-05	1.23		
9891	NUAK1	CDK8-repressed	3.57E-05	1.67		
7263	TST	CDK8-repressed	3.57E-05	1.42		Yes
5754	PTK7	CDK8-repressed	3.58E-05	1.57		
51264	MRPL27	CDK8-repressed	3.61E-05	1.31	Yes	Yes
58506	SR-A1	CDK8-repressed	3.67E-05	1.43		
3006	HIST1H1C	CDK8-repressed	3.67E-05	1.31	Yes	
826	CAPNS1	CDK8-repressed	3.75E-05	1.21		Yes
22931	RAB18	CDK8-repressed	3.80E-05	1.22		Yes
57210	SLC45A4	CDK8-repressed	3.81E-05	3.19		
55332	FLJ11259	CDK8-repressed	3.85E-05	2.60		
51287	CHCHD8	CDK8-repressed	3.87E-05	1.16		Yes
29844	TFPT	CDK8-repressed	3.87E-05	1.17		Yes
90	ACVR1	CDK8-repressed	3.91E-05	1.75		
50855	PARD6A	CDK8-repressed	3.97E-05	1.27		
118471	PRAP1	CDK8-repressed	3.97E-05	1.48		
9537	TP53I11	CDK8-repressed	3.99E-05	2.09		
26509	FER1L3	CDK8-repressed	4.00E-05	1.38		
57698	KIAA1598	CDK8-repressed	4.04E-05	2.07		
55717	BRWD2	CDK8-repressed	4.07E-05	1.26		
113402	SFT2D1	CDK8-repressed	4.09E-05	1.09		
79027	ZNF655	CDK8-repressed	4.09E-05	1.69		Yes
56674	TMEM9B	CDK8-repressed	4.24E-05	1.32		
57142	RTN4	CDK8-repressed	4.25E-05	1.38		
5530	PPP3CA	CDK8-repressed	4.26E-05	1.50		
140465	MYL6B	CDK8-repressed	4.35E-05	1.44		
374907	B3GNT8	CDK8-repressed	4.46E-05	2.19		
85378	TUBGCP6	CDK8-repressed	4.54E-05	1.38		
55150	FLJ10490	CDK8-repressed	4.64E-05	1.16		
23396	PIP5K1C	CDK8-repressed	4.64E-05	1.19		
79676	OGFOD2	CDK8-repressed	4.69E-05	1.54		
83719	YPEL3	CDK8-repressed	4.73E-05	1.79		
8460	TPST1	CDK8-repressed	4.79E-05	1.53		
6923	TCEB2	CDK8-repressed	4.85E-05	1.18		
84236	RHBDD1	CDK8-repressed	4.90E-05	1.36		
3013	HIST1H2AD	CDK8-repressed	4.93E-05	1.49		
1788	DNMT3A	CDK8-repressed	4.95E-05	2.07		

4232	MEST	CDK8-repressed	5.00E-05	1.87	Yes	Yes
254359	ZDHHC24	CDK8-repressed	5.01E-05	1.54		
257364	SH3PX3	CDK8-repressed	5.02E-05	1.65		
23370	ARHGEF18	CDK8-repressed	5.03E-05	1.51		
57720	GPR107	CDK8-repressed	5.05E-05	1.68		
84286	MGC4618	CDK8-repressed	5.06E-05	1.14		
197258	FUK	CDK8-repressed	5.07E-05	1.35		
54785	C17orf59	CDK8-repressed	5.14E-05	1.36		Yes
163033	ZNF579	CDK8-repressed	5.26E-05	1.24		
57623	ZNF406	CDK8-repressed	5.38E-05	1.17		
81533	ITFG1	CDK8-repressed	5.46E-05	1.27		
23318	ZCCHC11	CDK8-repressed	5.48E-05	1.38		
2589	GALNT1	CDK8-repressed	5.48E-05	1.48		
25807	RHBDD3	CDK8-repressed	5.51E-05	1.27		Yes
5270	SERPINE2	CDK8-repressed	5.56E-05	1.30	Yes	
7005	TEAD3	CDK8-repressed	5.67E-05	1.11		
9032	TM4SF5	CDK8-repressed	5.67E-05	1.37		
55763	EXOC1	CDK8-repressed	5.69E-05	1.37		
11258	DCTN3	CDK8-repressed	5.71E-05	1.12		
51586	PCQAP	CDK8-repressed	5.75E-05	1.27		
9159	PCSK7	CDK8-repressed	5.81E-05	1.64		
6253	RTN2	CDK8-repressed	5.86E-05	1.36		
55653	BCAS4	CDK8-repressed	5.86E-05	1.29		
11236	RNF139	CDK8-repressed	5.90E-05	1.31		Yes
9147	SDCCAG1	CDK8-repressed	6.00E-05	1.27		
6499	SKIV2L	CDK8-repressed	6.03E-05	1.20		
53938	PPIL3	CDK8-repressed	6.14E-05	1.23		Yes
192670	EIF2C4	CDK8-repressed	6.15E-05	1.71		
57192	MCOLN1	CDK8-repressed	6.16E-05	1.42		
26086	GPSM1	CDK8-repressed	6.16E-05	1.50		
84034	EMILIN2	CDK8-repressed	6.18E-05	2.64		
55529	TMEM55A	CDK8-repressed	6.23E-05	1.26		
4580	MTX1	CDK8-repressed	6.25E-05	1.34		
55629	PNRC2	CDK8-repressed	6.28E-05	1.35		
5447	POR	CDK8-repressed	6.28E-05	1.19		
440335	LOC440335	CDK8-repressed	6.31E-05	1.26		
80301	PLEKHQ1	CDK8-repressed	6.37E-05	1.37		
55640	C14orf58	CDK8-repressed	6.54E-05	3.10		
4507	MTAP	CDK8-repressed	6.58E-05	1.59		
51109	RDH11	CDK8-repressed	6.73E-05	1.18		Yes
648245	LOC648245	CDK8-repressed	6.74E-05	1.18		
4217	MAP3K5	CDK8-repressed	6.86E-05	1.81		
54765	TRIM44	CDK8-repressed	7.05E-05	1.35		
93949	CXorf10	CDK8-repressed	7.16E-05	1.36		
84952	CGNL1	CDK8-repressed	7.21E-05	2.65		
828	CAPS	CDK8-repressed	7.34E-05	2.40		
84717	HDGF2	CDK8-repressed	7.38E-05	1.33		
26039	SS18L1	CDK8-repressed	7.45E-05	1.25		Yes
9605	C16orf7	CDK8-repressed	7.51E-05	1.36		
2633	GBP1	CDK8-repressed	7.56E-05	2.24		
148223	C19orf25	CDK8-repressed	7.57E-05	1.16		Yes
5828	PXMP3	CDK8-repressed	7.61E-05	1.27		
9049	AIP	CDK8-repressed	7.67E-05	1.36		
53349	ZFYVE1	CDK8-repressed	7.75E-05	1.56		
155061	ZNF746	CDK8-repressed	7.85E-05	1.09		
6908	TBP	CDK8-repressed	7.87E-05	1.11		Yes
84958	SYTL1	CDK8-repressed	7.87E-05	1.89		
25894	PLEKHG4	CDK8-repressed	7.91E-05	1.86		
5600	MAPK11	CDK8-repressed	8.03E-05	1.39		

548593	GIYD1	CDK8-repressed	8.05E-05	1.36		
255743	NPNT	CDK8-repressed	8.05E-05	1.49		
130535	KCTD18	CDK8-repressed	8.40E-05	2.74		
114908	TMEM123	CDK8-repressed	8.40E-05	1.37		
23158	TBC1D9	CDK8-repressed	8.58E-05	1.43		
284361	LOC284361	CDK8-repressed	8.61E-05	1.32		
10591	C6orf108	CDK8-repressed	8.66E-05	1.78		
9185	REPS2	CDK8-repressed	8.74E-05	1.26		
79991	OBFC1	CDK8-repressed	8.80E-05	1.28		
1652	DDT	CDK8-repressed	8.88E-05	1.57		
79717	PPCS	CDK8-repressed	9.01E-05	1.27		Yes
51430	C1orf9	CDK8-repressed	9.16E-05	1.16		
54461	FBXW5	CDK8-repressed	9.21E-05	1.36		
837	CASP4	CDK8-repressed	9.34E-05	1.28		
10445	MCRS1	CDK8-repressed	9.43E-05	1.53		
5607	MAP2K5	CDK8-repressed	9.48E-05	1.91		Yes
4157	MC1R	CDK8-repressed	9.48E-05	1.69		
5652	PRSS8	CDK8-repressed	9.58E-05	1.47		Yes
391356	LOC391356	CDK8-repressed	9.59E-05	1.28		
80736	SLC44A4	CDK8-repressed	9.63E-05	1.20		Yes
5873	RAB27A	CDK8-repressed	9.68E-05	1.69		Yes
114904	C1QTNF6	CDK8-repressed	9.83E-05	2.17		
63906	GPATC3	CDK8-repressed	1.00E-04	1.71		
5380	PMS2L2	CDK8-repressed	1.01E-04	1.41		
10025	THRAP5	CDK8-repressed	1.01E-04	1.24		
387733	IFITM5	CDK8-repressed	1.02E-04	1.25		Yes
836	CASP3	CDK8-repressed	1.04E-04	1.19		
6455	SH3GL1	CDK8-repressed	1.04E-04	1.13		
8567	MADD	CDK8-repressed	1.05E-04	1.38		
286053	NSMCE2	CDK8-repressed	1.06E-04	1.33		
56204	KIAA1370	CDK8-repressed	1.06E-04	1.46		
8086	AAAS	CDK8-repressed	1.08E-04	1.18	Yes	Yes
79903	FLJ14154	CDK8-repressed	1.08E-04	1.42		
10106	CTDSP2	CDK8-repressed	1.09E-04	1.30		
26000	TBC1D10B	CDK8-repressed	1.09E-04	1.15		
79415	C17orf62	CDK8-repressed	1.09E-04	1.33		
54910	SEMA4C	CDK8-repressed	1.10E-04	1.65		
84292	MORG1	CDK8-repressed	1.11E-04	1.58		Yes
29082	CHMP4A	CDK8-repressed	1.12E-04	1.15		
116541	MRPL54	CDK8-repressed	1.13E-04	1.37	Yes	Yes
11284	PNKP	CDK8-repressed	1.14E-04	1.17		Yes
192286	HIGD2A	CDK8-repressed	1.14E-04	1.12		Yes
92017	LOC92017	CDK8-repressed	1.15E-04	1.47		
7108	TM7SF2	CDK8-repressed	1.16E-04	1.36		
112495	C6orf51	CDK8-repressed	1.17E-04	1.31		Yes
51504	HSPC152	CDK8-repressed	1.17E-04	1.60		Yes
8353	HIST1H3E	CDK8-repressed	1.19E-04	1.64		
26995	TRUB2	CDK8-repressed	1.21E-04	1.53		Yes
387921	RP11-50D16.3	CDK8-repressed	1.22E-04	1.26		Yes
8356	HIST1H3J	CDK8-repressed	1.22E-04	1.38		
29886	SNX8	CDK8-repressed	1.23E-04	1.29		Yes
80006	FLJ13611	CDK8-repressed	1.23E-04	1.39		Yes
10213	PSMD14	CDK8-repressed	1.24E-04	1.16	Yes	
4130	MAP1A	CDK8-repressed	1.26E-04	1.35		
51614	ERGIC3	CDK8-repressed	1.26E-04	1.15		
54432	YIPF1	CDK8-repressed	1.27E-04	1.44		
9601	PDIA4	CDK8-repressed	1.29E-04	1.89	Yes	Yes
3566	IL4R	CDK8-repressed	1.31E-04	1.20		
10610	ST6GALNAC2	CDK8-repressed	1.32E-04	1.56		

8720	MBTPS1	CDK8-repressed	1.34E-04	1.82		Yes
55049	FLJ20850	CDK8-repressed	1.36E-04	1.45		Yes
266740	MAGEA2B	CDK8-repressed	1.37E-04	1.34		
130074	LOC130074	CDK8-repressed	1.37E-04	1.40		
51063	FAM26B	CDK8-repressed	1.38E-04	1.81		
392	ARHGAP1	CDK8-repressed	1.39E-04	1.21		Yes
514	ATP5E	CDK8-repressed	1.39E-04	1.11	Yes	Yes
79671	NOD9	CDK8-repressed	1.40E-04	1.97		
81573	ANKRD13C	CDK8-repressed	1.42E-04	1.50		
489	ATP2A3	CDK8-repressed	1.42E-04	2.20		
6692	SPINT1	CDK8-repressed	1.42E-04	1.24		
90522	YIF1B	CDK8-repressed	1.43E-04	1.20		Yes
8694	DGAT1	CDK8-repressed	1.43E-04	1.26		
57418	WDR18	CDK8-repressed	1.45E-04	1.16		Yes
10908	PNPLA6	CDK8-repressed	1.45E-04	1.33		
4695	NDUFA2	CDK8-repressed	1.46E-04	1.23		
60312	AFAP	CDK8-repressed	1.47E-04	1.92		Yes
130814	PQLC3	CDK8-repressed	1.49E-04	1.74		
9655	SOCS5	CDK8-repressed	1.49E-04	1.57		
2815	GP9	CDK8-repressed	1.50E-04	1.16		
84304	NUDT22	CDK8-repressed	1.51E-04	1.58		
1870	E2F2	CDK8-repressed	1.51E-04	1.23	Yes	
6398	SECTM1	CDK8-repressed	1.52E-04	1.33		
5794	PTPRH	CDK8-repressed	1.54E-04	1.21		
7091	TLE4	CDK8-repressed	1.57E-04	1.97	Yes	
435	ASL	CDK8-repressed	1.57E-04	1.41		
29100	HSPC171	CDK8-repressed	1.57E-04	1.20		Yes
83707	TRPT1	CDK8-repressed	1.59E-04	1.24		
80024	SLC24A6	CDK8-repressed	1.59E-04	1.34		
326624	RAB37	CDK8-repressed	1.59E-04	2.95		
6659	SOX4	CDK8-repressed	1.60E-04	1.73		
130355	LOC130355	CDK8-repressed	1.63E-04	1.32		
9604	RNF14	CDK8-repressed	1.63E-04	1.35		
345757	TMEM157	CDK8-repressed	1.65E-04	1.49		
84525	HOP	CDK8-repressed	1.65E-04	2.66		
5585	PKN1	CDK8-repressed	1.65E-04	1.24		
9653	HS2ST1	CDK8-repressed	1.66E-04	1.23		Yes
240	ALOX5	CDK8-repressed	1.67E-04	1.66		
378	ARF4	CDK8-repressed	1.69E-04	1.26	Yes	
339983	FLJ37478	CDK8-repressed	1.71E-04	5.66		
9445	ITM2B	CDK8-repressed	1.71E-04	1.36		
1465	CSRP1	CDK8-repressed	1.72E-04	1.18		
11201	POLI	CDK8-repressed	1.72E-04	2.03		Yes
9513	FXR2	CDK8-repressed	1.74E-04	1.38		
10094	ARPC3	CDK8-repressed	1.74E-04	1.28		Yes
421	ARVCF	CDK8-repressed	1.75E-04	1.59		
94121	SYTL4	CDK8-repressed	1.75E-04	1.37		
5641	LGMN	CDK8-repressed	1.76E-04	1.29		
10769	PLK2	CDK8-repressed	1.76E-04	1.23		
118487	CHCHD1	CDK8-repressed	1.78E-04	1.17		Yes
57148	KIAA1219	CDK8-repressed	1.80E-04	1.32		
1201	CLN3	CDK8-repressed	1.81E-04	1.14		Yes
389058	SP5	CDK8-repressed	1.83E-04	1.99		
23263	MCF2L	CDK8-repressed	1.84E-04	1.49		Yes
256281	NUDT14	CDK8-repressed	1.87E-04	1.50		
114782	KIAA1881	CDK8-repressed	1.87E-04	2.41		
5693	PSMB5	CDK8-repressed	1.89E-04	1.30	Yes	
6913	TBX15	CDK8-repressed	1.90E-04	3.09		
11334	TUSC2	CDK8-repressed	1.90E-04	1.12		

1801	DPH1	CDK8-repressed	1.91E-04	1.11		Yes
7125	TNNC2	CDK8-repressed	1.95E-04	2.50		
63935	C20orf67	CDK8-repressed	1.99E-04	1.23		
55684	C9orf86	CDK8-repressed	2.00E-04	1.18		
5428	POLG	CDK8-repressed	2.02E-04	1.25		
83998	REG4	CDK8-repressed	2.02E-04	5.01		
89845	ABCC10	CDK8-repressed	2.05E-04	1.25		
340348	TSPAN33	CDK8-repressed	2.06E-04	3.29		
318	NUDT2	CDK8-repressed	2.06E-04	1.35		
5364	PLXNB1	CDK8-repressed	2.06E-04	1.29		
51129	ANGPTL4	CDK8-repressed	2.07E-04	1.47		Yes
57630	SH3RF1	CDK8-repressed	2.07E-04	1.17		
22933	SIRT2	CDK8-repressed	2.08E-04	1.33		
1645	AKR1C1	CDK8-repressed	2.13E-04	1.36		
54585	LZTFL1	CDK8-repressed	2.13E-04	1.58		
4696	NDUFA3	CDK8-repressed	2.15E-04	1.08		
114609	TIRAP	CDK8-repressed	2.15E-04	1.41		
157927	C9orf62	CDK8-repressed	2.19E-04	1.33		
55890	GPRC5C	CDK8-repressed	2.19E-04	2.04		Yes
1603	DAD1	CDK8-repressed	2.20E-04	1.15		
8517	IKBKG	CDK8-repressed	2.20E-04	1.10		
2717	GLA	CDK8-repressed	2.20E-04	1.19		Yes
80164	FLJ22184	CDK8-repressed	2.20E-04	1.22		
6845	SYBL1	CDK8-repressed	2.20E-04	1.45		
1001	CDH3	CDK8-repressed	2.21E-04	1.27		
123036	MTAC2D1	CDK8-repressed	2.22E-04	1.88		
64081	MAWBP	CDK8-repressed	2.23E-04	1.74		
3636	INPPL1	CDK8-repressed	2.24E-04	1.31	Yes	
4779	NFE2L1	CDK8-repressed	2.24E-04	1.22		Yes
10840	ALDH1L1	CDK8-repressed	2.25E-04	1.56		
124936	CYB5D2	CDK8-repressed	2.28E-04	1.65		Yes
3292	HSD17B1	CDK8-repressed	2.29E-04	1.24		
4682	NUBP1	CDK8-repressed	2.30E-04	1.17		Yes
27249	C2orf25	CDK8-repressed	2.32E-04	1.38		Yes
57116	ZNF695	CDK8-repressed	2.33E-04	1.28		
51368	TEX264	CDK8-repressed	2.33E-04	1.26		Yes
5493	PPL	CDK8-repressed	2.34E-04	1.63		
7016	TESK1	CDK8-repressed	2.38E-04	1.19		Yes
55225	RAVER2	CDK8-repressed	2.38E-04	1.80		
84364	ZNF289	CDK8-repressed	2.39E-04	1.21		
5480	PPIC	CDK8-repressed	2.39E-04	1.24	Yes	
3663	IRF5	CDK8-repressed	2.39E-04	1.80		
389692	MAFA	CDK8-repressed	2.42E-04	1.24		
256329	C11orf35	CDK8-repressed	2.45E-04	1.57		
79652	C16orf30	CDK8-repressed	2.45E-04	2.03		
389289	LOC389289	CDK8-repressed	2.47E-04	1.21		
7084	TK2	CDK8-repressed	2.48E-04	1.31		Yes
10735	STAG2	CDK8-repressed	2.51E-04	1.32		
5728	PTEN	CDK8-repressed	2.53E-04	1.21		Yes
353134	LCE1D	CDK8-repressed	2.55E-04	1.21		
2178	FANCE	CDK8-repressed	2.55E-04	1.07		
54998	AURKAIP1	CDK8-repressed	2.55E-04	1.08	Yes	
23129	PLXND1	CDK8-repressed	2.59E-04	1.42		
26007	DAK	CDK8-repressed	2.62E-04	1.48		Yes
51734	SEPX1	CDK8-repressed	2.63E-04	1.16		
79144	C20orf149	CDK8-repressed	2.64E-04	1.30		
56654	NPDC1	CDK8-repressed	2.64E-04	1.81		
91272	FAM44B	CDK8-repressed	2.66E-04	2.05		
6714	SRC	CDK8-repressed	2.68E-04	1.27		

6905	TBCE	CDK8-repressed	2.69E-04	1.18		
55311	ZNF444	CDK8-repressed	2.73E-04	1.14		Yes
6690	SPINK1	CDK8-repressed	2.74E-04	1.59		
84299	C17orf37	CDK8-repressed	2.74E-04	1.19		Yes
57460	PPM1H	CDK8-repressed	2.75E-04	1.57		
3983	ABLIM1	CDK8-repressed	2.75E-04	1.37		
2634	GBP2	CDK8-repressed	2.76E-04	1.54		
340198	IFITM4P	CDK8-repressed	2.78E-04	1.27		
9788	MTSS1	CDK8-repressed	2.78E-04	1.67		
155465	BCMP11	CDK8-repressed	2.79E-04	1.72		
686	BTD	CDK8-repressed	2.81E-04	1.57		
346950	RPL37P6	CDK8-repressed	2.81E-04	1.14		
23335	WDR7	CDK8-repressed	2.84E-04	1.27		
54751	FBLIM1	CDK8-repressed	2.84E-04	1.29		
91949	COG7	CDK8-repressed	2.86E-04	1.38		
57161	PELI2	CDK8-repressed	2.89E-04	1.23		
219738	C10orf35	CDK8-repressed	2.89E-04	1.82		
401577	LOC401577	CDK8-repressed	2.90E-04	1.59		
10406	WFDC2	CDK8-repressed	2.92E-04	1.84	Yes	
55734	ZFP64	CDK8-repressed	2.93E-04	1.18		
114971	PTPMT1	CDK8-repressed	2.96E-04	2.67		
26128	KIAA1279	CDK8-repressed	2.98E-04	1.35		
64172	OSGEPL1	CDK8-repressed	2.99E-04	1.62		
9950	GOLGA5	CDK8-repressed	2.99E-04	1.27		
1573	CYP2J2	CDK8-repressed	3.03E-04	1.40		
2630	GBAP	CDK8-repressed	3.05E-04	1.75		
2039	EPB49	CDK8-repressed	3.08E-04	2.03		
246184	CDC26	CDK8-repressed	3.09E-04	1.32		
57146	TMEM159	CDK8-repressed	3.13E-04	1.47		
53635	PTOV1	CDK8-repressed	3.13E-04	1.26		
861	RUNX1	CDK8-repressed	3.16E-04	1.25		
8705	B3GALT4	CDK8-repressed	3.19E-04	1.62		Yes
9905	RUTBC1	CDK8-repressed	3.20E-04	1.36		Yes
439951	LOC439951	CDK8-repressed	3.22E-04	1.24		
23586	DDX58	CDK8-repressed	3.22E-04	1.48		
2746	GLUD1	CDK8-repressed	3.22E-04	1.49		
81605	C9orf74	CDK8-repressed	3.23E-04	1.22		
4688	NCF2	CDK8-repressed	3.24E-04	3.05		
65094	JMJD4	CDK8-repressed	3.25E-04	1.26		Yes
51164	DCTN4	CDK8-repressed	3.26E-04	1.15		
3704	ITPA	CDK8-repressed	3.28E-04	1.24		Yes
23557	SNAPAP	CDK8-repressed	3.29E-04	1.12		Yes
554202	LOC554202	CDK8-repressed	3.29E-04	3.04		
339122	RAB43	CDK8-repressed	3.31E-04	1.28		
10982	MAPRE2	CDK8-repressed	3.32E-04	1.33		Yes
10371	SEMA3A	CDK8-repressed	3.36E-04	1.33		
493754	LOC493754	CDK8-repressed	3.37E-04	1.15		
55072	RNF31	CDK8-repressed	3.39E-04	1.35		
55168	MRPS18A	CDK8-repressed	3.40E-04	1.10		Yes
1675	CFD	CDK8-repressed	3.45E-04	1.61		
51019	CCDC53	CDK8-repressed	3.46E-04	1.39		Yes
6698	SPRR1A	CDK8-repressed	3.46E-04	1.59		
57488	FAM62B	CDK8-repressed	3.51E-04	1.47		Yes
54921	CTF8	CDK8-repressed	3.52E-04	1.18		Yes
6948	TCN2	CDK8-repressed	3.52E-04	1.80		
80325	ABTB1	CDK8-repressed	3.54E-04	1.50		
51227	PIGP	CDK8-repressed	3.56E-04	1.33		
10474	TADA3L	CDK8-repressed	3.58E-04	1.45		
56928	SPPL2B	CDK8-repressed	3.60E-04	1.22		Yes

84888	SPPL2A	CDK8-repressed	3.63E-04	1.25		
268	AMH	CDK8-repressed	3.64E-04	1.33		Yes
5805	PTS	CDK8-repressed	3.69E-04	1.20		Yes
124997	WDR81	CDK8-repressed	3.72E-04	1.96		
23300	ASCIZ	CDK8-repressed	3.74E-04	1.20		
259307	IL4I1	CDK8-repressed	3.76E-04	1.26		Yes
23515	MORC3	CDK8-repressed	3.78E-04	1.33		Yes
84667	HES7	CDK8-repressed	3.79E-04	1.26		
6539	SLC6A12	CDK8-repressed	3.82E-04	2.09		
1050	CEBPA	CDK8-repressed	3.86E-04	1.26		
64221	ROBO3	CDK8-repressed	3.86E-04	1.14		
57549	IGSF9	CDK8-repressed	3.88E-04	1.60		Yes
149420	PDIK1L	CDK8-repressed	3.91E-04	1.19		
1479	CSTF3	CDK8-repressed	3.93E-04	1.10	Yes	Yes
4987	OPRL1	CDK8-repressed	3.93E-04	1.23		
3028	HADH2	CDK8-repressed	3.94E-04	1.19		
57707	KIAA1609	CDK8-repressed	3.95E-04	1.23		
54680	C1orf181	CDK8-repressed	3.96E-04	1.69		
149951	COMMD7	CDK8-repressed	3.97E-04	1.42		
813	CALU	CDK8-repressed	3.98E-04	1.91		
5865	RAB3B	CDK8-repressed	3.99E-04	2.59		
64063	PRSS22	CDK8-repressed	4.00E-04	1.26		
7123	CLEC3B	CDK8-repressed	4.07E-04	1.16		
2952	GSTT1	CDK8-repressed	4.07E-04	1.41		
80279	CDK5RAP3	CDK8-repressed	4.08E-04	1.44		Yes
84219	WDR24	CDK8-repressed	4.10E-04	1.76		
79666	PLEKHF2	CDK8-repressed	4.14E-04	1.27		
973	CD79A	CDK8-repressed	4.17E-04	1.11		
114787	KIAA1893	CDK8-repressed	4.21E-04	1.66		
203260	CCDC107	CDK8-repressed	4.22E-04	1.11		
7264	TSTA3	CDK8-repressed	4.23E-04	1.24		
284252	KCTD1	CDK8-repressed	4.29E-04	1.54		
90379	LOC90379	CDK8-repressed	4.31E-04	1.19		
10120	ACTR1B	CDK8-repressed	4.31E-04	1.22		
65244	SPATS2	CDK8-repressed	4.32E-04	1.32	Yes	Yes
29850	TRPM5	CDK8-repressed	4.33E-04	1.13		
599	BCL2L2	CDK8-repressed	4.33E-04	1.23		
9935	MAFB	CDK8-repressed	4.43E-04	1.66		
1026	CDKN1A	CDK8-repressed	4.44E-04	1.27	Yes	
22937	SCAP	CDK8-repressed	4.45E-04	1.66		
112398	EGLN2	CDK8-repressed	4.46E-04	1.30		Yes
10079	ATP9A	CDK8-repressed	4.48E-04	2.01		
84256	FLYWCH1	CDK8-repressed	4.49E-04	1.13		
54868	TMEM104	CDK8-repressed	4.49E-04	1.30		
55201	MAP1S	CDK8-repressed	4.53E-04	1.10		Yes
56948	C14orf124	CDK8-repressed	4.54E-04	1.16		
54961	SSH3	CDK8-repressed	4.56E-04	1.17		
2959	GTF2B	CDK8-repressed	4.57E-04	1.18		
166785	MMAA	CDK8-repressed	4.59E-04	1.57		Yes
22916	NCBP2	CDK8-repressed	4.64E-04	1.28	Yes	Yes
79794	C12orf49	CDK8-repressed	4.67E-04	1.29		
9114	ATP6V0D1	CDK8-repressed	4.68E-04	1.26		
9842	PLEKHM1	CDK8-repressed	4.70E-04	1.26		
348	APOE	CDK8-repressed	4.71E-04	1.11		
1471	CST3	CDK8-repressed	4.80E-04	1.22		
57175	CORO1B	CDK8-repressed	4.81E-04	1.42		
85376	KIAA1666	CDK8-repressed	4.84E-04	1.48		Yes
94134	ARHGAP12	CDK8-repressed	4.84E-04	1.32		
2906	GRIN2D	CDK8-repressed	4.86E-04	1.20		

5519	PPP2R1B	CDK8-repressed	4.86E-04	1.50	Yes	
9448	MAP4K4	CDK8-repressed	4.89E-04	1.72	Yes	
51371	POMP	CDK8-repressed	4.89E-04	1.16	Yes	
57719	TMEM16H	CDK8-repressed	4.90E-04	1.67		
57593	RP5-860F19.3	CDK8-repressed	4.96E-04	1.14		
3707	ITPKB	CDK8-repressed	4.99E-04	1.25		
6480	ST6GAL1	CDK8-repressed	5.01E-04	2.77		
285148	LOC285148	CDK8-repressed	5.02E-04	1.92		
26136	TES	CDK8-repressed	5.03E-04	1.23		
55359	STYK1	CDK8-repressed	5.06E-04	2.02		
6137	RPL13	CDK8-repressed	5.06E-04	1.18	Yes	Yes
644799	LOC644799	CDK8-repressed	5.08E-04	1.47		
10548	TM9SF1	CDK8-repressed	5.09E-04	1.17		
79803	HPS6	CDK8-repressed	5.09E-04	1.27		
124044	C16orf76	CDK8-repressed	5.11E-04	1.14		
2036	EPB41L1	CDK8-repressed	5.20E-04	2.37		
4070	TACSTD2	CDK8-repressed	5.21E-04	1.67		
29062	HSPC049	CDK8-repressed	5.26E-04	1.58		
84955	NUDCD1	CDK8-repressed	5.27E-04	1.30		Yes
10013	HDAC6	CDK8-repressed	5.28E-04	1.18		
26049	KIAA0888	CDK8-repressed	5.28E-04	1.35		
200576	PIP5K3	CDK8-repressed	5.30E-04	1.57		Yes
6885	MAP3K7	CDK8-repressed	5.31E-04	1.23		Yes
9581	PREPL	CDK8-repressed	5.32E-04	1.53		Yes
51411	BIN2	CDK8-repressed	5.35E-04	3.46		
149473	CCDC24	CDK8-repressed	5.35E-04	1.90		
221424	C6orf154	CDK8-repressed	5.38E-04	2.57		
56243	KIAA1217	CDK8-repressed	5.38E-04	1.82		
83743	GRWD1	CDK8-repressed	5.40E-04	1.29		Yes
4357	MPST	CDK8-repressed	5.41E-04	1.17		
85012	TCEAL3	CDK8-repressed	5.41E-04	1.89		
8723	SNX4	CDK8-repressed	5.44E-04	1.25	Yes	Yes
1339	COX6A2	CDK8-repressed	5.45E-04	1.25		
6879	TAF7	CDK8-repressed	5.46E-04	1.32		
529	ATP6V1E1	CDK8-repressed	5.47E-04	1.25		Yes
10184	LHFPL2	CDK8-repressed	5.51E-04	1.42		
9708	PCDHGA8	CDK8-repressed	5.53E-04	1.16		
10561	IFI44	CDK8-repressed	5.55E-04	1.20		
9920	KBTBD11	CDK8-repressed	5.56E-04	1.18		
90203	C20orf161	CDK8-repressed	5.59E-04	1.74		
55743	CHFR	CDK8-repressed	5.61E-04	1.86		
148932	MOBKL2C	CDK8-repressed	5.61E-04	1.42		
60343	FAM3A	CDK8-repressed	5.61E-04	1.30		
11267	SNF8	CDK8-repressed	5.69E-04	1.14		
7010	TEK	CDK8-repressed	5.72E-04	3.05		
57153	SLC44A2	CDK8-repressed	5.73E-04	1.32		
10410	IFITM3	CDK8-repressed	5.77E-04	1.28		
8408	ULK1	CDK8-repressed	5.79E-04	1.91		
54935	DUSP23	CDK8-repressed	5.80E-04	1.14		
2934	GSN	CDK8-repressed	5.83E-04	1.36		
221184	CPNE2	CDK8-repressed	5.83E-04	1.57		
59347	FKSG2	CDK8-repressed	5.86E-04	1.17		
414	ARSD	CDK8-repressed	5.88E-04	1.42		
55665	URG4	CDK8-repressed	5.90E-04	1.21		
25998	IBTK	CDK8-repressed	5.90E-04	1.33		
5308	PITX2	CDK8-repressed	5.95E-04	1.45		
284498	C1orf167	CDK8-repressed	5.98E-04	4.06		
84976	DISP1	CDK8-repressed	6.00E-04	1.71		
79734	KCTD17	CDK8-repressed	6.19E-04	1.31		

537	ATP6AP1	CDK8-repressed	6.26E-04	1.23		
8888	MCM3AP	CDK8-repressed	6.31E-04	1.26		
6874	TAF4	CDK8-repressed	6.31E-04	1.34		
1473	CST5	CDK8-repressed	6.34E-04	1.16		
4296	MAP3K11	CDK8-repressed	6.37E-04	1.26		Yes
55911	APOB48R	CDK8-repressed	6.39E-04	2.36		Yes
221491	C6orf1	CDK8-repressed	6.40E-04	1.97		
144717	FAM109A	CDK8-repressed	6.44E-04	1.28		
9540	TP53I3	CDK8-repressed	6.48E-04	1.62		
10491	CRTAP	CDK8-repressed	6.50E-04	1.36	Yes	Yes
6804	STX1A	CDK8-repressed	6.54E-04	1.31		
5379	PMS2L1	CDK8-repressed	6.56E-04	1.36		
113878	DTX2	CDK8-repressed	6.58E-04	1.33	Yes	
8662	EIF3S9	CDK8-repressed	6.58E-04	1.39		Yes
150383	LOC150383	CDK8-repressed	6.62E-04	1.40		
90024	FLJ20021	CDK8-repressed	6.62E-04	1.14		
124359	CDYL2	CDK8-repressed	6.64E-04	1.60		
284996	RNF149	CDK8-repressed	6.65E-04	1.15		
4669	NAGLU	CDK8-repressed	6.67E-04	1.94		Yes
10133	OPTN	CDK8-repressed	6.74E-04	1.14		
5095	PCCA	CDK8-repressed	6.75E-04	1.41		
23513	SCRIB	CDK8-repressed	6.75E-04	1.19		
6160	RPL31	CDK8-repressed	6.76E-04	1.12		Yes
2020	EN2	CDK8-repressed	6.80E-04	1.21		
10067	SCAMP3	CDK8-repressed	6.85E-04	1.14		
9858	KIAA0649	CDK8-repressed	6.91E-04	1.16		
5624	PROC	CDK8-repressed	6.98E-04	1.38		
2166	FAAH	CDK8-repressed	7.00E-04	1.50		
26012	NELF	CDK8-repressed	7.02E-04	1.42		
8771	TNFRSF6B	CDK8-repressed	7.03E-04	1.49		
25814	ATXN10	CDK8-repressed	7.03E-04	1.26	Yes	
64924	SLC30A5	CDK8-repressed	7.05E-04	1.18		
84002	B3GNT5	CDK8-repressed	7.09E-04	1.30		
6415	SEPW1	CDK8-repressed	7.12E-04	1.31		
3074	HEXB	CDK8-repressed	7.16E-04	1.14		
1789	DNMT3B	CDK8-repressed	7.16E-04	2.26		
158931	TCEAL6	CDK8-repressed	7.21E-04	1.85		
8650	NUMB	CDK8-repressed	7.22E-04	1.16		
57480	PLEKHG1	CDK8-repressed	7.24E-04	2.52		
84311	MRPL45	CDK8-repressed	7.24E-04	1.17	Yes	
84153	AYP1	CDK8-repressed	7.29E-04	1.15	Yes	
3087	HHEX	CDK8-repressed	7.34E-04	1.87		Yes
113026	PLCD3	CDK8-repressed	7.38E-04	1.71		
84937	ZNRF1	CDK8-repressed	7.45E-04	1.57		
23412	COMMD3	CDK8-repressed	7.46E-04	1.64		
540	ATP7B	CDK8-repressed	7.50E-04	1.37		
64284	RAB17	CDK8-repressed	7.59E-04	1.27		
54923	LIME1	CDK8-repressed	7.59E-04	1.29		
9686	VGLL4	CDK8-repressed	7.71E-04	1.25		
6897	TARS	CDK8-repressed	7.74E-04	1.17		Yes
147650	LOC147650	CDK8-repressed	7.78E-04	1.21		
51634	RBMX2	CDK8-repressed	7.82E-04	1.19		
8674	VAMP4	CDK8-repressed	7.85E-04	1.47		
51024	FIS1	CDK8-repressed	7.85E-04	1.18		
7158	TP53BP1	CDK8-repressed	7.86E-04	1.30		
90427	BMF	CDK8-repressed	7.90E-04	2.16		
401472	FLJ45248	CDK8-repressed	7.93E-04	1.57		
9908	G3BP2	CDK8-repressed	7.96E-04	1.33		Yes
130557	ZNF513	CDK8-repressed	7.97E-04	1.25		Yes

6452	SH3BP2	CDK8-repressed	7.99E-04	1.08	
79744	ZNF419	CDK8-repressed	8.02E-04	1.26	
399687	MYO18A	CDK8-repressed	8.23E-04	1.33	
79053	ALG8	CDK8-repressed	8.24E-04	1.16	Yes
200958	MUC20	CDK8-repressed	8.30E-04	1.27	
65010	SLC26A6	CDK8-repressed	8.38E-04	1.32	
91978	C19orf20	CDK8-repressed	8.41E-04	1.38	
124221	MGC52282	CDK8-repressed	8.42E-04	2.78	
57512	GPR158	CDK8-repressed	8.49E-04	1.39	
55344	PLCXD1	CDK8-repressed	8.50E-04	1.25	Yes
51750	RTEL1	CDK8-repressed	8.56E-04	1.31	Yes
83547	RILP	CDK8-repressed	8.57E-04	1.46	
5796	PTPRK	CDK8-repressed	8.61E-04	1.30	
838	CASP5	CDK8-repressed	8.62E-04	1.19	
29125	C11orf21	CDK8-repressed	8.63E-04	1.67	
81846	SBF2	CDK8-repressed	8.63E-04	1.21	
340543	TCEAL5	CDK8-repressed	8.64E-04	1.91	
473	RERE	CDK8-repressed	8.67E-04	1.32	
57326	PBXIP1	CDK8-repressed	8.68E-04	1.77	Yes
3831	KNS2	CDK8-repressed	8.68E-04	1.12	
55312	RFK	CDK8-repressed	8.74E-04	1.60	
6594	SMARCA1	CDK8-repressed	8.76E-04	1.77	
5292	PIM1	CDK8-repressed	8.83E-04	1.68	Yes
80381	CD276	CDK8-repressed	8.87E-04	1.42	
150290	DUSP18	CDK8-repressed	8.92E-04	1.52	Yes
55818	JMJD1A	CDK8-repressed	9.09E-04	1.55	
23625	FAM89B	CDK8-repressed	9.13E-04	1.31	
147798	TMC4	CDK8-repressed	9.16E-04	1.72	
57617	VPS18	CDK8-repressed	9.19E-04	1.42	
54991	C1orf159	CDK8-repressed	9.20E-04	1.25	
26056	RAB11FIP5	CDK8-repressed	9.20E-04	1.25	
22977	AKR7A3	CDK8-repressed	9.25E-04	1.25	
84869	CBR4	CDK8-repressed	9.26E-04	1.32	
3695	ITGB7	CDK8-repressed	9.34E-04	1.15	
2792	GNGT1	CDK8-repressed	9.35E-04	2.31	

Table 3. CDK8-regulated genes in mouse R1 ES cells.
Provided are the top 1500 genes that significantly changed upon CDK8 loss prior to differentiation at Day 8 in R1 ES cells. The fold change is relative to shNTC control. *P*-value is a Student's *t*-Test between shNTC and two independent CDK8 shRNAs.

Mouse Entrez ID	Gene Symbol	CDK8-induced/repressed	*P*-value	Fold change
12159	Bmp4	CDK8-induced	1.73E-09	1.70
231507	Plac8	CDK8-induced	3.97E-08	1.80
66855	Tcf25	CDK8-induced	6.01E-08	1.37
19124	Procr	CDK8-induced	6.66E-08	1.60
227753	Gsn	CDK8-induced	1.48E-07	1.66
16324	Inhbb	CDK8-induced	2.22E-07	1.69
58206	Zbtb32	CDK8-induced	2.54E-07	1.41
15370	Nr4a1	CDK8-induced	2.87E-07	1.42
20170	Hps6	CDK8-induced	3.09E-07	1.18
18553	Pcsk6	CDK8-induced	3.14E-07	1.77
53379	Hnrpa2b1	CDK8-induced	3.41E-07	1.43
170761	Pdzd3	CDK8-induced	7.60E-07	2.39
18787	Serpine1	CDK8-induced	7.86E-07	2.35
16582	Kifc3	CDK8-induced	8.19E-07	1.65
13521	Slc26a2	CDK8-induced	9.26E-07	1.45
21345	Tagln	CDK8-induced	9.94E-07	1.66
69698	2310046K01Rik	CDK8-induced	1.19E-06	1.96
74134	Cyp2s1	CDK8-induced	1.50E-06	1.66
12457	Ccrn4l	CDK8-induced	1.56E-06	1.40
320191	Hook3	CDK8-induced	1.71E-06	1.41
330064	Slc5a6	CDK8-induced	1.80E-06	1.18
381110	AW061290	CDK8-induced	1.98E-06	1.58
108143	Taf9	CDK8-induced	2.20E-06	1.25
70207	Ccdc44	CDK8-induced	2.46E-06	1.33
70574	Cpm	CDK8-induced	2.48E-06	1.73
230908	Tardbp	CDK8-induced	2.61E-06	1.34
673378	LOC673378	CDK8-induced	2.89E-06	1.33
15974	Ifnab	CDK8-induced	2.98E-06	1.15
67797	6530403A03Rik	CDK8-induced	3.26E-06	1.52
109168	5730596K20Rik	CDK8-induced	3.26E-06	1.29
68024	Hist1h2bc	CDK8-induced	3.43E-06	1.97
13722	Scye1	CDK8-induced	3.67E-06	1.11
17120	Mad1l1	CDK8-induced	4.21E-06	1.08
14622	Gjb5	CDK8-induced	4.69E-06	2.01
15200	Hbegf	CDK8-induced	5.18E-06	1.50
28109	D10Wsu102e	CDK8-induced	6.04E-06	1.33
14620	Gjb3	CDK8-induced	6.32E-06	1.70
76453	Prss23	CDK8-induced	7.71E-06	2.11
77929	Yipf6	CDK8-induced	8.01E-06	1.35
170749	Mtmr4	CDK8-induced	8.31E-06	1.28
268697	Ccnb1	CDK8-induced	8.93E-06	1.16
72351	Ptar1	CDK8-induced	8.96E-06	1.34
78781	Zc3hav1	CDK8-induced	9.59E-06	1.38
380836	Mrs2l	CDK8-induced	1.07E-05	1.23
207742	Rnf43	CDK8-induced	1.14E-05	1.38
545714	LOC545714	CDK8-induced	1.18E-05	1.37
21767	Tex264	CDK8-induced	1.25E-05	1.14
260409	Cdc42ep3	CDK8-induced	1.27E-05	1.53
23828	Bves	CDK8-induced	1.30E-05	1.37
56418	Ykt6	CDK8-induced	1.43E-05	1.33
217837	Itpk1	CDK8-induced	1.45E-05	1.26
225651	Mppe1	CDK8-induced	1.45E-05	1.39

78560	Gpr124	CDK8-induced	1.55E-05	1.61
52700	Txnl5	CDK8-induced	1.60E-05	1.23
16852	Lgals1	CDK8-induced	1.65E-05	1.40
21664	Phlda1	CDK8-induced	1.81E-05	1.55
67800	Dgat2	CDK8-induced	1.85E-05	1.21
216134	Pdxk	CDK8-induced	1.86E-05	1.45
14066	F3	CDK8-induced	1.87E-05	2.25
19224	Ptgs1	CDK8-induced	1.90E-05	1.48
101543	Wtip	CDK8-induced	1.92E-05	1.17
73385	1700047I17Rik	CDK8-induced	1.92E-05	1.24
214855	Arid5a	CDK8-induced	1.95E-05	1.22
50766	Crim1	CDK8-induced	1.95E-05	1.36
19285	Ptrf	CDK8-induced	1.95E-05	1.36
213827	Arcn1	CDK8-induced	2.01E-05	1.19
20200	S100a6	CDK8-induced	2.03E-05	1.61
69993	Chn2	CDK8-induced	2.07E-05	1.70
19087	Prkar2a	CDK8-induced	2.08E-05	1.62
211323	Nrg1	CDK8-induced	2.11E-05	1.51
13731	Emp2	CDK8-induced	2.16E-05	1.53
17425	Foxk1	CDK8-induced	2.24E-05	1.24
12450	Ccng1	CDK8-induced	2.25E-05	1.23
94092	Trim16	CDK8-induced	2.25E-05	1.53
68272	Rbm28	CDK8-induced	2.32E-05	1.31
94066	Mrpl36	CDK8-induced	2.42E-05	1.18
14701	Gng12	CDK8-induced	2.46E-05	1.57
28018	D7Wsu128e	CDK8-induced	2.54E-05	1.19
14187	Akr1b8	CDK8-induced	2.55E-05	1.35
67434	5730557B15Rik	CDK8-induced	2.63E-05	1.90
93689	Lmod1	CDK8-induced	2.72E-05	1.48
18597	Pdha1	CDK8-induced	2.93E-05	1.21
13356	Dgcr2	CDK8-induced	3.04E-05	1.34
18590	Pdgfa	CDK8-induced	3.12E-05	1.40
66997	Psmd12	CDK8-induced	3.23E-05	1.17
55984	Camkk1	CDK8-induced	3.26E-05	1.26
102423	Mizf	CDK8-induced	3.26E-05	1.30
19317	Qk	CDK8-induced	3.26E-05	1.40
18590	Pdgfa	CDK8-induced	3.27E-05	1.35
67268	2900073G15Rik	CDK8-induced	3.35E-05	1.19
231327	Ppat	CDK8-induced	3.35E-05	1.37
232807	Ppp1r12c	CDK8-induced	3.37E-05	1.40
226517	Smg7	CDK8-induced	3.38E-05	1.25
21817	Tgm2	CDK8-induced	3.44E-05	1.20
19128	Pros1	CDK8-induced	3.45E-05	1.28
67588	Rnf41	CDK8-induced	3.51E-05	1.15
21428	Mlx	CDK8-induced	3.53E-05	1.21
76400	Pbp2	CDK8-induced	3.61E-05	2.08
76779	Cluap1	CDK8-induced	3.65E-05	1.14
231452	Sdad1	CDK8-induced	3.69E-05	1.38
231147	Sh3tc1	CDK8-induced	3.83E-05	1.33
109168	5730596K20Rik	CDK8-induced	3.93E-05	1.36
71147	Oxsm	CDK8-induced	4.23E-05	1.59
18612	Etv4	CDK8-induced	4.26E-05	1.29
26879	B3galnt1	CDK8-induced	4.34E-05	1.33
11459	Acta1	CDK8-induced	4.48E-05	1.90
217149	Mel13	CDK8-induced	4.66E-05	1.23
14066	F3	CDK8-induced	4.72E-05	2.44
22135	Tgoln2	CDK8-induced	4.89E-05	1.21
56418	Ykt6	CDK8-induced	4.98E-05	1.40
21345	Tagln	CDK8-induced	5.03E-05	1.68

50850	Spast	CDK8-induced	5.30E-05	1.26
230257	Rod1	CDK8-induced	5.80E-05	1.26
20401	Sh3bp1	CDK8-induced	5.82E-05	1.27
231571	AW060207	CDK8-induced	5.85E-05	1.16
27273	Pdk4	CDK8-induced	5.85E-05	1.28
68553	1110001D15Rik	CDK8-induced	5.88E-05	1.50
320214	4932425I24Rik	CDK8-induced	5.98E-05	1.44
76375	Det1	CDK8-induced	6.14E-05	1.25
11898	Ass1	CDK8-induced	6.15E-05	1.15
12053	Bcl6	CDK8-induced	6.16E-05	1.26
67225	Rnpc3	CDK8-induced	6.46E-05	1.22
226982	Eif5b	CDK8-induced	6.50E-05	1.23
71517	9030624J02Rik	CDK8-induced	6.56E-05	1.18
381549	Zfp69	CDK8-induced	7.00E-05	1.21
67955	Sugt1	CDK8-induced	7.04E-05	1.17
230582	2810410C14Rik	CDK8-induced	7.11E-05	1.28
623548	LOC623548	CDK8-induced	7.24E-05	1.41
15270	H2afx	CDK8-induced	7.27E-05	1.30
71323	Rassf8	CDK8-induced	7.33E-05	1.20
353282	Sfmbt2	CDK8-induced	7.35E-05	1.16
13859	Eps15l1	CDK8-induced	7.45E-05	1.28
319651	Usp37	CDK8-induced	7.56E-05	1.28
217122	A430060F13Rik	CDK8-induced	7.56E-05	1.61
12322	Camk2a	CDK8-induced	7.63E-05	1.39
66405	Mcts2	CDK8-induced	7.66E-05	1.29
67463	1200014M14Rik	CDK8-induced	7.83E-05	1.18
319158	Hist1h4i	CDK8-induced	7.88E-05	1.72
226849	Ppp2r5a	CDK8-induced	7.98E-05	1.35
20680	Sox7	CDK8-induced	8.30E-05	3.26
56213	Htra1	CDK8-induced	8.37E-05	1.79
67800	Dgat2	CDK8-induced	8.39E-05	1.29
65961	Crlz1	CDK8-induced	8.57E-05	1.19
66089	Rmnd5b	CDK8-induced	8.85E-05	1.18
17762	Mapt	CDK8-induced	9.10E-05	1.48
56046	2410003P15Rik	CDK8-induced	9.35E-05	1.25
245828	Trappc1	CDK8-induced	9.81E-05	1.11
71667	0610007L01Rik	CDK8-induced	9.90E-05	1.10
235283	Gramd1b	CDK8-induced	9.91E-05	1.32
240832	Tor1aip2	CDK8-induced	1.00E-04	1.13
218978	D14Ertd436e	CDK8-induced	1.01E-04	1.14
18452	P4ha2	CDK8-induced	1.03E-04	1.60
11975	Atp6v0a1	CDK8-induced	1.03E-04	1.59
225912	Cybasc3	CDK8-induced	1.09E-04	1.21
77411	Rbm35b	CDK8-induced	1.10E-04	1.27
56717	Frap1	CDK8-induced	1.14E-04	1.58
17873	Gadd45b	CDK8-induced	1.15E-04	1.18
109778	Blvra	CDK8-induced	1.16E-04	1.26
72183	Snx6	CDK8-induced	1.17E-04	1.23
211945	Plekhh1	CDK8-induced	1.17E-04	1.56
52245	Commd2	CDK8-induced	1.19E-04	1.13
27279	Tnfrsf12a	CDK8-induced	1.22E-04	1.18
72113	Adck1	CDK8-induced	1.26E-04	1.16
55978	Ift20	CDK8-induced	1.29E-04	1.21
382522	Hist3h2bb	CDK8-induced	1.30E-04	1.34
74218	1700016H13Rik	CDK8-induced	1.33E-04	1.42
78303	Hist3h2ba	CDK8-induced	1.33E-04	1.31
17342	Mitf	CDK8-induced	1.34E-04	1.36
20194	S100a10	CDK8-induced	1.34E-04	1.19
140858	Wdr5	CDK8-induced	1.35E-04	1.47

66395	Ahnak	CDK8-induced	1.37E-04	1.34
26893	Cops6	CDK8-induced	1.38E-04	1.15
74412	Gle1l	CDK8-induced	1.38E-04	1.21
70829	Ccdc93	CDK8-induced	1.43E-04	1.27
19359	Rad23b	CDK8-induced	1.46E-04	1.25
22719	Zfp61	CDK8-induced	1.48E-04	1.17
21767	Tex264	CDK8-induced	1.51E-04	1.17
381110	AW061290	CDK8-induced	1.54E-04	1.61
11890	Asgr2	CDK8-induced	1.58E-04	1.34
77430	9430081H08Rik	CDK8-induced	1.58E-04	1.24
13002	Dnajc5	CDK8-induced	1.59E-04	1.27
21871	Atp6v0a2	CDK8-induced	1.60E-04	1.28
20851	Stat5b	CDK8-induced	1.60E-04	1.23
53334	Gosr1	CDK8-induced	1.61E-04	1.37
242083	Ppm1l	CDK8-induced	1.61E-04	1.18
52430	Echdc2	CDK8-induced	1.62E-04	1.33
20181	Rxra	CDK8-induced	1.66E-04	1.35
225651	Mppe1	CDK8-induced	1.68E-04	1.35
387524	Znrf2	CDK8-induced	1.73E-04	1.42
13132	Dab2	CDK8-induced	1.77E-04	1.90
66310	2810410M20Rik	CDK8-induced	1.77E-04	1.26
67247	Mosc2	CDK8-induced	1.78E-04	1.18
212679	Mars2	CDK8-induced	1.79E-04	1.25
26425	Nubp1	CDK8-induced	1.83E-04	1.09
121022	Mrps6	CDK8-induced	1.83E-04	1.11
71929	Tmem123	CDK8-induced	1.86E-04	1.59
19244	Ptp4a2	CDK8-induced	1.89E-04	1.16
69743	Casz1	CDK8-induced	1.93E-04	1.22
57741	Noc2l	CDK8-induced	1.93E-04	1.20
18617	Rhox5	CDK8-induced	1.98E-04	1.39
23806	Arih1	CDK8-induced	1.99E-04	1.30
26932	Ppp2r5e	CDK8-induced	2.05E-04	1.26
66603	Sip1	CDK8-induced	2.05E-04	1.28
98732	Rab3gap2	CDK8-induced	2.06E-04	1.13
56207	Uchl5	CDK8-induced	2.09E-04	1.27
226849	Ppp2r5a	CDK8-induced	2.15E-04	1.45
74471	4933440N22Rik	CDK8-induced	2.17E-04	1.35
208177	Phldb2	CDK8-induced	2.18E-04	1.36
16324	Inhbb	CDK8-induced	2.18E-04	1.44
76142	Ppp1r14c	CDK8-induced	2.19E-04	1.28
57434	Xrcc2	CDK8-induced	2.20E-04	1.40
545136	LOC545136	CDK8-induced	2.21E-04	1.34
232910	Ap2s1	CDK8-induced	2.24E-04	1.12
66432	Slc7a6os	CDK8-induced	2.25E-04	1.21
245945	BC013481	CDK8-induced	2.30E-04	1.73
13168	Dbil5	CDK8-induced	2.31E-04	1.87
14645	Glul	CDK8-induced	2.32E-04	1.35
18631	Pex11a	CDK8-induced	2.36E-04	1.31
70646	Nat12	CDK8-induced	2.45E-04	1.23
235380	Dmxl2	CDK8-induced	2.45E-04	1.62
214290	Zcchc6	CDK8-induced	2.47E-04	1.32
52036	Saps3	CDK8-induced	2.51E-04	1.27
20227	Sart1	CDK8-induced	2.52E-04	1.16
213027	B130050I23Rik	CDK8-induced	2.53E-04	1.41
242700	Il28ra	CDK8-induced	2.58E-04	1.32
114676	4930519F09Rik	CDK8-induced	2.60E-04	1.19
226419	Dyrk3	CDK8-induced	2.61E-04	1.30
15528	Hspe1	CDK8-induced	2.64E-04	1.15
16886	Limk2	CDK8-induced	2.66E-04	1.09

109229	C030004A17Rik	CDK8-induced	2.68E-04	1.18
21679	Tead4	CDK8-induced	2.70E-04	1.48
66805	Tspan1	CDK8-induced	2.73E-04	1.57
11491	Adam17	CDK8-induced	2.73E-04	1.29
66827	Ttc1	CDK8-induced	2.74E-04	1.27
20826	Nhp2l1	CDK8-induced	2.75E-04	1.14
67486	Polr3g	CDK8-induced	2.76E-04	1.15
232210	8430410A17Rik	CDK8-induced	2.78E-04	1.31
70445	Cd248	CDK8-induced	2.78E-04	1.74
71653	4930506M07Rik	CDK8-induced	2.85E-04	1.21
66912	Bzw2	CDK8-induced	2.92E-04	1.18
226856	Lpgat1	CDK8-induced	2.94E-04	1.32
69368	Wdfy1	CDK8-induced	2.99E-04	1.30
207785	BC035295	CDK8-induced	3.00E-04	1.51
19128	Pros1	CDK8-induced	3.00E-04	1.29
17847	Usp34	CDK8-induced	3.03E-04	1.16
72931	2900010J23Rik	CDK8-induced	3.07E-04	1.11
229905	Ccbl2	CDK8-induced	3.09E-04	1.33
21410	Tcf2	CDK8-induced	3.09E-04	1.88
18100	Mrpl40	CDK8-induced	3.12E-04	1.12
16582	Kifc3	CDK8-induced	3.13E-04	1.66
18087	Nktr	CDK8-induced	3.16E-04	1.24
55948	Sfn	CDK8-induced	3.18E-04	1.45
72658	2700097O09Rik	CDK8-induced	3.18E-04	1.12
14784	Grb2	CDK8-induced	3.25E-04	1.15
67451	Pkp2	CDK8-induced	3.25E-04	1.28
20402	Zfp106	CDK8-induced	3.28E-04	1.21
100213	Rusc2	CDK8-induced	3.28E-04	1.26
56298	Arl6ip2	CDK8-induced	3.34E-04	1.43
110606	Fntb	CDK8-induced	3.47E-04	1.20
12856	Cox17	CDK8-induced	3.49E-04	1.11
14598	Ggt1	CDK8-induced	3.53E-04	1.65
319186	Hist1h2bm	CDK8-induced	3.55E-04	1.29
72515	Wdr43	CDK8-induced	3.55E-04	1.31
50708	Hist1h1c	CDK8-induced	3.57E-04	1.93
108911	Rcc2	CDK8-induced	3.59E-04	1.15
56376	Pdlim5	CDK8-induced	3.61E-04	1.33
59009	Sh3rf1	CDK8-induced	3.61E-04	1.24
319162	Hist3h2a	CDK8-induced	3.62E-04	2.04
22156	Tuft1	CDK8-induced	3.63E-04	1.15
22004	Tpm2	CDK8-induced	3.63E-04	1.27
72136	D4st1	CDK8-induced	3.67E-04	1.23
16905	Lmna	CDK8-induced	3.68E-04	1.21
78938	Fbxo34	CDK8-induced	3.74E-04	1.17
58235	Pvrl1	CDK8-induced	3.75E-04	1.24
230738	Zc3h12a	CDK8-induced	3.79E-04	1.54
18632	Pex11b	CDK8-induced	3.82E-04	1.13
22004	Tpm2	CDK8-induced	3.83E-04	1.19
226747	Ahctf1	CDK8-induced	3.84E-04	1.15
53414	Bysl	CDK8-induced	3.85E-04	1.21
77593	Usp45	CDK8-induced	3.88E-04	1.52
73667	2410004P03Rik	CDK8-induced	3.88E-04	1.15
13803	Enc1	CDK8-induced	3.91E-04	1.40
226849	Ppp2r5a	CDK8-induced	3.95E-04	1.36
19679	Pitpnm2	CDK8-induced	3.95E-04	1.35
77803	A930021C24Rik	CDK8-induced	3.96E-04	2.17
72662	2810028N01Rik	CDK8-induced	4.03E-04	1.37
108062	Cstf2	CDK8-induced	4.06E-04	1.17
94061	Mrpl1	CDK8-induced	4.06E-04	1.26

69453	1700027L20Rik	CDK8-induced	4.09E-04	1.40
74552	Npal3	CDK8-induced	4.10E-04	1.31
97130	C77080	CDK8-induced	4.12E-04	1.29
66979	Pole4	CDK8-induced	4.16E-04	1.09
104732	4930427A07Rik	CDK8-induced	4.19E-04	1.44
328066	C920021A13	CDK8-induced	4.23E-04	1.31
56771	Trfp	CDK8-induced	4.28E-04	1.35
319184	Hist1h2bk	CDK8-induced	4.30E-04	1.33
229593	Golph3l	CDK8-induced	4.30E-04	1.19
67338	Rffl	CDK8-induced	4.38E-04	1.12
70359	Gtpbp3	CDK8-induced	4.40E-04	1.13
74766	Yipf2	CDK8-induced	4.40E-04	1.21
67226	Tmem19	CDK8-induced	4.41E-04	1.09
66805	Tspan1	CDK8-induced	4.43E-04	1.35
20671	Sox17	CDK8-induced	4.44E-04	1.79
67414	Mfn1	CDK8-induced	4.45E-04	1.11
56807	Scamp5	CDK8-induced	4.52E-04	1.18
67532	Mfap1	CDK8-induced	4.52E-04	1.14
73533	1700080G18Rik	CDK8-induced	4.52E-04	1.25
16002	Igf2	CDK8-induced	4.53E-04	2.08
19414	Rasa3	CDK8-induced	4.54E-04	1.53
12449	Ccnf	CDK8-induced	4.57E-04	1.15
215615	Rnpep	CDK8-induced	4.60E-04	1.19
70454	Cenpl	CDK8-induced	4.61E-04	1.09
75991	5033405K12Rik	CDK8-induced	4.65E-04	1.34
71099	Tssk4	CDK8-induced	4.69E-04	1.19
67469	Abhd5	CDK8-induced	4.70E-04	1.46
231452	Sdad1	CDK8-induced	4.72E-04	1.15
21859	Timp3	CDK8-induced	4.73E-04	1.46
68620	1110025D03Rik	CDK8-induced	4.78E-04	1.40
80914	Uck2	CDK8-induced	4.83E-04	1.14
97159	A430005L14Rik	CDK8-induced	4.94E-04	1.10
106564	Ppcs	CDK8-induced	4.96E-04	1.19
215201	4732479N06Rik	CDK8-induced	5.03E-04	1.72
77106	Gpr178	CDK8-induced	5.04E-04	1.49
140486	Igf2bp1	CDK8-induced	5.06E-04	1.22
76824	2410166I05Rik	CDK8-induced	5.10E-04	1.14
16180	Il1rap	CDK8-induced	5.18E-04	1.56
66391	2310061J03Rik	CDK8-induced	5.21E-04	1.20
13132	Dab2	CDK8-induced	5.23E-04	1.66
68970	Wdr40a	CDK8-induced	5.26E-04	1.11
19395	Rasgrp2	CDK8-induced	5.28E-04	1.14
232339	Ankrd26	CDK8-induced	5.33E-04	1.22
14786	Grb7	CDK8-induced	5.36E-04	1.12
225791	Zadh2	CDK8-induced	5.36E-04	1.27
56200	Ddx21	CDK8-induced	5.42E-04	1.34
12817	Col13a1	CDK8-induced	5.45E-04	1.61
259108	Olfr550	CDK8-induced	5.48E-04	1.49
54401	Ywhab	CDK8-induced	5.49E-04	1.20
18950	Pnp	CDK8-induced	5.51E-04	1.34
69082	2610312B22Rik	CDK8-induced	5.52E-04	1.23
231727	B3gnt4	CDK8-induced	5.57E-04	1.36
16865	Lgtn	CDK8-induced	5.62E-04	1.32
67459	Nvl	CDK8-induced	5.65E-04	1.24
214253	Etnk2	CDK8-induced	5.66E-04	1.26
71673	0610009J22Rik	CDK8-induced	5.69E-04	1.16
19727	Rfxank	CDK8-induced	5.70E-04	1.13
15467	Eif2ak1	CDK8-induced	5.70E-04	1.15
68833	Pdcl3	CDK8-induced	5.77E-04	1.25

140781	Myh7	CDK8-induced	5.78E-04	1.54
56376	Pdlim5	CDK8-induced	5.86E-04	1.31
74048	4632428N05Rik	CDK8-induced	5.87E-04	1.58
17248	Mdm4	CDK8-induced	5.89E-04	1.37
18700	Piga	CDK8-induced	5.91E-04	1.36
17425	Foxk1	CDK8-induced	5.98E-04	1.26
66787	4933433P14Rik	CDK8-induced	6.09E-04	1.20
321022	Cdv3	CDK8-induced	6.12E-04	1.10
320940	Atp11c	CDK8-induced	6.14E-04	1.34
114873	Dscaml1	CDK8-induced	6.14E-04	1.29
70639	5730521K06Rik	CDK8-induced	6.16E-04	1.42
18020	Nfatc2ip	CDK8-induced	6.16E-04	1.63
223864	Rapgef3	CDK8-induced	6.23E-04	1.51
18707	Pik3cd	CDK8-induced	6.23E-04	1.23
238247	Arid4a	CDK8-induced	6.25E-04	1.28
71389	Chd6	CDK8-induced	6.25E-04	1.41
55948	Sfn	CDK8-induced	6.27E-04	1.38
214639	4930486L24Rik	CDK8-induced	6.29E-04	1.28
69327	1700007K13Rik	CDK8-induced	6.33E-04	1.36
69663	Ddx51	CDK8-induced	6.38E-04	1.18
99683	Sec24b	CDK8-induced	6.41E-04	1.16
21380	Tbx1	CDK8-induced	6.44E-04	1.82
80985	Trim44	CDK8-induced	6.53E-04	1.40
268294	Zbtb24	CDK8-induced	6.58E-04	1.39
76803	2410141K09Rik	CDK8-induced	6.59E-04	1.55
229681	St7l	CDK8-induced	6.70E-04	1.43
212647	Aldh4a1	CDK8-induced	6.71E-04	1.17
66352	Blzf1	CDK8-induced	6.82E-04	1.13
70240	2700038N03Rik	CDK8-induced	6.86E-04	1.25
66654	Tex12	CDK8-induced	6.89E-04	1.36
108737	Oxsr1	CDK8-induced	6.92E-04	1.38
19181	Psmc2	CDK8-induced	6.92E-04	1.12
208760	Aqp12	CDK8-induced	6.95E-04	4.43
11733	Ank1	CDK8-induced	7.03E-04	1.88
258706	Olfr43	CDK8-induced	7.03E-04	1.15
232236	C130022K22Rik	CDK8-induced	7.05E-04	1.24
17762	Mapt	CDK8-induced	7.07E-04	1.45
319188	Hist1h2bp	CDK8-induced	7.07E-04	1.74
13167	Dbi	CDK8-induced	7.09E-04	1.09
67939	2010316F05Rik	CDK8-induced	7.13E-04	1.15
53312	6330412F12Rik	CDK8-induced	7.15E-04	1.26
67247	Mosc2	CDK8-induced	7.20E-04	1.15
12161	Bmp6	CDK8-induced	7.20E-04	1.44
67379	Dedd2	CDK8-induced	7.22E-04	1.13
21961	Tns1	CDK8-induced	7.25E-04	1.18
18516	Pbx3	CDK8-induced	7.26E-04	1.28
232164	BC017133	CDK8-induced	7.30E-04	1.49
77579	Myh10	CDK8-induced	7.35E-04	1.15
109624	Cald1	CDK8-induced	7.37E-04	1.64
230967	BC046331	CDK8-induced	7.40E-04	1.17
75079	Zfp509	CDK8-induced	7.42E-04	1.10
259036	Olfr713	CDK8-induced	7.45E-04	2.01
270627	Taf1	CDK8-induced	7.47E-04	1.24
68252	A030007L17Rik	CDK8-induced	7.51E-04	1.14
83675	Bicc1	CDK8-induced	7.57E-04	1.32
11490	Adam15	CDK8-induced	7.58E-04	1.17
69253	Hspb2	CDK8-induced	7.64E-04	1.56
232210	8430410A17Rik	CDK8-induced	7.68E-04	1.24
15278	Tfb2m	CDK8-induced	7.73E-04	1.15

11745	Anxa3	CDK8-induced	7.74E-04	1.52
264064	CDK8	CDK8-induced	7.81E-04	1.41
71804	2610016C23Rik	CDK8-induced	7.95E-04	1.15
67264	Ndufb8	CDK8-induced	7.97E-04	1.60
69288	Rhobtb1	CDK8-induced	8.01E-04	1.66
338351	Akap17b	CDK8-induced	8.04E-04	1.46
226971	Plekhb2	CDK8-induced	8.11E-04	1.30
13380	Dkk1	CDK8-induced	8.30E-04	3.71
72102	Dusp11	CDK8-induced	8.32E-04	1.16
67967	Pold3	CDK8-induced	8.34E-04	1.13
22761	Zfpm1	CDK8-induced	8.35E-04	1.15
68876	Xrcc6bp1	CDK8-induced	8.39E-04	1.26
227960	Gca	CDK8-induced	8.40E-04	1.32
108800	Ston2	CDK8-induced	8.46E-04	1.31
259000	Olfr195	CDK8-induced	8.47E-04	1.13
235956	BC012278	CDK8-induced	8.47E-04	1.16
81489	Dnajb1	CDK8-induced	8.51E-04	1.22
22420	Wnt6	CDK8-induced	8.54E-04	1.34
67059	2810409H07Rik	CDK8-induced	8.54E-04	1.13
67136	Kbtbd4	CDK8-induced	8.58E-04	1.12
56036	Ccnl2	CDK8-induced	8.60E-04	1.38
52014	D10Ertd438e	CDK8-induced	8.62E-04	1.21
68981	Snrpa1	CDK8-induced	8.66E-04	1.23
66395	Ahnak	CDK8-induced	8.67E-04	1.32
12798	Cnn2	CDK8-induced	8.76E-04	1.21
14300	Frg1	CDK8-induced	8.77E-04	1.12
18799	Plcd1	CDK8-induced	8.78E-04	1.11
53869	Rab11a	CDK8-induced	8.79E-04	1.12
19202	Rhox6	CDK8-induced	8.85E-04	1.55
19384	Ran	CDK8-induced	8.89E-04	1.17
216831	AU040829	CDK8-induced	8.93E-04	1.26
225432	Rbm27	CDK8-induced	8.96E-04	1.33
239739	Lamp3	CDK8-induced	9.03E-04	1.23
269252	Gtf3c4	CDK8-induced	9.08E-04	1.18
52705	Krr1	CDK8-induced	9.13E-04	1.31
14165	Fgf10	CDK8-induced	9.14E-04	2.54
67705	1810058I24Rik	CDK8-induced	9.24E-04	1.18
17131	Smad7	CDK8-induced	9.24E-04	1.19
227644	Snapc4	CDK8-induced	9.30E-04	1.13
26893	Cops6	CDK8-induced	9.30E-04	1.15
27083	Xlr4b	CDK8-induced	9.39E-04	1.45
230579	BC026682	CDK8-induced	9.40E-04	1.69
67333	Stk35	CDK8-induced	9.41E-04	1.35
77411	Rbm35b	CDK8-induced	9.51E-04	1.25
68655	Fndc1	CDK8-induced	9.59E-04	1.35
67089	Psmc6	CDK8-induced	9.59E-04	1.13
68342	Ndufb10	CDK8-induced	9.61E-04	1.15
67590	4930521E07Rik	CDK8-induced	9.65E-04	1.57
320769	Prdx6-rs1	CDK8-induced	9.77E-04	1.16
266459	MGC107533	CDK8-induced	9.90E-04	2.17
72584	Cul4b	CDK8-induced	9.96E-04	1.24
194162	BC035954	CDK8-induced	1.00E-03	1.17
109163	3010003L21Rik	CDK8-induced	1.00E-03	1.30
353258	Ltv1	CDK8-induced	1.01E-03	1.28
269113	Nup54	CDK8-induced	1.01E-03	1.44
18041	Nfs1	CDK8-induced	1.01E-03	1.11
110147	Ehmt2	CDK8-induced	1.01E-03	1.18
67618	Aasdhppt	CDK8-induced	1.03E-03	1.15
353170	4932441K18Rik	CDK8-induced	1.03E-03	1.38

26876	Adh4	CDK8-induced	1.03E-03	1.58
319594	Hif1an	CDK8-induced	1.04E-03	1.27
233552	Gdpd5	CDK8-induced	1.05E-03	1.29
106931	Kctd1	CDK8-induced	1.05E-03	1.25
22680	Zfp207	CDK8-induced	1.05E-03	1.19
226101	Fer1l3	CDK8-induced	1.05E-03	1.21
217431	Nol10	CDK8-induced	1.07E-03	1.37
18158	Nppb	CDK8-induced	1.07E-03	1.29
11981	Atp9a	CDK8-induced	1.07E-03	1.29
65969	Cubn	CDK8-induced	1.07E-03	3.20
67588	Rnf41	CDK8-induced	1.08E-03	1.14
94061	Mrpl1	CDK8-induced	1.10E-03	1.25
18596	Pdgfrb	CDK8-induced	1.10E-03	1.60
11544	Adprh	CDK8-induced	1.10E-03	1.10
71679	Atp5h	CDK8-induced	1.10E-03	1.10
110532	Adarb1	CDK8-induced	1.10E-03	2.24
68002	1110058L19Rik	CDK8-induced	1.11E-03	1.16
18158	Nppb	CDK8-induced	1.11E-03	1.42
69606	Mtfmt	CDK8-induced	1.11E-03	1.30
57816	Tesc	CDK8-induced	1.12E-03	1.33
72568	Lin9	CDK8-induced	1.12E-03	1.10
240753	Plekha6	CDK8-induced	1.13E-03	1.23
211253	Mtrf1	CDK8-induced	1.13E-03	1.20
12445	Ccnd3	CDK8-induced	1.14E-03	1.32
74201	Lrriq2	CDK8-induced	1.14E-03	1.38
72508	Rps6kb1	CDK8-induced	1.14E-03	1.32
78581	D530033C11Rik	CDK8-induced	1.16E-03	1.18
210146	Irgq	CDK8-induced	1.16E-03	1.10
13639	Efna4	CDK8-induced	1.18E-03	1.28
66493	Mrpl51	CDK8-induced	1.19E-03	1.13
67480	Ccdc49	CDK8-induced	1.19E-03	1.28
67881	1810034K20Rik	CDK8-induced	1.19E-03	1.18
78781	Zc3hav1	CDK8-induced	1.20E-03	1.42
228765	Sdcbp2	CDK8-induced	1.21E-03	1.36
218275	BC051665	CDK8-induced	1.21E-03	1.38
234733	Ddx19b	CDK8-induced	1.21E-03	1.22
94067	Mrpl43	CDK8-induced	1.22E-03	1.09
74136	Sec14l1	CDK8-induced	1.23E-03	1.18
110611	Hdlbp	CDK8-induced	1.23E-03	1.14
50868	Keap1	CDK8-induced	1.24E-03	1.25
50850	Spast	CDK8-induced	1.24E-03	1.20
53414	Bysl	CDK8-induced	1.24E-03	1.10
268490	2600001B17Rik	CDK8-induced	1.24E-03	1.20
433004	B830017H08Rik	CDK8-induced	1.24E-03	1.61
77049	4921528I07Rik	CDK8-induced	1.25E-03	1.88
278279	Tmtc2	CDK8-induced	1.25E-03	1.27
56427	Tubd1	CDK8-induced	1.25E-03	1.19
75767	Rab11fip1	CDK8-induced	1.27E-03	1.10
242642	Gloxd1	CDK8-induced	1.27E-03	1.25
258748	Olfr1195	CDK8-induced	1.29E-03	1.29
22654	Zfp13	CDK8-induced	1.29E-03	1.09
50527	Ero1l	CDK8-induced	1.29E-03	1.28
435336	LOC435336	CDK8-induced	1.30E-03	1.19
69582	Plekhm2	CDK8-induced	1.30E-03	1.31
67681	Mrpl18	CDK8-induced	1.31E-03	1.16
76223	Agbl3	CDK8-induced	1.31E-03	1.20
101540	Prkd2	CDK8-induced	1.32E-03	1.22
75600	Calml4	CDK8-induced	1.32E-03	1.54
76073	Pcgf5	CDK8-induced	1.33E-03	1.17

66356	2310008H09Rik	CDK8-induced	1.34E-03	1.13
74302	Mtmr3	CDK8-induced	1.34E-03	1.14
619605	Zcchc17	CDK8-induced	1.34E-03	1.23
226026	Smc5	CDK8-induced	1.35E-03	1.26
381605	Tbc1d2	CDK8-induced	1.35E-03	1.20
23830	Capn10	CDK8-induced	1.35E-03	1.21
17904	Myl6	CDK8-induced	1.35E-03	1.15
68090	Yif1a	CDK8-induced	1.35E-03	1.22
22661	Zfp148	CDK8-induced	1.38E-03	1.14
16857	Lgals6	CDK8-induced	1.38E-03	1.41
73167	3110043J09Rik	CDK8-induced	1.38E-03	1.16
209225	Zfp710	CDK8-induced	1.38E-03	1.16
14958	H1f0	CDK8-induced	1.39E-03	1.42
20692	Sparc	CDK8-induced	1.39E-03	1.37
54632	Ftsj1	CDK8-induced	1.39E-03	1.20
329003	Zfp516	CDK8-induced	1.41E-03	1.18
27392	Pign	CDK8-induced	1.42E-03	1.18
19244	Ptp4a2	CDK8-induced	1.42E-03	1.19
16162	Il12rb2	CDK8-induced	1.42E-03	1.84
17762	Mapt	CDK8-induced	1.42E-03	1.27
18004	Nek1	CDK8-induced	1.42E-03	1.40
22343	Lin7c	CDK8-induced	1.43E-03	1.18
55944	Eif3s7	CDK8-induced	1.43E-03	1.13
319475	Zfp672	CDK8-induced	1.43E-03	1.44
76894	Mett5d1	CDK8-induced	1.43E-03	1.16
66585	Wdr57	CDK8-induced	1.43E-03	1.13
20439	Siah2	CDK8-induced	1.43E-03	1.18
73385	1700047I17Rik	CDK8-induced	1.44E-03	1.36
74150	Slc35f5	CDK8-induced	1.44E-03	1.14
57750	Wdr12	CDK8-induced	1.44E-03	1.27
268749	Rnf31	CDK8-induced	1.45E-03	1.11
66642	Ctnnbl1	CDK8-induced	1.46E-03	1.13
27381	Tcl1b2	CDK8-induced	1.47E-03	1.14
666060	Frmpd1	CDK8-induced	1.47E-03	1.36
66395	Ahnak	CDK8-induced	1.48E-03	1.39
114673	4930433N12Rik	CDK8-induced	1.48E-03	2.35
83409	Mapbpip	CDK8-induced	1.49E-03	1.14
75796	Cdyl2	CDK8-induced	1.49E-03	1.36
17907	Mylpf	CDK8-induced	1.50E-03	1.29
237422	Ric8b	CDK8-induced	1.51E-03	1.25
24071	Synj2bp	CDK8-induced	1.51E-03	1.12
14745	Edg2	CDK8-induced	1.52E-03	1.49
330474	BC057627	CDK8-induced	1.53E-03	1.10
68190	5330426P16Rik	CDK8-induced	1.53E-03	1.26
66242	Mrps16	CDK8-induced	1.55E-03	1.13
230073	Ddx58	CDK8-induced	1.55E-03	1.55
69179	Tmem110	CDK8-induced	1.55E-03	1.18
319710	Frmd6	CDK8-induced	1.56E-03	1.24
108954	Ppp1r15b	CDK8-induced	1.56E-03	1.24
99371	Arfgef2	CDK8-induced	1.57E-03	1.18
11539	Adora1	CDK8-induced	1.57E-03	1.35
76246	Rtf1	CDK8-induced	1.58E-03	1.10
56217	Mpp5	CDK8-induced	1.59E-03	1.10
81879	Tcfcp2l1	CDK8-induced	1.59E-03	1.41
232339	Ankrd26	CDK8-induced	1.60E-03	1.38
269113	Nup54	CDK8-induced	1.61E-03	1.32
231510	A230097K15Rik	CDK8-induced	1.62E-03	1.45
56444	Actr10	CDK8-induced	1.62E-03	1.09
67574	Glt28d1	CDK8-induced	1.63E-03	1.20

17919	Myo5b	CDK8-induced	1.63E-03	1.39
52713	Ccdc59	CDK8-induced	1.64E-03	1.21
68966	1500001L15Rik	CDK8-induced	1.64E-03	1.11
68017	Ftsj2	CDK8-induced	1.64E-03	1.28
28146	D3Ucla1	CDK8-induced	1.66E-03	1.20
22680	Zfp207	CDK8-induced	1.66E-03	1.20
64659	Mrps14	CDK8-induced	1.67E-03	1.18
56284	Mrpl19	CDK8-induced	1.68E-03	1.14
54608	Abhd2	CDK8-induced	1.68E-03	1.36
53886	Cdkl2	CDK8-induced	1.69E-03	1.26
71011	4933401B06Rik	CDK8-induced	1.70E-03	1.21
72828	2810457I06Rik	CDK8-induced	1.71E-03	1.74
229007	Zgpat	CDK8-induced	1.71E-03	1.18
11475	Acta2	CDK8-induced	1.72E-03	1.44
50766	Crim1	CDK8-induced	1.72E-03	1.40
52398	11-Sep	CDK8-induced	1.73E-03	1.16
18141	Nup50	CDK8-induced	1.75E-03	1.17
26932	Ppp2r5e	CDK8-induced	1.75E-03	1.26
66070	0610040D20Rik	CDK8-induced	1.76E-03	1.10
73945	Otud4	CDK8-induced	1.76E-03	1.15
67912	1600012H06Rik	CDK8-induced	1.78E-03	1.11
546077	LOC546077	CDK8-induced	1.78E-03	1.16
66667	Hspbap1	CDK8-induced	1.78E-03	1.19
268465	Eme1	CDK8-induced	1.78E-03	1.13
240641	Mphosph1	CDK8-induced	1.78E-03	1.12
106021	Topors	CDK8-induced	1.78E-03	1.20
59044	Rnf130	CDK8-induced	1.80E-03	1.08
56405	Dusp14	CDK8-induced	1.80E-03	1.40
270192	Rab6b	CDK8-induced	1.81E-03	1.35
57260	Ltb4r2	CDK8-induced	1.82E-03	1.24
68493	1110007M04Rik	CDK8-induced	1.82E-03	1.09
18020	Nfatc2ip	CDK8-induced	1.84E-03	1.17
74107	Cep55	CDK8-induced	1.84E-03	1.24
67973	Mphosph10	CDK8-induced	1.85E-03	1.26
64010	Sav1	CDK8-induced	1.85E-03	1.20
28077	D13Wsu50e	CDK8-induced	1.85E-03	1.11
75717	Cul5	CDK8-induced	1.86E-03	1.12
433771	2310028O11Rik	CDK8-induced	1.87E-03	1.19
66225	1190005P17Rik	CDK8-induced	1.87E-03	1.20
14841	Gsg2	CDK8-induced	1.87E-03	1.20
109331	Rnf20	CDK8-induced	1.89E-03	1.58
77011	5730590G19Rik	CDK8-induced	1.90E-03	1.18
22320	Vamp8	CDK8-induced	1.91E-03	1.22
12797	Cnn1	CDK8-induced	1.91E-03	1.35
11781	Ap4m1	CDK8-induced	1.91E-03	1.19
66395	Ahnak	CDK8-induced	1.91E-03	1.25
14120	Fbp2	CDK8-induced	1.92E-03	2.77
231130	Tnip2	CDK8-induced	1.93E-03	1.34
73486	1700084J12Rik	CDK8-induced	1.93E-03	1.21
13990	Smarcad1	CDK8-induced	1.94E-03	1.19
67621	2310026E23Rik	CDK8-induced	1.96E-03	1.18
231713	C330023M02Rik	CDK8-induced	1.97E-03	1.16
21825	Thbs1	CDK8-induced	1.97E-03	1.43
22411	Wnt11	CDK8-induced	1.98E-03	1.23
11475	Acta2	CDK8-induced	1.98E-03	2.04
69982	Spink2	CDK8-induced	1.99E-03	1.27
16978	Lrrfip1	CDK8-induced	1.99E-03	1.24
26901	Deb1	CDK8-induced	1.99E-03	1.12
16569	Kif3b	CDK8-induced	2.01E-03	1.17

70678	3021401C12Rik	CDK8-induced	2.02E-03	2.24
14489	Mtpn	CDK8-induced	2.02E-03	1.12
106264	0610012G03Rik	CDK8-induced	2.04E-03	1.15
21339	Taf1a	CDK8-induced	2.04E-03	1.15
94092	Trim16	CDK8-induced	2.05E-03	1.70
17096	Lyn	CDK8-induced	2.05E-03	1.55
99045	Mrps26	CDK8-induced	2.06E-03	1.10
68592	Syf2	CDK8-induced	2.06E-03	1.25
74600	Mrpl47	CDK8-induced	2.07E-03	1.15
108735	Sft2d2	CDK8-induced	2.07E-03	1.34
57741	Noc2l	CDK8-induced	2.08E-03	1.09
22214	Ube2h	CDK8-induced	2.09E-03	1.34
70713	6330416L11Rik	CDK8-induced	2.10E-03	1.39
74414	Polr3c	CDK8-induced	2.11E-03	1.14
68999	Anapc10	CDK8-induced	2.11E-03	1.12
59091	Jph2	CDK8-induced	2.12E-03	1.51
74766	Yipf2	CDK8-induced	2.12E-03	1.22
69464	2300006N05Rik	CDK8-induced	2.14E-03	1.74
64658	Mrps25	CDK8-induced	2.15E-03	1.25
66467	Gtf2h5	CDK8-induced	2.15E-03	1.12
228913	Zfp217	CDK8-induced	2.15E-03	1.46
224833	AI661453	CDK8-induced	2.15E-03	1.18
11898	Ass1	CDK8-induced	2.16E-03	1.17
223881	Rnd1	CDK8-induced	2.17E-03	1.26
99683	Sec24b	CDK8-induced	2.17E-03	1.15
73703	Dppa2	CDK8-induced	2.18E-03	1.39
67890	Ufm1	CDK8-induced	2.18E-03	1.29
102060	Gadd45gip1	CDK8-induced	2.19E-03	1.12
77744	6720463M24Rik	CDK8-induced	2.20E-03	1.14
99480	Dnttip2	CDK8-induced	2.20E-03	1.15
270627	Taf1	CDK8-induced	2.21E-03	1.37
66935	1700023B02Rik	CDK8-induced	2.21E-03	1.22
319166	Hist1h2ae	CDK8-induced	2.21E-03	1.63
67454	1200009F10Rik	CDK8-induced	2.24E-03	1.10
12017	Bag1	CDK8-induced	2.25E-03	1.11
226101	Fer1l3	CDK8-induced	2.25E-03	1.24
74080	Nmnat3	CDK8-induced	2.27E-03	1.36
12345	Capzb	CDK8-induced	2.27E-03	1.18
64164	Ifrg15	CDK8-induced	2.28E-03	1.11
22172	Tyms-ps	CDK8-induced	2.28E-03	1.18
13418	Dnajc1	CDK8-induced	2.30E-03	1.46
70611	Fbxo33	CDK8-induced	2.30E-03	1.18
22158	Tulp3	CDK8-induced	2.30E-03	1.93
106264	0610012G03Rik	CDK8-induced	2.31E-03	1.14
574428	Zmynd15	CDK8-induced	2.31E-03	1.55
68904	Abhd13	CDK8-induced	2.31E-03	1.20
56405	Dusp14	CDK8-induced	2.31E-03	1.41
19258	Ptpn4	CDK8-induced	2.33E-03	1.17
56279	B230317C12Rik	CDK8-induced	2.33E-03	1.30
75590	Dusp9	CDK8-induced	2.34E-03	1.26
66352	Blzf1	CDK8-induced	2.34E-03	1.32
70675	Vcpip1	CDK8-induced	2.34E-03	1.37
98238	Lrrc59	CDK8-induced	2.35E-03	1.10
245190	6430704N06	CDK8-induced	2.35E-03	1.23
81879	Tcfcp2l1	CDK8-induced	2.36E-03	1.35
140781	Myh7	CDK8-induced	2.36E-03	1.49
64292	Ptges	CDK8-induced	2.37E-03	1.73
258512	Olfr530	CDK8-induced	2.38E-03	1.20
28035	Usp39	CDK8-induced	2.39E-03	1.18

12757	Clta	CDK8-induced	2.40E-03	1.14
56299	Fkbpl	CDK8-induced	2.41E-03	1.12
64385	Cyp4f14	CDK8-induced	2.41E-03	2.32
69259	Kctd5	CDK8-induced	2.41E-03	1.16
11992	Auh	CDK8-induced	2.41E-03	1.31
319371	D030028A08Rik	CDK8-induced	2.42E-03	1.83
71974	Prmt3	CDK8-induced	2.42E-03	1.18
77371	Sec24a	CDK8-induced	2.43E-03	1.40
74268	Aven	CDK8-induced	2.43E-03	1.26
108841	Rdh13	CDK8-induced	2.43E-03	1.24
74202	Fblim1	CDK8-induced	2.43E-03	1.30
66126	Elof1	CDK8-induced	2.43E-03	1.13
53356	Eif3s4	CDK8-induced	2.44E-03	1.15
17117	Amacr	CDK8-induced	2.44E-03	1.07
215051	Bud13	CDK8-induced	2.44E-03	1.15
232146	BC014699	CDK8-induced	2.45E-03	1.79
12263	C2	CDK8-induced	2.45E-03	1.30
11637	Ak2	CDK8-induced	2.45E-03	1.25
628882	LOC628882	CDK8-induced	2.46E-03	1.11
231252	Chrna9	CDK8-induced	2.46E-03	2.13
231440	9130213B05Rik	CDK8-induced	2.46E-03	1.25
68118	9430023L20Rik	CDK8-induced	2.47E-03	1.20
109232	Sccpdh	CDK8-induced	2.48E-03	1.22
238317	C130039O16Rik	CDK8-induced	2.48E-03	1.23
213326	Scyl2	CDK8-induced	2.48E-03	1.19
20851	Stat5b	CDK8-induced	2.50E-03	1.55
17765	Mtf2	CDK8-induced	2.52E-03	1.25
320718	Slc26a9	CDK8-induced	2.53E-03	1.67
68695	Hddc3	CDK8-induced	2.53E-03	1.41
140477	Dmbx1	CDK8-induced	2.54E-03	1.50
107732	Mrpl10	CDK8-induced	2.56E-03	1.10
225341	Lims2	CDK8-induced	2.58E-03	1.57
56403	Syncrip	CDK8-induced	2.59E-03	1.13
235315	D130054N24Rik	CDK8-induced	2.59E-03	1.23
18740	Pitx1	CDK8-induced	2.59E-03	1.80
14976	H2-Ke2	CDK8-induced	2.60E-03	1.12
16649	Kpna4	CDK8-induced	2.60E-03	1.50
67273	Ndufa10	CDK8-induced	2.60E-03	1.10
225518	Gm92	CDK8-induced	2.61E-03	1.42
17979	Ncoa3	CDK8-induced	2.61E-03	1.26
67075	2610529C04Rik	CDK8-induced	2.62E-03	1.27
67958	2610101N10Rik	CDK8-induced	2.62E-03	1.13
81702	Ankrd17	CDK8-induced	2.64E-03	1.24
11491	Adam17	CDK8-induced	2.65E-03	1.19
94181	Nans	CDK8-induced	2.66E-03	1.15
67290	3110040N11Rik	CDK8-induced	2.66E-03	1.17
230967	BC046331	CDK8-induced	2.66E-03	1.34
68041	Mid1ip1	CDK8-repressed	5.13E-08	1.39
78339	Ttyh3	CDK8-repressed	1.83E-07	1.29
16842	Lef1	CDK8-repressed	3.01E-07	1.67
23965	Odz3	CDK8-repressed	4.09E-07	1.38
320145	Sp8	CDK8-repressed	6.66E-07	2.78
76582	Ipo11	CDK8-repressed	7.76E-07	1.30
16362	Irf1	CDK8-repressed	9.49E-07	1.41
18115	Nnt	CDK8-repressed	1.10E-06	1.55
12794	Cnih2	CDK8-repressed	1.52E-06	1.39
18741	Pitx2	CDK8-repressed	1.54E-06	2.77
12055	Bcl7c	CDK8-repressed	1.54E-06	1.45

56403	Syncrip	CDK8-repressed	1.69E-06	1.30
104418	Dgkz	CDK8-repressed	1.71E-06	1.21
13004	Cspg3	CDK8-repressed	1.72E-06	1.58
64209	Herpud1	CDK8-repressed	1.81E-06	1.76
209446	Tcfe3	CDK8-repressed	2.39E-06	1.35
14025	Bcl11a	CDK8-repressed	2.52E-06	2.79
76055	Mgea5	CDK8-repressed	2.58E-06	1.31
11735	Ank3	CDK8-repressed	3.21E-06	1.45
78885	Coro7	CDK8-repressed	3.22E-06	1.23
20741	Spnb1	CDK8-repressed	3.39E-06	1.69
22142	Tuba1	CDK8-repressed	3.90E-06	1.33
14088	Fancc	CDK8-repressed	3.91E-06	1.14
170770	Bbc3	CDK8-repressed	4.02E-06	1.27
19191	Psme2b-ps	CDK8-repressed	4.17E-06	1.28
14025	Bcl11a	CDK8-repressed	4.40E-06	2.06
15944	Irgm	CDK8-repressed	5.80E-06	1.57
70974	Pgm2l1	CDK8-repressed	5.89E-06	1.35
54367	Zfp326	CDK8-repressed	5.90E-06	1.23
18803	Plcg1	CDK8-repressed	6.11E-06	1.29
232288	Frmd4b	CDK8-repressed	6.32E-06	1.89
20168	Rtn3	CDK8-repressed	7.14E-06	1.35
69683	2310044H10Rik	CDK8-repressed	8.10E-06	1.31
73047	Camk2n2	CDK8-repressed	8.27E-06	1.33
14664	Slc6a9	CDK8-repressed	8.46E-06	1.45
110006	Gusb	CDK8-repressed	9.24E-06	1.16
67030	Fancl	CDK8-repressed	9.55E-06	1.27
80743	Vps16	CDK8-repressed	1.01E-05	1.15
13527	Dtna	CDK8-repressed	1.04E-05	1.71
329540	8430427H17Rik	CDK8-repressed	1.20E-05	2.07
226154	Lzts2	CDK8-repressed	1.20E-05	1.33
22431	Wt1	CDK8-repressed	1.21E-05	1.75
50790	Acsl4	CDK8-repressed	1.22E-05	1.35
13424	Dync1h1	CDK8-repressed	1.27E-05	1.35
77048	4921537D05Rik	CDK8-repressed	1.29E-05	1.22
54135	Lsr	CDK8-repressed	1.43E-05	1.17
53761	Bat2	CDK8-repressed	1.53E-05	1.05
20975	Synj2	CDK8-repressed	1.65E-05	1.46
14897	Trip12	CDK8-repressed	1.66E-05	1.20
67803	Limd2	CDK8-repressed	1.82E-05	1.49
83925	Trps1	CDK8-repressed	1.83E-05	1.28
94190	Ophn1	CDK8-repressed	1.84E-05	1.33
99633	Lphn2	CDK8-repressed	1.86E-05	1.25
80898	Arts1	CDK8-repressed	1.87E-05	1.85
225995	D030056L22Rik	CDK8-repressed	1.96E-05	1.22
19025	Ppgb	CDK8-repressed	1.97E-05	1.19
235472	Prtg	CDK8-repressed	2.04E-05	1.31
219189	1300010F03Rik	CDK8-repressed	2.23E-05	1.29
100620	AI413194	CDK8-repressed	2.31E-05	1.32
13197	Gadd45a	CDK8-repressed	2.33E-05	1.38
76901	Phf15	CDK8-repressed	2.34E-05	1.55
20522	Slc23a1	CDK8-repressed	2.48E-05	2.44
13836	Epha2	CDK8-repressed	2.50E-05	1.30
66822	Fbxo25	CDK8-repressed	2.56E-05	1.06
269700	AU042671	CDK8-repressed	2.57E-05	1.23
54126	Arhgef7	CDK8-repressed	2.59E-05	1.34
14870	Gstp1	CDK8-repressed	2.60E-05	1.21
16593	Kns2	CDK8-repressed	2.64E-05	1.32
78248	Armcx1	CDK8-repressed	2.64E-05	1.38
69870	Polr3gl	CDK8-repressed	2.66E-05	1.47

70408	Polr3f	CDK8-repressed	2.68E-05	2.39
66725	Lrrk2	CDK8-repressed	2.70E-05	1.51
67111	Asahl	CDK8-repressed	2.71E-05	1.32
83679	Pde4dip	CDK8-repressed	2.75E-05	1.34
59026	Huwe1	CDK8-repressed	2.76E-05	1.31
56195	Ptbp2	CDK8-repressed	2.89E-05	1.62
110350	Dync2h1	CDK8-repressed	2.97E-05	1.29
66272	1810020G14Rik	CDK8-repressed	2.97E-05	1.24
71375	Ches1	CDK8-repressed	3.03E-05	1.37
94176	Dock2	CDK8-repressed	3.06E-05	1.58
54353	Scap2	CDK8-repressed	3.07E-05	1.24
78266	Zfp687	CDK8-repressed	3.12E-05	1.20
619750	LOC619750	CDK8-repressed	3.17E-05	1.27
107503	Atf5	CDK8-repressed	3.21E-05	1.20
229599	Gm129	CDK8-repressed	3.21E-05	1.29
101563	Al426330	CDK8-repressed	3.23E-05	1.53
72519	Tmem55a	CDK8-repressed	3.27E-05	1.40
11782	Ap4s1	CDK8-repressed	3.28E-05	1.24
20775	Sqle	CDK8-repressed	3.48E-05	1.31
66880	Rsrc1	CDK8-repressed	3.52E-05	1.37
270685	Mthfd1l	CDK8-repressed	3.58E-05	1.27
53310	Dlgh3	CDK8-repressed	3.58E-05	1.14
217666	L2hgdh	CDK8-repressed	3.75E-05	1.35
83997	Slmap	CDK8-repressed	3.84E-05	1.21
210766	Brcc3	CDK8-repressed	3.89E-05	1.72
434166	LOC434166	CDK8-repressed	3.94E-05	1.65
320895	C030025P15Rik	CDK8-repressed	4.00E-05	1.31
72416	Lrpprc	CDK8-repressed	4.01E-05	1.15
100986	Akap9	CDK8-repressed	4.02E-05	1.29
26422	Nbea	CDK8-repressed	4.15E-05	1.79
234258	Neil3	CDK8-repressed	4.30E-05	1.48
15944	Irgm	CDK8-repressed	4.37E-05	1.55
78887	Sfi1	CDK8-repressed	4.41E-05	1.55
244579	Tnrc9	CDK8-repressed	4.56E-05	2.25
245670	Rragb	CDK8-repressed	4.75E-05	1.79
58172	Sertad2	CDK8-repressed	4.88E-05	1.30
69478	2300009A05Rik	CDK8-repressed	4.95E-05	1.18
19025	Ppgb	CDK8-repressed	5.05E-05	1.22
109910	Zfp91	CDK8-repressed	5.16E-05	1.43
19652	Rbm3	CDK8-repressed	5.18E-05	1.33
236511	Eif2c1	CDK8-repressed	5.22E-05	1.53
329540	8430427H17Rik	CDK8-repressed	5.45E-05	1.26
268515	Bahcc1	CDK8-repressed	5.63E-05	1.26
22343	Lin7c	CDK8-repressed	5.84E-05	1.37
20522	Slc23a1	CDK8-repressed	5.86E-05	3.56
14469	Gbp2	CDK8-repressed	5.94E-05	1.71
14050	Eya3	CDK8-repressed	6.01E-05	1.29
19191	Psme2b-ps	CDK8-repressed	6.06E-05	1.29
19272	Ptprk	CDK8-repressed	6.36E-05	1.27
18115	Nnt	CDK8-repressed	6.46E-05	1.55
209497	Tmem164	CDK8-repressed	6.60E-05	1.49
100986	Akap9	CDK8-repressed	6.68E-05	1.32
170677	Pcdh21	CDK8-repressed	6.82E-05	1.73
18823	Plp1	CDK8-repressed	6.96E-05	1.66
244745	Dpy19l1	CDK8-repressed	7.00E-05	1.30
16561	Kif1b	CDK8-repressed	7.15E-05	1.21
74996	Usp47	CDK8-repressed	7.19E-05	1.18
67115	Rpl14	CDK8-repressed	7.25E-05	1.16
23962	Oasl2	CDK8-repressed	7.30E-05	2.38

20975	Synj2	CDK8-repressed	7.37E-05	1.33
74256	Cyld	CDK8-repressed	7.42E-05	1.43
66976	2410002F23Rik	CDK8-repressed	7.49E-05	1.25
207521	Dtx4	CDK8-repressed	7.58E-05	1.89
207521	Dtx4	CDK8-repressed	7.64E-05	1.77
17319	Mif	CDK8-repressed	7.76E-05	1.19
14864	Gstm3	CDK8-repressed	7.94E-05	1.37
101476	Plekha1	CDK8-repressed	8.04E-05	1.20
208618	BC026657	CDK8-repressed	8.12E-05	1.23
14758	Gpm6b	CDK8-repressed	8.14E-05	1.51
277333	MGC68323	CDK8-repressed	8.20E-05	1.14
66880	Rsrc1	CDK8-repressed	8.32E-05	1.35
171207	Arhgap4	CDK8-repressed	8.37E-05	1.24
67095	Trak1	CDK8-repressed	8.68E-05	1.25
18115	Nnt	CDK8-repressed	8.70E-05	1.48
58246	Slc35b4	CDK8-repressed	8.82E-05	1.19
21827	Thbs3	CDK8-repressed	9.04E-05	1.53
238799	Tnpo1	CDK8-repressed	9.21E-05	1.24
13196	Ddef1	CDK8-repressed	9.38E-05	1.18
67306	3110050N22Rik	CDK8-repressed	9.42E-05	1.23
50524	Sall2	CDK8-repressed	9.54E-05	2.28
59092	Pcbp4	CDK8-repressed	9.64E-05	1.21
57265	Fzd2	CDK8-repressed	9.70E-05	1.42
20451	St8sia3	CDK8-repressed	1.00E-04	2.21
100504048	LOC100504048	CDK8-repressed	1.02E-04	1.55
241062	D230012E17Rik	CDK8-repressed	1.04E-04	1.36
237775	BC050078	CDK8-repressed	1.04E-04	1.25
71779	8-Mar	CDK8-repressed	1.05E-04	1.24
110265	Msra	CDK8-repressed	1.08E-04	1.22
14468	Gbp1	CDK8-repressed	1.09E-04	2.02
108138	Xrcc4	CDK8-repressed	1.09E-04	1.33
26897	Acot1	CDK8-repressed	1.09E-04	1.28
17909	Myo10	CDK8-repressed	1.10E-04	1.28
55932	Gbp4	CDK8-repressed	1.12E-04	1.91
17309	Mgat3	CDK8-repressed	1.12E-04	1.16
59079	Erbb2ip	CDK8-repressed	1.13E-04	1.25
19056	Ppp3cb	CDK8-repressed	1.14E-04	1.19
20901	Strap	CDK8-repressed	1.16E-04	1.25
20937	Suv39h1	CDK8-repressed	1.22E-04	1.27
16008	Igfbp2	CDK8-repressed	1.23E-04	1.31
77980	Sbf1	CDK8-repressed	1.24E-04	1.17
230753	Thrap3	CDK8-repressed	1.25E-04	1.21
77963	Hook1	CDK8-repressed	1.26E-04	1.87
20317	Serpinf1	CDK8-repressed	1.27E-04	1.59
18574	Pde1b	CDK8-repressed	1.27E-04	1.38
21417	Zfhx1a	CDK8-repressed	1.30E-04	1.28
70021	Nt5dc2	CDK8-repressed	1.35E-04	1.26
215748	Cnksr3	CDK8-repressed	1.36E-04	1.27
14862	Gstm1	CDK8-repressed	1.40E-04	1.46
19280	Ptprs	CDK8-repressed	1.47E-04	1.17
230721	Pabpc4	CDK8-repressed	1.49E-04	1.16
72722	2810405J04Rik	CDK8-repressed	1.53E-04	1.15
69051	Pycr2	CDK8-repressed	1.55E-04	1.17
71306	Mfap3l	CDK8-repressed	1.60E-04	1.60
56741	Nope	CDK8-repressed	1.60E-04	1.83
75430	3200002M19Rik	CDK8-repressed	1.64E-04	1.13
18129	Notch2	CDK8-repressed	1.67E-04	1.23
102910	AI448196	CDK8-repressed	1.69E-04	1.51
140740	Sec63	CDK8-repressed	1.69E-04	1.47

237877	C130052G03Rik	CDK8-repressed	1.69E-04	1.19
71703	Armcx3	CDK8-repressed	1.71E-04	1.75
27223	Trp53bp1	CDK8-repressed	1.72E-04	1.29
106585	Ankrd12	CDK8-repressed	1.72E-04	1.26
270163	Myo9a	CDK8-repressed	1.73E-04	2.53
207521	Dtx4	CDK8-repressed	1.78E-04	1.69
20319	Sfrp2	CDK8-repressed	1.78E-04	1.50
71974	Prmt3	CDK8-repressed	1.80E-04	1.18
104248	Cabin1	CDK8-repressed	1.83E-04	1.14
17967	Ncam1	CDK8-repressed	1.88E-04	1.24
72668	2810030E01Rik	CDK8-repressed	1.89E-04	2.01
67629	Spbc24	CDK8-repressed	1.89E-04	1.18
233204	Tbc1d17	CDK8-repressed	1.90E-04	1.23
140488	Igf2bp3	CDK8-repressed	1.91E-04	1.60
217734	Pomt2	CDK8-repressed	1.92E-04	1.27
670106	LOC670106	CDK8-repressed	1.98E-04	1.23
216440	4632413K17Rik	CDK8-repressed	2.00E-04	1.26
13356	Dgcr2	CDK8-repressed	2.03E-04	1.13
66179	1110031I02Rik	CDK8-repressed	2.05E-04	1.18
78330	1500032D16Rik	CDK8-repressed	2.07E-04	1.16
228880	Prkcbp1	CDK8-repressed	2.08E-04	1.15
14151	Fech	CDK8-repressed	2.09E-04	1.14
116870	Mta1	CDK8-repressed	2.11E-04	1.20
19272	Ptprk	CDK8-repressed	2.11E-04	1.41
16913	Psmb8	CDK8-repressed	2.13E-04	1.94
19094	Mapk11	CDK8-repressed	2.13E-04	1.27
11632	Aip	CDK8-repressed	2.17E-04	1.20
170742	Sertad3	CDK8-repressed	2.17E-04	1.15
20947	Swap70	CDK8-repressed	2.18E-04	1.26
233913	BC017158	CDK8-repressed	2.19E-04	1.19
13518	Dst	CDK8-repressed	2.23E-04	1.24
232664	4921511K06Rik	CDK8-repressed	2.24E-04	1.42
98386	Lbr	CDK8-repressed	2.24E-04	1.18
320508	Cachd1	CDK8-repressed	2.25E-04	1.98
65973	Asph	CDK8-repressed	2.25E-04	1.29
17748	Mt1	CDK8-repressed	2.29E-04	1.23
227693	Zyg11bl	CDK8-repressed	2.29E-04	1.48
320472	Ppm1e	CDK8-repressed	2.32E-04	1.91
56392	Shoc2	CDK8-repressed	2.32E-04	1.22
22359	Vldlr	CDK8-repressed	2.32E-04	1.42
13642	Efnb2	CDK8-repressed	2.33E-04	1.65
239273	Abcc4	CDK8-repressed	2.34E-04	1.24
57439	1300007B12Rik	CDK8-repressed	2.35E-04	1.36
30963	Ptpla	CDK8-repressed	2.35E-04	1.24
53896	Slc7a10	CDK8-repressed	2.36E-04	2.67
16842	Lef1	CDK8-repressed	2.37E-04	1.61
20788	Srebf2	CDK8-repressed	2.38E-04	1.21
218850	D14Abb1e	CDK8-repressed	2.41E-04	1.21
19186	Psme1	CDK8-repressed	2.43E-04	1.20
106369	Ypel1	CDK8-repressed	2.43E-04	1.19
99061	C130057N11Rik	CDK8-repressed	2.47E-04	1.70
12176	Bnip3	CDK8-repressed	2.53E-04	1.35
246104	Rhbdl3	CDK8-repressed	2.57E-04	1.42
15499	Hsf1	CDK8-repressed	2.62E-04	1.15
20843	Stag2	CDK8-repressed	2.63E-04	1.33
16541	Napsa	CDK8-repressed	2.63E-04	2.04
12488	Cd2ap	CDK8-repressed	2.64E-04	1.13
59046	Arpp19	CDK8-repressed	2.65E-04	1.45
20185	Ncor1	CDK8-repressed	2.66E-04	1.51

22404	Wiz	CDK8-repressed	2.70E-04	1.20
30940	Usp25	CDK8-repressed	2.71E-04	1.51
16562	Kif1c	CDK8-repressed	2.72E-04	1.17
77519	5730601F06Rik	CDK8-repressed	2.77E-04	1.28
14183	Fgfr2	CDK8-repressed	2.80E-04	1.37
14872	Gstt2	CDK8-repressed	2.85E-04	1.51
19376	Rab34	CDK8-repressed	2.85E-04	1.34
12068	Bet1	CDK8-repressed	2.85E-04	1.30
71389	Chd6	CDK8-repressed	2.88E-04	1.32
18606	Enpp2	CDK8-repressed	2.91E-04	2.16
23802	Amfr	CDK8-repressed	2.92E-04	1.21
270163	Myo9a	CDK8-repressed	2.94E-04	1.28
217558	6030408C04Rik	CDK8-repressed	2.96E-04	1.56
216860	0610025P10Rik	CDK8-repressed	2.97E-04	1.23
320827	C530008M17Rik	CDK8-repressed	2.98E-04	1.54
381157	AK220484	CDK8-repressed	3.06E-04	1.37
52874	D19Bwg1357e	CDK8-repressed	3.09E-04	1.26
13512	Dsg3	CDK8-repressed	3.17E-04	1.99
103534	Mgat4b	CDK8-repressed	3.20E-04	1.08
23966	Odz4	CDK8-repressed	3.26E-04	1.24
70377	Derl3	CDK8-repressed	3.32E-04	1.37
26559	Hunk	CDK8-repressed	3.33E-04	1.22
319263	Pcmtd1	CDK8-repressed	3.41E-04	1.23
56291	Styx	CDK8-repressed	3.41E-04	1.26
105670	Rcbtb2	CDK8-repressed	3.44E-04	1.17
18715	Pim2	CDK8-repressed	3.44E-04	1.86
23965	Odz3	CDK8-repressed	3.45E-04	1.56
231798	Lrch4	CDK8-repressed	3.48E-04	1.16
215748	Cnksr3	CDK8-repressed	3.49E-04	1.28
68915	Vars2l	CDK8-repressed	3.51E-04	1.14
78174	4930503B16Rik	CDK8-repressed	3.53E-04	1.44
66771	4933439F18Rik	CDK8-repressed	3.68E-04	1.35
20856	Stc2	CDK8-repressed	3.68E-04	1.43
214505	Gnptg	CDK8-repressed	3.72E-04	2.79
207474	Kctd12b	CDK8-repressed	3.75E-04	1.99
19703	Renbp	CDK8-repressed	3.75E-04	1.17
15382	Hnrpa1	CDK8-repressed	3.76E-04	1.11
109676	Ank2	CDK8-repressed	3.80E-04	1.50
18751	Prkcb1	CDK8-repressed	3.82E-04	1.75
16563	Kif2a	CDK8-repressed	3.84E-04	1.17
381508	LOC381508	CDK8-repressed	3.86E-04	1.46
109880	Braf	CDK8-repressed	3.87E-04	1.30
71148	Mier1	CDK8-repressed	3.90E-04	1.16
320024	Aadacl1	CDK8-repressed	3.91E-04	1.10
235574	Atp2c1	CDK8-repressed	3.92E-04	1.21
105298	Epdr2	CDK8-repressed	3.93E-04	1.55
20843	Stag2	CDK8-repressed	3.95E-04	1.37
99324	D030029J20Rik	CDK8-repressed	3.95E-04	1.28
238130	Dock4	CDK8-repressed	3.96E-04	1.42
105178	AI452195	CDK8-repressed	4.00E-04	1.31
268752	Wdfy2	CDK8-repressed	4.00E-04	1.29
217351	Tnrc6c	CDK8-repressed	4.05E-04	1.17
228790	Asxl1	CDK8-repressed	4.06E-04	1.21
15982	Ifrd1	CDK8-repressed	4.06E-04	1.15
12795	Plk3	CDK8-repressed	4.08E-04	1.18
319683	E230008J23Rik	CDK8-repressed	4.09E-04	1.89
225875	Lrfn4	CDK8-repressed	4.12E-04	1.16
67776	Loh11cr2a	CDK8-repressed	4.15E-04	1.28
235472	Prtg	CDK8-repressed	4.15E-04	1.41

319757	Smo	CDK8-repressed	4.22E-04	1.17
77268	9330180L21Rik	CDK8-repressed	4.22E-04	1.62
26570	Slc7a11	CDK8-repressed	4.23E-04	2.38
58887	Repin1	CDK8-repressed	4.23E-04	1.34
56294	Ptpn9	CDK8-repressed	4.26E-04	1.34
50887	Nsbp1	CDK8-repressed	4.34E-04	1.40
69368	Wdfy1	CDK8-repressed	4.36E-04	1.20
232906	Grlf1	CDK8-repressed	4.37E-04	1.11
20648	Snta1	CDK8-repressed	4.40E-04	1.21
23789	Coro1b	CDK8-repressed	4.52E-04	1.20
11782	Ap4s1	CDK8-repressed	4.56E-04	1.20
270096	Mon1b	CDK8-repressed	4.58E-04	1.19
16438	Itpr1	CDK8-repressed	4.60E-04	1.33
69116	Zubr1	CDK8-repressed	4.63E-04	1.19
20148	Dhrs3	CDK8-repressed	4.64E-04	1.33
100763	Ube3c	CDK8-repressed	4.65E-04	1.27
14536	Nr6a1	CDK8-repressed	4.65E-04	1.29
108645	Mat2b	CDK8-repressed	4.69E-04	1.20
72075	Ogfr	CDK8-repressed	4.75E-04	1.30
26422	Nbea	CDK8-repressed	4.77E-04	1.83
76293	Mfap4	CDK8-repressed	4.78E-04	1.56
105727	Slc38a1	CDK8-repressed	4.78E-04	1.20
109905	Rap1a	CDK8-repressed	4.82E-04	1.13
12009	Azi1	CDK8-repressed	4.84E-04	1.11
67160	Eef1g	CDK8-repressed	4.85E-04	1.27
52910	D16Bwg1543e	CDK8-repressed	4.86E-04	1.44
12297	Cacnb3	CDK8-repressed	4.93E-04	1.48
13388	Dll1	CDK8-repressed	4.96E-04	1.88
16913	Psmb8	CDK8-repressed	4.97E-04	1.75
73181	Nfatc4	CDK8-repressed	5.02E-04	1.28
233912	Armc5	CDK8-repressed	5.05E-04	1.14
29815	Bcar3	CDK8-repressed	5.08E-04	1.27
235323	Usp28	CDK8-repressed	5.08E-04	1.22
14862	Gstm1	CDK8-repressed	5.19E-04	1.47
19063	Ppt1	CDK8-repressed	5.22E-04	1.21
66259	Camk2n1	CDK8-repressed	5.25E-04	2.19
94346	Tmem40	CDK8-repressed	5.26E-04	1.25
69917	Obfc2b	CDK8-repressed	5.29E-04	1.27
16709	Ktn1	CDK8-repressed	5.31E-04	1.20
65105	Arl6ip4	CDK8-repressed	5.32E-04	1.18
18824	Plp2	CDK8-repressed	5.35E-04	1.13
71710	Lrrcc1	CDK8-repressed	5.36E-04	1.70
378954	3000002C10Rik	CDK8-repressed	5.39E-04	1.14
214917	BC008155	CDK8-repressed	5.39E-04	1.17
74143	Opa1	CDK8-repressed	5.44E-04	1.30
71704	Arhgef3	CDK8-repressed	5.54E-04	1.56
20408	Sh3gl3	CDK8-repressed	5.59E-04	1.34
73242	2610110G12Rik	CDK8-repressed	5.63E-04	1.26
72050	Kdelc1	CDK8-repressed	5.68E-04	1.19
76378	Ropn1	CDK8-repressed	5.81E-04	1.50
56307	Metap2	CDK8-repressed	5.82E-04	1.16
20409	Ostf1	CDK8-repressed	5.84E-04	1.21
14182	Fgfr1	CDK8-repressed	5.85E-04	1.22
217198	Plekhh3	CDK8-repressed	5.88E-04	1.25
67795	6530404N21Rik	CDK8-repressed	5.90E-04	1.51
320969	D930050A07Rik	CDK8-repressed	5.95E-04	1.28
78255	Ralgps2	CDK8-repressed	5.96E-04	1.34
66625	5730406M06Rik	CDK8-repressed	5.97E-04	1.37
12361	Cask	CDK8-repressed	5.99E-04	1.25

78833	Gins3	CDK8-repressed	6.00E-04	1.14
54004	Diap2	CDK8-repressed	6.00E-04	1.29
18133	Nov	CDK8-repressed	6.01E-04	2.61
68169	A930038C07Rik	CDK8-repressed	6.04E-04	4.46
66079	Tmem42	CDK8-repressed	6.07E-04	1.18
12564	Cdh8	CDK8-repressed	6.16E-04	2.10
56044	Rala	CDK8-repressed	6.23E-04	1.24
17876	Myef2	CDK8-repressed	6.24E-04	1.29
140577	Ankrd6	CDK8-repressed	6.24E-04	1.50
70394	Kptn	CDK8-repressed	6.25E-04	1.15
104871	Spata7	CDK8-repressed	6.27E-04	1.39
12890	Cplx2	CDK8-repressed	6.28E-04	2.58
19090	Prkdc	CDK8-repressed	6.28E-04	1.35
19934	Rpl22	CDK8-repressed	6.29E-04	1.33
17345	Mki67	CDK8-repressed	6.29E-04	1.25
93840	Vangl2	CDK8-repressed	6.32E-04	1.22
219140	Spata13	CDK8-repressed	6.32E-04	1.51
72844	Kctd17	CDK8-repressed	6.33E-04	1.21
230863	Sh2d5	CDK8-repressed	6.40E-04	1.25
228071	Sestd1	CDK8-repressed	6.41E-04	1.22
72469	Plcd3	CDK8-repressed	6.44E-04	1.31
70951	Spata1	CDK8-repressed	6.45E-04	1.36
84544	Cd96	CDK8-repressed	6.46E-04	1.74
11980	Atp8a1	CDK8-repressed	6.46E-04	1.40
67358	1700093K21Rik	CDK8-repressed	6.53E-04	3.10
57261	Brd4	CDK8-repressed	6.58E-04	1.14
214931	Fbxl16	CDK8-repressed	6.61E-04	1.28
268445	Ankrd13b	CDK8-repressed	6.62E-04	1.26
66235	Eif1ay	CDK8-repressed	6.62E-04	1.14
242291	Impad1	CDK8-repressed	6.63E-04	1.28
214162	Mll1	CDK8-repressed	6.68E-04	1.24
93687	Csnk1a1	CDK8-repressed	6.71E-04	1.23
52004	Cdk2ap2	CDK8-repressed	6.74E-04	1.20
56224	Tspan5	CDK8-repressed	6.79E-04	1.36
74781	Wipi2	CDK8-repressed	6.82E-04	1.15
225028	Map4k3	CDK8-repressed	6.87E-04	1.27
106504	Stk38	CDK8-repressed	6.94E-04	1.23
93747	Echs1	CDK8-repressed	7.02E-04	1.18
110350	Dync2h1	CDK8-repressed	7.07E-04	1.29
68480	1110007C09Rik	CDK8-repressed	7.07E-04	1.54
57257	Vav3	CDK8-repressed	7.09E-04	1.20
16987	Lss	CDK8-repressed	7.11E-04	1.35
75613	Med25	CDK8-repressed	7.17E-04	1.16
237082	Nxt2	CDK8-repressed	7.25E-04	1.42
233789	2610207I05Rik	CDK8-repressed	7.29E-04	1.16
50850	Spast	CDK8-repressed	7.30E-04	1.15
22359	Vldlr	CDK8-repressed	7.37E-04	1.55
72515	Wdr43	CDK8-repressed	7.48E-04	1.15
12313	Calm1	CDK8-repressed	7.49E-04	1.56
17534	Mrc2	CDK8-repressed	7.54E-04	1.32
231858	D930005D10Rik	CDK8-repressed	7.56E-04	1.39
53379	Hnrpa2b1	CDK8-repressed	7.58E-04	1.20
107895	Mgat5	CDK8-repressed	7.59E-04	1.31
14025	Bcl11a	CDK8-repressed	7.71E-04	3.62
18521	Pcbp2	CDK8-repressed	7.83E-04	1.13
63985	Gmfb	CDK8-repressed	7.91E-04	1.25
208968	Suhw3	CDK8-repressed	7.95E-04	1.59
544818	LOC544818	CDK8-repressed	8.03E-04	1.59
17686	Msh3	CDK8-repressed	8.05E-04	1.19

668299	LOC668299	CDK8-repressed	8.05E-04	1.11
76969	Chst1	CDK8-repressed	8.08E-04	1.48
66414	Ndufa12	CDK8-repressed	8.08E-04	1.12
227292	Ctdsp1	CDK8-repressed	8.11E-04	1.19
320790	Chd7	CDK8-repressed	8.12E-04	1.53
17966	Nbr1	CDK8-repressed	8.13E-04	1.09
268859	Rbfox1	CDK8-repressed	8.15E-04	2.43
110639	Prps2	CDK8-repressed	8.23E-04	1.20
112407	Egln3	CDK8-repressed	8.25E-04	1.39
66884	Appbp2	CDK8-repressed	8.26E-04	1.27
17428	Mnt	CDK8-repressed	8.39E-04	1.12
52323	Klhl7	CDK8-repressed	8.42E-04	1.37
18128	Notch1	CDK8-repressed	8.43E-04	1.33
72121	Dennd2d	CDK8-repressed	8.52E-04	1.41
140792	Colec12	CDK8-repressed	8.60E-04	1.11
330485	Tmem145	CDK8-repressed	8.62E-04	1.99
72735	2810442I21Rik	CDK8-repressed	8.72E-04	1.45
14755	Pigq	CDK8-repressed	8.73E-04	1.08
72475	Ssbp3	CDK8-repressed	8.73E-04	1.24
20947	Swap70	CDK8-repressed	8.73E-04	1.26
319236	9230105E10Rik	CDK8-repressed	8.77E-04	2.68
12228	Btg3	CDK8-repressed	8.80E-04	1.19
18139	Zfml	CDK8-repressed	8.81E-04	1.17
18508	Pax6	CDK8-repressed	8.83E-04	1.58
15024	H2-T10	CDK8-repressed	8.83E-04	1.19
21848	Trim24	CDK8-repressed	8.93E-04	1.28
56306	Tera	CDK8-repressed	8.96E-04	1.26
14105	Fusip1	CDK8-repressed	8.99E-04	1.31
75731	5133401N09Rik	CDK8-repressed	9.00E-04	1.11
67534	Ttll4	CDK8-repressed	9.02E-04	1.40
228880	Prkcbp1	CDK8-repressed	9.05E-04	1.37
16795	Large	CDK8-repressed	9.05E-04	1.22
72061	2010111I01Rik	CDK8-repressed	9.09E-04	1.25
217463	Snx13	CDK8-repressed	9.10E-04	1.32
13417	Dnahc8	CDK8-repressed	9.13E-04	1.53
75974	Dock11	CDK8-repressed	9.16E-04	1.42
15976	Ifnar2	CDK8-repressed	9.20E-04	1.20
209558	Enpp3	CDK8-repressed	9.27E-04	1.70
71592	Pogk	CDK8-repressed	9.27E-04	1.95
269437	Plch1	CDK8-repressed	9.29E-04	2.03
56013	P140	CDK8-repressed	9.29E-04	1.27
237353	4831416G18Rik	CDK8-repressed	9.30E-04	1.28
224826	Ubr2	CDK8-repressed	9.31E-04	1.16
66272	1810020G14Rik	CDK8-repressed	9.32E-04	1.21
16565	Kif21b	CDK8-repressed	9.33E-04	1.15
140559	Igsf8	CDK8-repressed	9.39E-04	1.27
76927	1700021C14Rik	CDK8-repressed	9.41E-04	1.25
56473	Fads2	CDK8-repressed	9.45E-04	1.17
11757	Prdx3	CDK8-repressed	9.46E-04	1.40
18641	Pfkl	CDK8-repressed	9.50E-04	1.19
18548	Pcsk1	CDK8-repressed	9.51E-04	4.88
15258	Hipk2	CDK8-repressed	9.56E-04	1.20
83453	Chrdl1	CDK8-repressed	9.73E-04	1.71
19699	Reln	CDK8-repressed	9.75E-04	1.31
433667	Ankrd13c	CDK8-repressed	9.77E-04	1.24
229663	Csde1	CDK8-repressed	9.80E-04	1.11
74154	Unkl	CDK8-repressed	9.87E-04	1.11
19363	Rad51l1	CDK8-repressed	9.91E-04	1.23
56531	Ylpm1	CDK8-repressed	9.95E-04	1.16

53901	Dscr1l1	CDK8-repressed	9.95E-04	1.37
17775	Laptm4a	CDK8-repressed	1.01E-03	1.07
114128	Laptm4b	CDK8-repressed	1.01E-03	1.25
21968	Tom1	CDK8-repressed	1.01E-03	1.17
77480	C330002I19Rik	CDK8-repressed	1.02E-03	1.25
71458	Bcor	CDK8-repressed	1.02E-03	1.27
229473	D930015E06Rik	CDK8-repressed	1.03E-03	1.38
58800	Trpm7	CDK8-repressed	1.03E-03	1.29
14421	B4galnt1	CDK8-repressed	1.05E-03	1.23
215748	Cnksr3	CDK8-repressed	1.05E-03	1.28
225115	Svil	CDK8-repressed	1.06E-03	1.18
73251	Setd7	CDK8-repressed	1.06E-03	1.22
14571	Gpd2	CDK8-repressed	1.07E-03	1.24
59020	Pdzk1	CDK8-repressed	1.07E-03	1.87
17181	Matn2	CDK8-repressed	1.08E-03	1.73
94332	Igsf4b	CDK8-repressed	1.09E-03	1.25
70797	Ankib1	CDK8-repressed	1.09E-03	1.15
414077	BC056474	CDK8-repressed	1.09E-03	1.24
547176	Zc3h12b	CDK8-repressed	1.10E-03	2.77
67109	2210018M03Rik	CDK8-repressed	1.10E-03	1.38
207777	Bzrap1	CDK8-repressed	1.11E-03	1.27
30935	Tor3a	CDK8-repressed	1.11E-03	1.25
319974	Auts2	CDK8-repressed	1.12E-03	1.37
67392	4833420G17Rik	CDK8-repressed	1.12E-03	2.53
19108	Prkx	CDK8-repressed	1.12E-03	1.19
77733	Rnf170	CDK8-repressed	1.13E-03	1.47
230809	Pdik1l	CDK8-repressed	1.13E-03	1.29
629974	D11Ertd759e	CDK8-repressed	1.13E-03	1.77
17069	Ly6e	CDK8-repressed	1.13E-03	1.24
73296	Rhobtb3	CDK8-repressed	1.14E-03	1.47
71750	R3hdm2	CDK8-repressed	1.14E-03	1.27
20451	St8sia3	CDK8-repressed	1.15E-03	2.31
224640	Lemd2	CDK8-repressed	1.15E-03	1.19
75974	Dock11	CDK8-repressed	1.15E-03	1.36
71448	Tmem80	CDK8-repressed	1.16E-03	1.34
28193	D10Ucla1	CDK8-repressed	1.16E-03	1.29
269473	Lrig2	CDK8-repressed	1.17E-03	1.34
19046	Ppp1cb	CDK8-repressed	1.17E-03	1.14
98415	Nucks1	CDK8-repressed	1.18E-03	1.14
14348	Fut9	CDK8-repressed	1.18E-03	1.80
106338	Nsun3	CDK8-repressed	1.19E-03	1.21
76809	Bri3bp	CDK8-repressed	1.19E-03	1.27
50926	Hnrpdl	CDK8-repressed	1.20E-03	1.24
105689	Phr1	CDK8-repressed	1.20E-03	1.30
107515	Lgr4	CDK8-repressed	1.21E-03	1.28
329908	Usp24	CDK8-repressed	1.22E-03	1.27
71461	Ptk7	CDK8-repressed	1.24E-03	1.36
234779	Plcg2	CDK8-repressed	1.24E-03	1.36
72238	Tbc1d5	CDK8-repressed	1.24E-03	1.14
20379	Sfrp4	CDK8-repressed	1.25E-03	1.39
66826	Taz	CDK8-repressed	1.25E-03	1.23
66990	Tmem134	CDK8-repressed	1.26E-03	1.15
209737	Kif15	CDK8-repressed	1.27E-03	1.27
109075	Exosc4	CDK8-repressed	1.27E-03	1.36
22042	Tfrc	CDK8-repressed	1.27E-03	1.14
239393	Lrp12	CDK8-repressed	1.28E-03	1.18
14871	Gstt1	CDK8-repressed	1.29E-03	1.19
546001	D030022P06Rik	CDK8-repressed	1.30E-03	2.13
18762	Prkcz	CDK8-repressed	1.31E-03	1.29

17281	Fyco1	CDK8-repressed	1.31E-03	1.47
74754	Dhcr24	CDK8-repressed	1.32E-03	1.15
20666	Sox11	CDK8-repressed	1.32E-03	1.26
117146	Ube3b	CDK8-repressed	1.32E-03	1.09
64652	Nisch	CDK8-repressed	1.33E-03	1.20
22240	Dpysl3	CDK8-repressed	1.33E-03	1.19
74596	Cds1	CDK8-repressed	1.34E-03	2.59
224020	Pik4ca	CDK8-repressed	1.35E-03	1.22
68813	Dock5	CDK8-repressed	1.35E-03	1.18
277360	BC067047	CDK8-repressed	1.35E-03	1.25
233065	Alkbh6	CDK8-repressed	1.36E-03	1.16
21847	Klf10	CDK8-repressed	1.36E-03	1.18
71742	Ulk3	CDK8-repressed	1.36E-03	1.22
78195	4930528J18Rik	CDK8-repressed	1.37E-03	2.05
20480	Clpb	CDK8-repressed	1.38E-03	1.38
20588	Smarcc1	CDK8-repressed	1.39E-03	1.18
66311	2610036L11Rik	CDK8-repressed	1.39E-03	1.56
72519	Tmem55a	CDK8-repressed	1.39E-03	1.18
74356	4931428F04Rik	CDK8-repressed	1.39E-03	1.21
78832	2700078E11Rik	CDK8-repressed	1.40E-03	1.32
170753	Zfp704	CDK8-repressed	1.41E-03	1.35
101148	B630005N14Rik	CDK8-repressed	1.41E-03	1.29
67468	Mmd	CDK8-repressed	1.42E-03	1.43
14886	Gtf2i	CDK8-repressed	1.43E-03	1.15
105855	Nckap1l	CDK8-repressed	1.43E-03	1.28
98170	Tmem132a	CDK8-repressed	1.44E-03	1.21
231238	2310045A20Rik	CDK8-repressed	1.44E-03	1.43
224020	Pik4ca	CDK8-repressed	1.44E-03	1.22
18973	Pole	CDK8-repressed	1.45E-03	1.20
107045	Lars	CDK8-repressed	1.45E-03	1.15
16564	Kif21a	CDK8-repressed	1.45E-03	2.03
93761	Smarca1	CDK8-repressed	1.45E-03	1.42
18715	Pim2	CDK8-repressed	1.46E-03	1.90
72050	Kdelc1	CDK8-repressed	1.47E-03	1.18
100662	D930016D06Rik	CDK8-repressed	1.48E-03	1.18
66074	0610041E09Rik	CDK8-repressed	1.48E-03	1.27
73389	Hbp1	CDK8-repressed	1.49E-03	1.21
66923	Pb1	CDK8-repressed	1.49E-03	1.27
66905	M6prbp1	CDK8-repressed	1.49E-03	1.17
12491	Cd36	CDK8-repressed	1.49E-03	2.57
75871	4930566A11Rik	CDK8-repressed	1.49E-03	1.22
14731	Gpaa1	CDK8-repressed	1.50E-03	1.13
338362	Ust	CDK8-repressed	1.50E-03	1.67
140500	Centb5	CDK8-repressed	1.51E-03	1.23
18715	Pim2	CDK8-repressed	1.55E-03	1.84
213819	Casd1	CDK8-repressed	1.57E-03	1.23
320879	B230217O12Rik	CDK8-repressed	1.57E-03	2.18
29876	Clic4	CDK8-repressed	1.58E-03	1.26
53416	Stk39	CDK8-repressed	1.58E-03	1.11
21912	Tspan7	CDK8-repressed	1.59E-03	1.29
20910	Stxbp1	CDK8-repressed	1.59E-03	1.38
67702	Rnf149	CDK8-repressed	1.59E-03	1.28
17868	Mybpc3	CDK8-repressed	1.61E-03	1.42
66602	1700020I14Rik	CDK8-repressed	1.61E-03	1.27
218442	Serinc5	CDK8-repressed	1.61E-03	1.80
66559	Metapl1	CDK8-repressed	1.62E-03	1.30
13361	Dhfr	CDK8-repressed	1.63E-03	1.32
84585	Rnf123	CDK8-repressed	1.63E-03	1.29
330817	Dhps	CDK8-repressed	1.63E-03	1.14

170753	Zfp704	CDK8-repressed	1.63E-03	1.11
20603	Sms	CDK8-repressed	1.64E-03	1.27
24136	Zfhx1b	CDK8-repressed	1.65E-03	1.59
12282	Hyou1	CDK8-repressed	1.67E-03	1.20
71745	Cul2	CDK8-repressed	1.67E-03	1.33
214058	Megf11	CDK8-repressed	1.69E-03	2.27
99311	Commd7	CDK8-repressed	1.69E-03	1.17
19206	Ptch1	CDK8-repressed	1.69E-03	1.45
69188	Mll5	CDK8-repressed	1.69E-03	1.25
12737	Cldn1	CDK8-repressed	1.69E-03	1.54
209707	Lcorl	CDK8-repressed	1.70E-03	1.43
105727	Slc38a1	CDK8-repressed	1.71E-03	1.29
74026	4121402D02Rik	CDK8-repressed	1.71E-03	1.22
18709	Pik3r2	CDK8-repressed	1.71E-03	1.13
216848	Chd3	CDK8-repressed	1.72E-03	1.26
77015	Mpped2	CDK8-repressed	1.73E-03	1.20
30838	Fbxw4	CDK8-repressed	1.73E-03	1.35
23827	Bpnt1	CDK8-repressed	1.77E-03	1.24
21951	Tnks	CDK8-repressed	1.77E-03	1.21
68961	Phkg2	CDK8-repressed	1.78E-03	1.09
76820	D12Ertd553e	CDK8-repressed	1.78E-03	1.49
78654	1700066C05Rik	CDK8-repressed	1.79E-03	1.46
19671	Rce1	CDK8-repressed	1.79E-03	1.12
233806	Tmem159	CDK8-repressed	1.79E-03	1.14
22003	Tpm1	CDK8-repressed	1.80E-03	1.15
13121	Cyp51	CDK8-repressed	1.80E-03	1.25
67967	Pold3	CDK8-repressed	1.81E-03	1.08
26451	Rpl27a	CDK8-repressed	1.83E-03	1.12
233107	Kctd15	CDK8-repressed	1.83E-03	1.27
66607	Ms4a4d	CDK8-repressed	1.83E-03	2.25
67030	Fancl	CDK8-repressed	1.83E-03	1.47
386612	Thoc6	CDK8-repressed	1.83E-03	1.09
81500	Sil1	CDK8-repressed	1.85E-03	1.17
233812	BC030336	CDK8-repressed	1.85E-03	1.22
23963	Odz1	CDK8-repressed	1.86E-03	2.12
15407	Hoxb1	CDK8-repressed	1.86E-03	1.80
108767	Pnrc1	CDK8-repressed	1.87E-03	1.37
22174	Tyro3	CDK8-repressed	1.88E-03	1.40
63828	Fn3k	CDK8-repressed	1.89E-03	1.55
30785	Cttnbp2	CDK8-repressed	1.89E-03	4.20
94245	Dtnbp1	CDK8-repressed	1.90E-03	1.12
14863	Gstm2	CDK8-repressed	1.91E-03	1.44
13204	Dhx15	CDK8-repressed	1.91E-03	1.15
74355	Smchd1	CDK8-repressed	1.91E-03	1.26
20474	Six4	CDK8-repressed	1.92E-03	1.53
69694	Tatdn1	CDK8-repressed	1.92E-03	1.76
69683	2310044H10Rik	CDK8-repressed	1.92E-03	1.31
230649	Atpaf1	CDK8-repressed	1.93E-03	1.23
103012	6720401G13Rik	CDK8-repressed	1.94E-03	1.43
11990	Atrn	CDK8-repressed	1.95E-03	1.18
338372	Map3k9	CDK8-repressed	1.96E-03	2.87
16898	Rps2	CDK8-repressed	1.96E-03	1.09
52838	D2Bwg1335e	CDK8-repressed	1.97E-03	1.10
18479	Pak1	CDK8-repressed	1.97E-03	1.29
319565	Syne2	CDK8-repressed	1.98E-03	1.58
68166	Spire1	CDK8-repressed	1.99E-03	1.57
56530	Tmem4	CDK8-repressed	2.00E-03	1.14
13019	Ctf1	CDK8-repressed	2.00E-03	1.15
328329	Mast4	CDK8-repressed	2.00E-03	1.29

319565	Syne2	CDK8-repressed	2.00E-03	1.63
233812	BC030336	CDK8-repressed	2.00E-03	1.26
27078	Eppb9	CDK8-repressed	2.01E-03	1.05
216350	Tspan8	CDK8-repressed	2.01E-03	1.38
19359	Rad23b	CDK8-repressed	2.02E-03	1.72
70757	Ptplb	CDK8-repressed	2.03E-03	1.33
68545	1110006O17Rik	CDK8-repressed	2.05E-03	1.19
69116	Zubr1	CDK8-repressed	2.05E-03	1.19
11477	Acvr1	CDK8-repressed	2.05E-03	1.22
246104	Rhbdl3	CDK8-repressed	2.06E-03	1.36
18530	Pcdh8	CDK8-repressed	2.06E-03	1.78
16776	Lama5	CDK8-repressed	2.07E-03	1.23
20529	Slc31a1	CDK8-repressed	2.07E-03	1.40
11622	Ahr	CDK8-repressed	2.08E-03	1.26
192193	Edem1	CDK8-repressed	2.08E-03	1.16
67443	Map1lc3b	CDK8-repressed	2.09E-03	1.27
319517	6430510M02Rik	CDK8-repressed	2.09E-03	1.45
214459	Fnbp1l	CDK8-repressed	2.09E-03	1.33
54004	Diap2	CDK8-repressed	2.09E-03	1.31
14030	Ewsr1	CDK8-repressed	2.10E-03	1.11
93842	Igsf9	CDK8-repressed	2.11E-03	1.20
67460	Decr1	CDK8-repressed	2.11E-03	1.70
12211	Birc6	CDK8-repressed	2.12E-03	1.26
18578	Pde4b	CDK8-repressed	2.14E-03	1.94
106522	AW548124	CDK8-repressed	2.16E-03	1.32
320252	C230047C07Rik	CDK8-repressed	2.17E-03	2.08
74143	Opa1	CDK8-repressed	2.19E-03	1.25
66209	1110054O05Rik	CDK8-repressed	2.21E-03	1.14
71089	4933413B09Rik	CDK8-repressed	2.21E-03	1.81
14009	Etv1	CDK8-repressed	2.22E-03	1.25
67979	Atad1	CDK8-repressed	2.23E-03	1.12
320790	Chd7	CDK8-repressed	2.24E-03	1.43
212772	2700007P21Rik	CDK8-repressed	2.24E-03	1.14
110959	Nudt19	CDK8-repressed	2.24E-03	1.13
170756	Slc24a6	CDK8-repressed	2.25E-03	1.30
319565	Syne2	CDK8-repressed	2.26E-03	1.87
75747	Sesn3	CDK8-repressed	2.27E-03	1.64
66121	Chchd1	CDK8-repressed	2.27E-03	1.11
69094	Tmem160	CDK8-repressed	2.27E-03	1.20
69617	Pitrm1	CDK8-repressed	2.27E-03	1.14
194388	D230004J03Rik	CDK8-repressed	2.27E-03	1.56
233833	Tnrc6a	CDK8-repressed	2.27E-03	1.29
100102	Pcsk9	CDK8-repressed	2.27E-03	1.17
11474	Actn3	CDK8-repressed	2.28E-03	1.39
16423	Cd47	CDK8-repressed	2.28E-03	1.49
171166	Mcoln3	CDK8-repressed	2.28E-03	2.32
19647	Rbbp6	CDK8-repressed	2.29E-03	1.11
100169	Phactr4	CDK8-repressed	2.29E-03	1.12
13665	Eif2s1	CDK8-repressed	2.29E-03	1.15
227620	Uap1l1	CDK8-repressed	2.30E-03	1.16
218203	Mylip	CDK8-repressed	2.30E-03	1.36
14723	Gp1ba	CDK8-repressed	2.30E-03	1.53
11426	Macf1	CDK8-repressed	2.30E-03	1.31
23992	Prkra	CDK8-repressed	2.30E-03	1.13
320538	D130059P03Rik	CDK8-repressed	2.31E-03	1.37
26462	Txnrd2	CDK8-repressed	2.32E-03	1.27
17755	Mtap1b	CDK8-repressed	2.32E-03	1.76
102105	AI481772	CDK8-repressed	2.32E-03	1.16
98417	Cnih4	CDK8-repressed	2.33E-03	1.22

69225	0710008K08Rik	CDK8-repressed	2.34E-03	1.12
17385	Mmp11	CDK8-repressed	2.36E-03	1.24
21843	Tial1	CDK8-repressed	2.36E-03	1.26
13542	Dvl1	CDK8-repressed	2.37E-03	1.09
399612	9630010G10Rik	CDK8-repressed	2.38E-03	1.54
76998	1700124P09Rik	CDK8-repressed	2.39E-03	1.24
76500	Ihpk2	CDK8-repressed	2.39E-03	1.12
26877	B3galt1	CDK8-repressed	2.40E-03	1.37
414077	BC056474	CDK8-repressed	2.40E-03	1.17
66855	Tcf25	CDK8-repressed	2.41E-03	1.14
19027	Sypl	CDK8-repressed	2.42E-03	1.14
15410	Hoxb3	CDK8-repressed	2.43E-03	2.31
19820	Rnf12	CDK8-repressed	2.47E-03	1.20
13047	Cutl1	CDK8-repressed	2.47E-03	1.17
240041	A630033E08Rik	CDK8-repressed	2.49E-03	1.23
71704	Arhgef3	CDK8-repressed	2.49E-03	1.48
74549	9130404D08Rik	CDK8-repressed	2.53E-03	1.31
59024	Med12	CDK8-repressed	2.53E-03	1.25
14176	Fgf5	CDK8-repressed	2.53E-03	2.53
77976	Nuak1	CDK8-repressed	2.54E-03	1.17
69239	2610034M16Rik	CDK8-repressed	2.55E-03	1.66
21822	Tgtp	CDK8-repressed	2.55E-03	2.66
112422	2610305D13Rik	CDK8-repressed	2.55E-03	1.17
14582	Gfi1b	CDK8-repressed	2.56E-03	1.25
232223	Txnrd3	CDK8-repressed	2.58E-03	1.28
56334	Tmed2	CDK8-repressed	2.58E-03	1.17
23922	Jtb	CDK8-repressed	2.59E-03	1.09
380694	Ccnjl	CDK8-repressed	2.59E-03	1.30
80909	Gats	CDK8-repressed	2.60E-03	1.15
219158	2610301G19Rik	CDK8-repressed	2.62E-03	1.20
14870	Gstp1	CDK8-repressed	2.63E-03	1.28
18481	Pak3	CDK8-repressed	2.64E-03	1.36
70082	Lysmd2	CDK8-repressed	2.65E-03	1.12

WHAT IS CLAIMED IS:

1) A method of screening for and/or identifying a CDK8 antagonist which promotes cell differentiation said method comprising: contacting a reference cell, wherein the reference cell is a stem cell and/or a cancer stem cell, with a CDK8 candidate antagonist, wherein the CDK8 candidate antagonist binds CDK8, and whereby differentiation of the reference cell into a differentiated cell identifies the CDK8 candidate antagonist as a CDK8 antagonist which promotes cell differentiation.

2) The method of claim 1, wherein the reference cell is a cancer stem cell.

3) The method of any one of claims 1-2, wherein the differentiated cell is a goblet cell and/or enterocyte cell.

4) The method of any one of claims 1-3, wherein the CDK8 candidate antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide.

5) A method of inducing differentiation comprising contacting the cell with an effective amount of CDK8 antagonist.

6) The method of claim 5, wherein the cell is a stem cell.

7) The method of claim 5, wherein the cell is a cancer stem cell.

8) A method of treating a cancer cell, wherein the cancer cell differentially expresses one or more biomarkers of a CDK8 gene signature (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)), the method comprising providing an effective amount of a CDK8 antagonist.

9) A method of treating cancer in an individual comprising administering to the individual an effective amount of a CDK8 antagonist, wherein treatment is based upon the cancer comprising cancer stem cell-like properties.

10) The method of claim 9, wherein the cancer stem cell-like properties comprise differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)).

11) A method of treating a disease or disorder in an individual comprising administering to the individual an effective amount of a CDK8 antagonist, wherein treatment is based upon differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)).

12) A method of treating a disease or disorder in an individual comprising administering to the individual an effective amount of a CDK8 antagonist, wherein treatment is continued based upon differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)).

13) A method for treating a disease or disorder in an individual, the method comprising: determining that a sample obtained from the individual comprises differential expression levels of one or more biomarkers of a CDK8 gene signature (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)), and administering an effective amount of a CDK8 antagonist to the individual, whereby the disease or disorder is treated.

14) A method of treating disease or disorder in an individual, comprising: (a) selecting an individual having differential expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)); and (b) administering to the individual thus selected an effective amount of a CDK8 antagonist, whereby the disease or disorder is treated.

15) A method of identifying an individual with a disease or disorder who is more or less likely to exhibit benefit from treatment with a therapy comprising a CDK8 antagonist, the method comprising: determining the expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, wherein differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is more likely to exhibit benefit from treatment with the therapy comprising the CDK8 antagonist and/or non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is less likely to exhibit benefit from treatment with the therapy comprising the CDK8 antagonist.

16) A method for predicting whether an individual with a disease or disorder is more or less likely to respond effectively to treatment with a therapy comprising a CDK8 antagonist, the method comprising assessing expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, whereby differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is more likely to respond effectively to treatment with the CDK8 antagonist and/or non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) indicates that the individual is less likely to respond effectively to treatment with the CDK8 antagonist.

17) A method of predicting the response or lack of response of an individual with a disease or disorder to a therapy comprising a CDK8 antagonist comprising measuring expression levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, wherein differential expression levels of one or

more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) is predictive of response of the individual to the therapy comprising the CDK8 antagonist and non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) is predictive of lack of response of the individual to the therapy comprising the CDK8 antagonist.

18) A method of determining whether an individual having a disease or disorder is more or less likely responding to therapy, wherein therapy comprises a CDK8 antagonist, based upon levels of one or more biomarkers of a CDK8 gene signature in a sample from the individual, wherein differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) identifies the individual as more likely responding to therapy comprising the CDK8 antagonist and non-differential expression levels of one or more biomarkers of the CDK8 gene signature in a sample from the individual (*e.g.*, compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (*e.g.*, housekeeping gene)) identifies the individual as less likely responding to therapy comprising the CDK8 antagonist.

19) The method of any one of claims 15-18, wherein the method further comprises administering an effective amount of a therapy comprising a CDK8 antagonist.

20) The method of any one of claims 8, 10-11, 13-17, and 19, wherein differential expression of one or more biomarkers of the CDK8 gene signature is elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or reduced expression of one or more CDK8-repressed biomarkers of the CDK8 gene signature.

21) The method of any one of claims 12 and 18-19, wherein differential expression of one or more biomarkers of the CDK8 gene signature is reduced expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or elevated expression of one or more CDK8-induced biomarkers of the CDK8 gene signature.

22) The method of any one of claims 8 and 10-21, wherein the one or more biomarkers of the CDK8 gene signature comprises one or more biomarkers of the CDK8 cancer cell gene signature.

23) The method of claim 22, wherein the one or more biomarkers of the CDK8 cancer cell gene signature comprises one or more genes listed in Table 2.

24) The method of claim 23, wherein the one or more genes listed in Table 2 comprises one or more ES cell-related genes, MYC ES target genes, p53 signalling genes, cell cycle genes, Wnt signalling genes, and/or SMAD/BMP signalling genes.

25) The method of any one of claims 8 and 10-24, wherein the one or more biomarkers of the CDK8 gene signature comprises one or more biomarkers of the CDK8 embryonic stem cell gene signature.

26) The method of any one of claims 22-24, wherein the one or more biomarkers of the CDK8 embryonic stem cell gene signature comprises one or more genes listed in Table 3.

27) The method of any one of claims 11-25, wherein the disease or disorder is cancer.

28) The method of any one of claims 8-14 and 19-26, wherein the CDK8 antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide.

29) The method of claim 27, wherein the CDK8 antagonist is an antibody.

30) The method of claim 27, wherein the CDK8 antagonist is a small molecule.

31) The method of claim 29, wherein the small molecule is a small molecule kinase inhibitor.

32) The method of claim 30, wherein the small molecule kinase inhibitor is selected from the group consisting of flavopiridol, ABT-869, AST-487, BMS-387032/SNS032, BIRB-796, sorafenib, staurosporine, cortistatin, cortistatin A, and/or a steroidal alkaloid or derivative thereof.

33) The method of any one of claims 27-31, wherein the CDK8 antagonist induces cell cycle arrest or is capable of promoting differentiation.

34) The method of claim 32, wherein the CDK8 antagonist is capable of promoting a change in cell fate and promoting differentiation is indicated by reduced expression of one or more CDK8-induced biomarkers of the CDK8 gene signature and/or elevated expression of one or more CDK8-reduced biomarkers of the CDK8 gene signature.

Figure 1

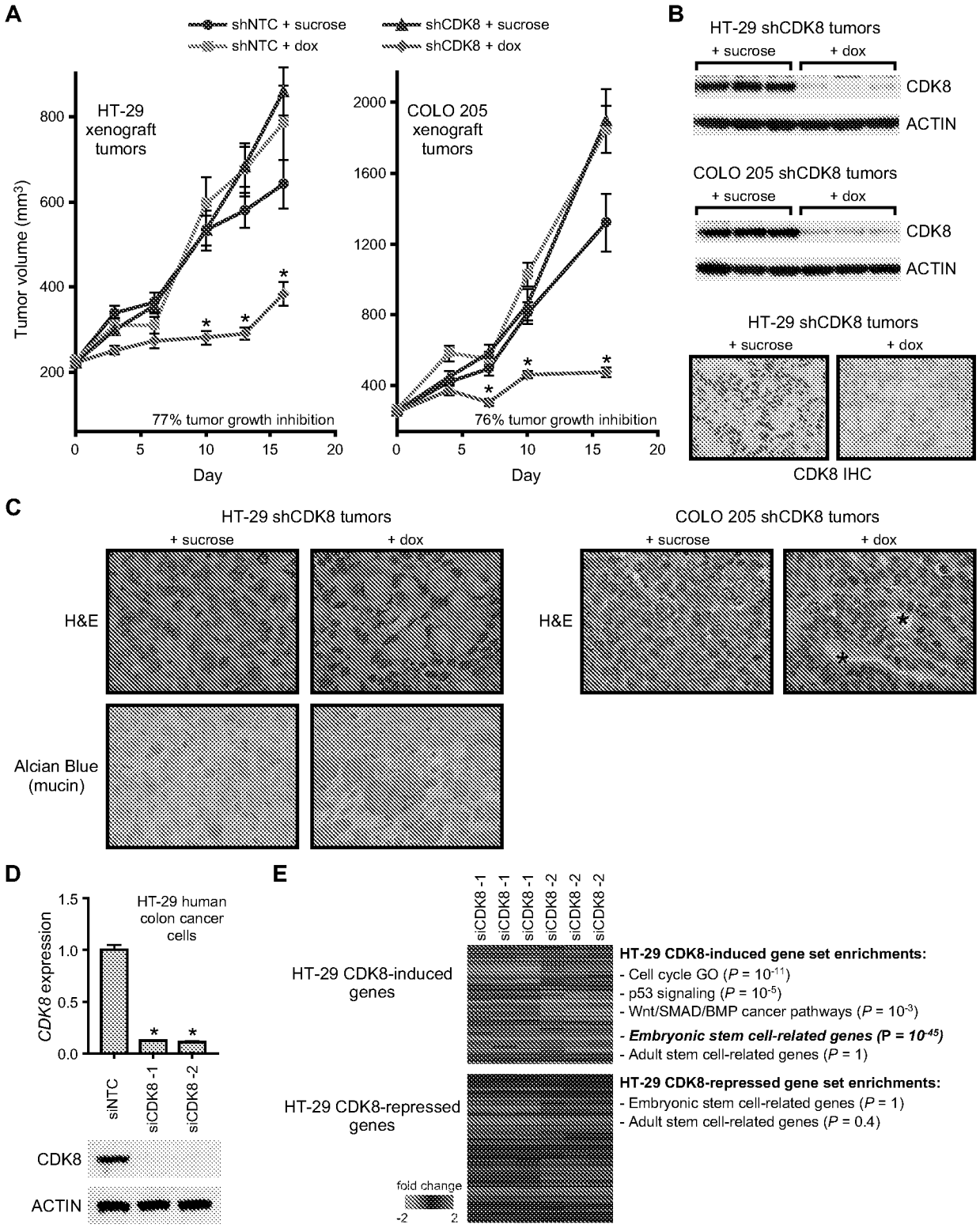

A
shNTC + sucrose
shNTC + dox
shCDK8 + sucrose
shCDK8 + dox
HT-29 xenograft tumors
COLO 205 xenograft tumors
Tumor volume (mm3)
77% tumor growth inhibition
76% tumor growth inhibition
Day
B
HT-29 shCDK8 tumors
+ sucrose
+ dox
CDK8
ACTIN
COLO 205 shCDK8 tumors
CDK8 IHC
C
HT-29 shCDK8 tumors
COLO 205 shCDK8 tumors
H&E
Alcian Blue (mucin)
D
HT-29 human colon cancer cells
CDK8 expression
siNTC
siCDK8 -1
siCDK8 -2
E
HT-29 CDK8-induced genes
HT-29 CDK8-repressed genes
fold change
HT-29 CDK8-induced gene set enrichments:
- Cell cycle GO (P = 10-11)
- p53 signaling (P = 10-5)
- Wnt/SMAD/BMP cancer pathways (P = 10-3)
- Embryonic stem cell-related genes (P = 10-45)
- Adult stem cell-related genes (P = 1)
HT-29 CDK8-repressed gene set enrichments:
- Embryonic stem cell-related genes (P = 1)
- Adult stem cell-related genes (P = 0.4)

Figure 2

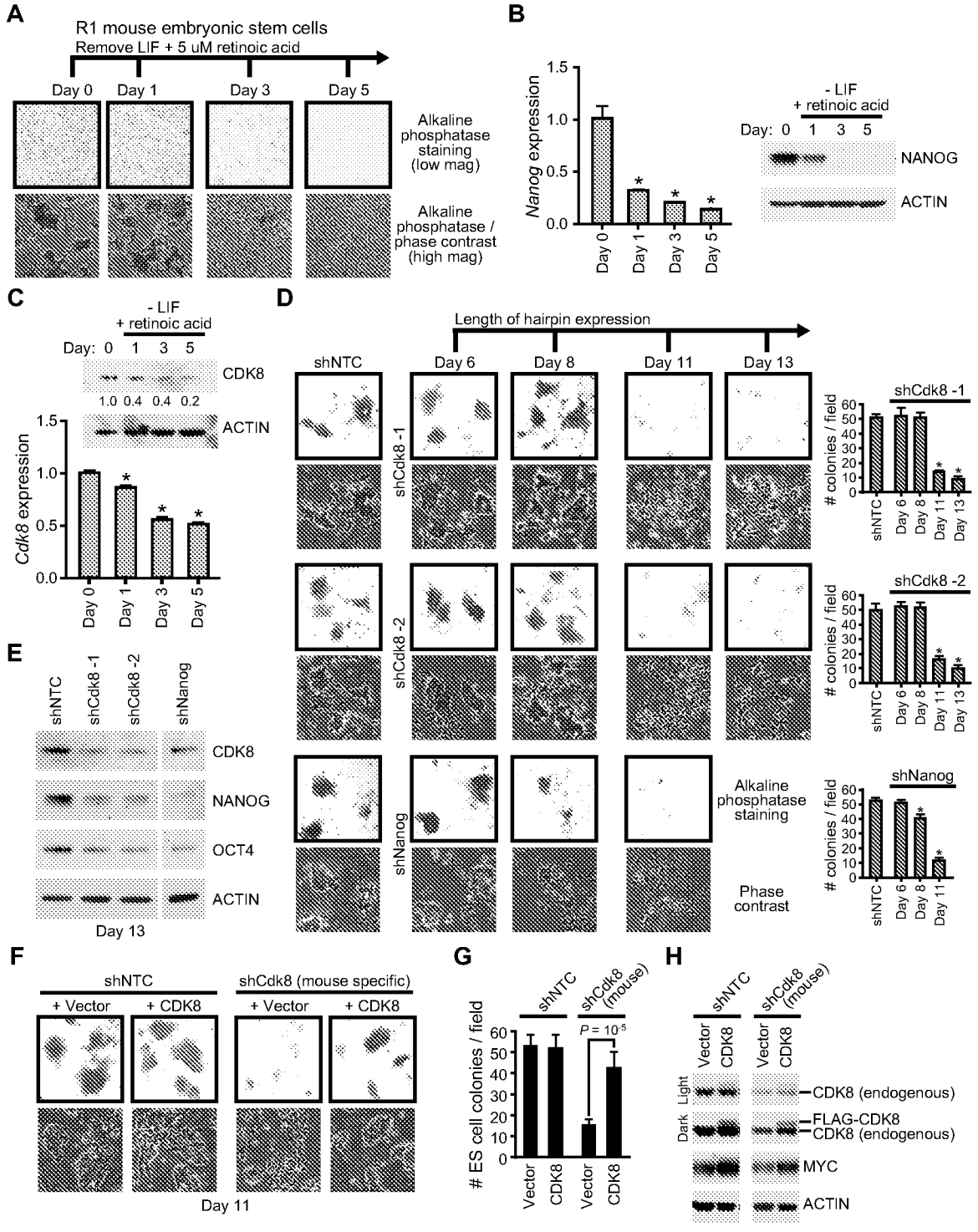

A
R1 mouse embryonic stem cells
Remove LIF + 5 uM retinoic acid
Day 0
Day 1
Day 3
Day 5
Alkaline phosphatase staining (low mag)
Alkaline phosphatase / phase contrast (high mag)
B
Nanog expression
1.5
1.0
0.5
0.0
Day 0
Day 1
Day 3
Day 5
- LIF
+ retinoic acid
Day: 0 1 3 5
NANOG
ACTIN
C
- LIF
+ retinoic acid
Day: 0 1 3 5
CDK8
1.0 0.4 0.4 0.2
ACTIN
Cdk8 expression
1.5
1.0
0.5
0.0
Day 0
Day 1
Day 3
Day 5
D
Length of hairpin expression
shNTC
Day 6
Day 8
Day 11
Day 13
shCdk8 -1
shCdk8 -2
shNanog
Alkaline phosphatase staining
Phase contrast
colonies / field
shCdk8 -1
shCdk8 -2
shNanog
shNTC
Day 6
Day 8
Day 11
Day 13
E
shNTC
shCdk8 -1
shCdk8 -2
shNanog
CDK8
NANOG
OCT4
ACTIN
Day 13
F
shNTC
shCdk8 (mouse specific)
+ Vector
+ CDK8
+ Vector
+ CDK8
Day 11
G
shNTC
shCdk8 (mouse)
P = 10-5
# ES cell colonies / field
60
50
40
30
20
10
0
Vector
CDK8
Vector
CDK8
H
shNTC
shCdk8 (mouse)
Vector
CDK8
Vector
CDK8
Light
Dark
CDK8 (endogenous)
FLAG-CDK8
CDK8 (endogenous)
MYC
ACTIN

Figure 3

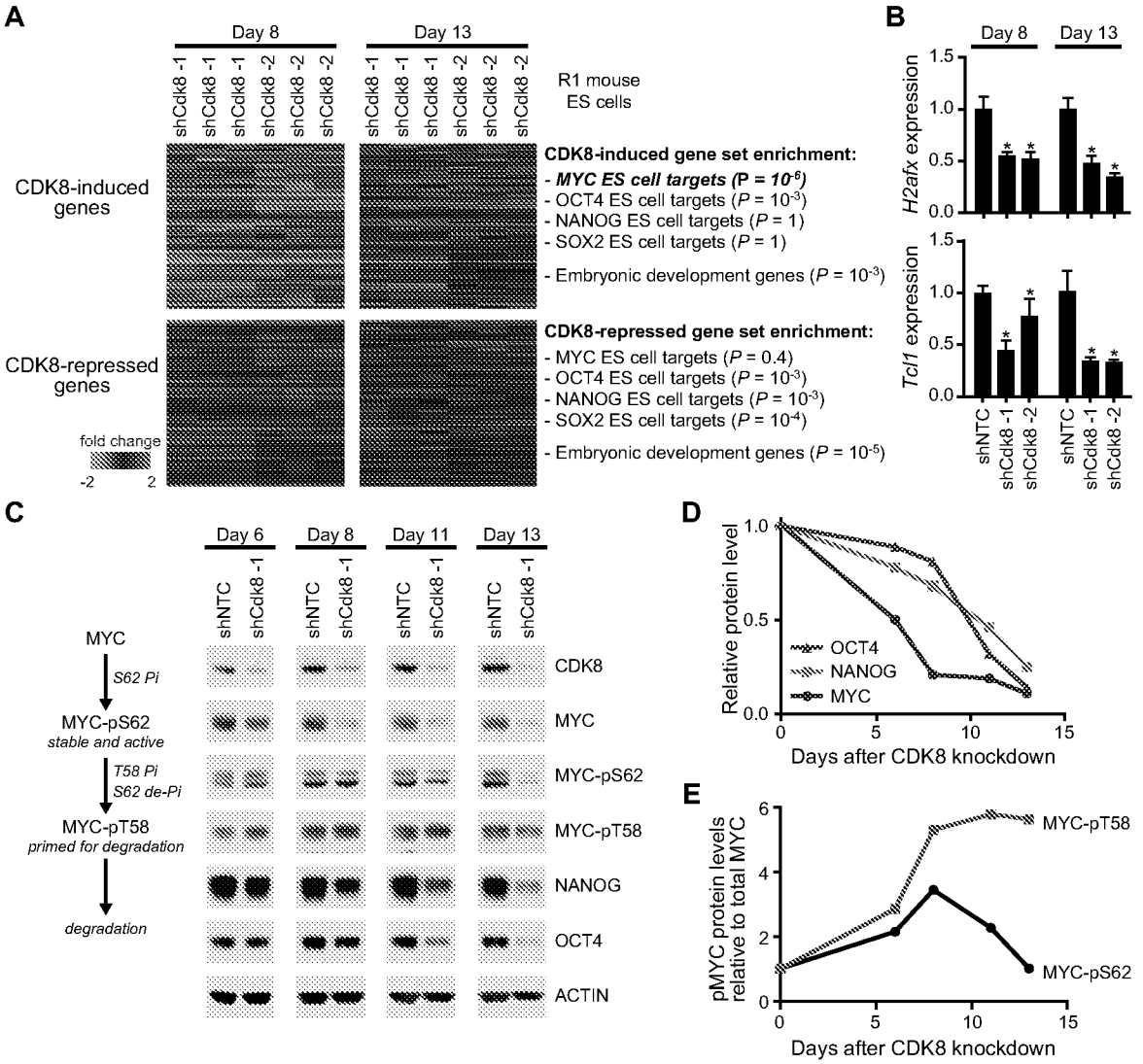

A
Day 8
Day 13
shCdk8 -1
shCdk8 -2
R1 mouse ES cells
CDK8-induced genes
CDK8-repressed genes
fold change
-2
2
CDK8-induced gene set enrichment:
- MYC ES cell targets (P = 10-6)
- OCT4 ES cell targets (P = 10-3)
- NANOG ES cell targets (P = 1)
- SOX2 ES cell targets (P = 1)
- Embryonic development genes (P = 10-3)
CDK8-repressed gene set enrichment:
- MYC ES cell targets (P = 0.4)
- OCT4 ES cell targets (P = 10-3)
- NANOG ES cell targets (P = 10-3)
- SOX2 ES cell targets (P = 10-4)
- Embryonic development genes (P = 10-5)
B
Day 8
Day 13
H2afx expression
Tcl1 expression
shNTC
shCdk8 -1
shCdk8 -2
C
Day 6
Day 8
Day 11
Day 13
shNTC
shCdk8 -1
MYC
S62 Pi
MYC-pS62
stable and active
T58 Pi
S62 de-Pi
MYC-pT58
primed for degradation
degradation
CDK8
MYC
MYC-pS62
MYC-pT58
NANOG
OCT4
ACTIN
D
Relative protein level
OCT4
NANOG
MYC
Days after CDK8 knockdown
E
pMYC protein levels relative to total MYC
MYC-pT58
MYC-pS62
Days after CDK8 knockdown

Figure 4

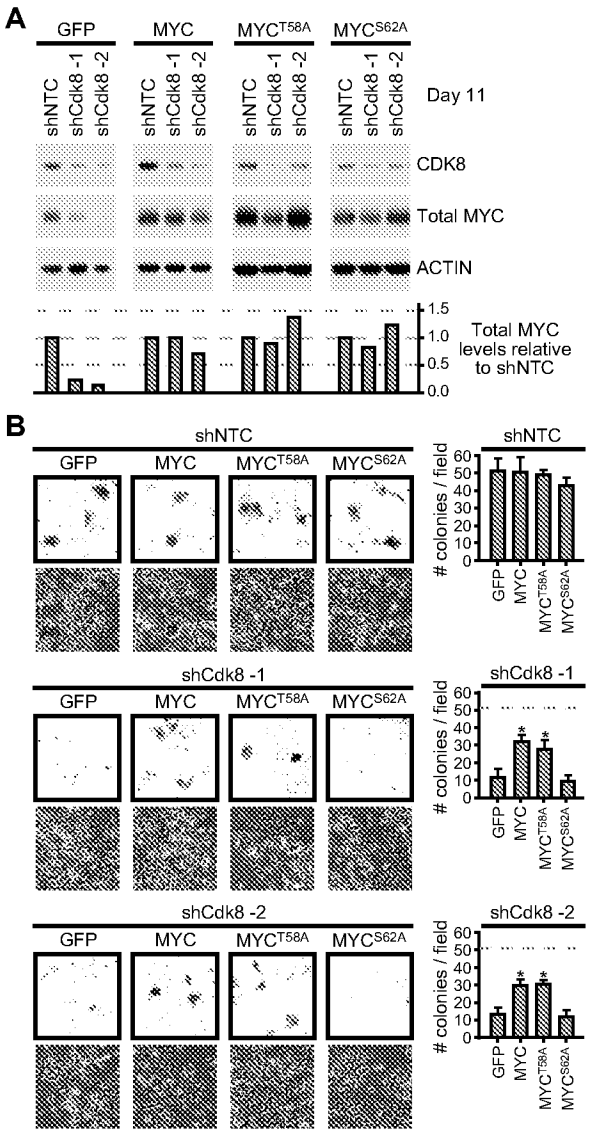

A
GFP
MYC
MYCT58A
MYCS62A
shNTC
shCdk8 -1
shCdk8 -2
Day 11
CDK8
Total MYC
ACTIN
1.5
1.0
0.5
0.0
Total MYC levels relative to shNTC
B
shNTC
shCdk8 -1
shCdk8 -2
colonies / field
60
50
40
30
20
10
0
*

Figure 5

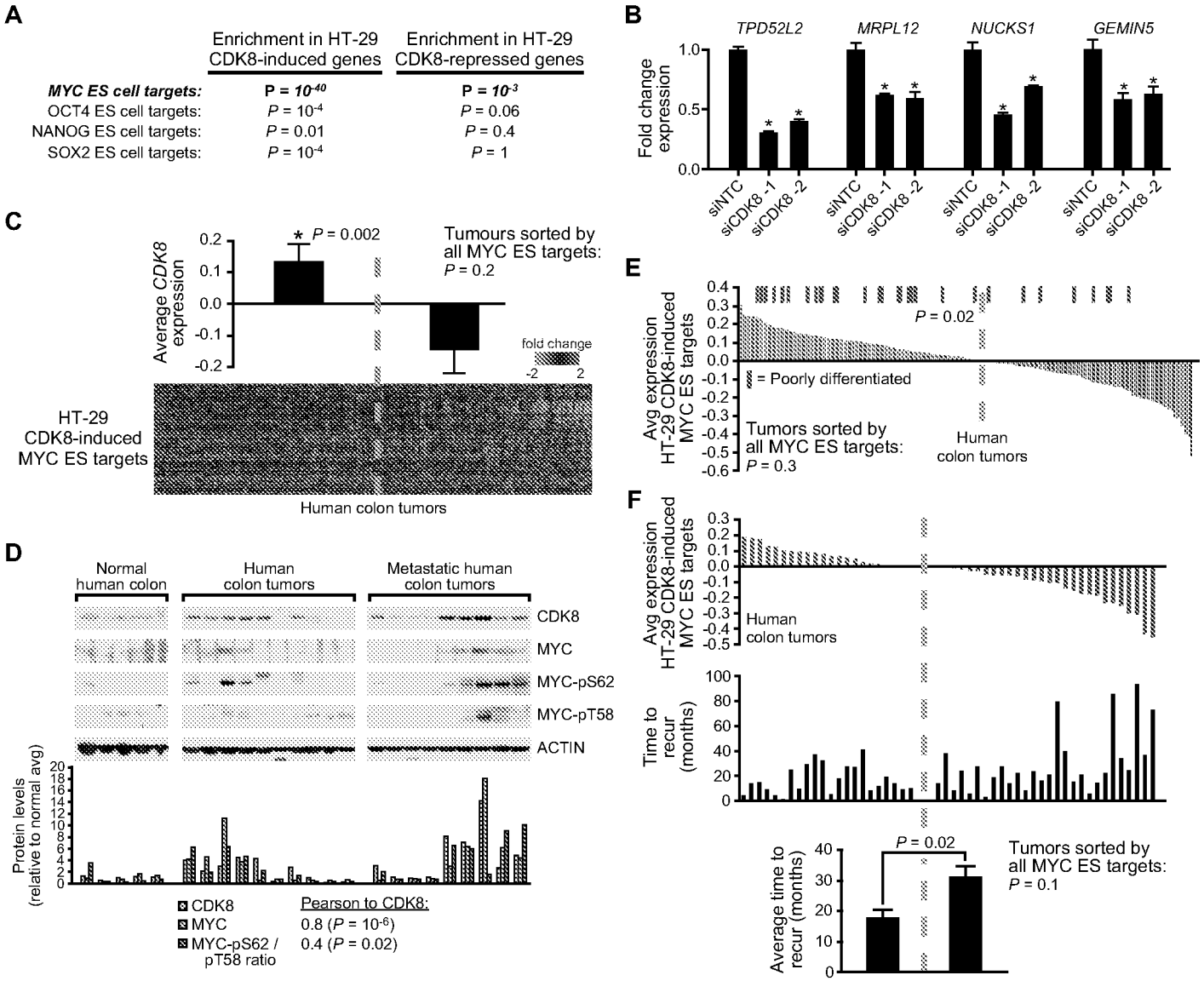

A
Enrichment in HT-29 CDK8-induced genes
Enrichment in HT-29 CDK8-repressed genes
MYC ES cell targets: P = 10-40 P = 10-3
OCT4 ES cell targets: P = 10-4 P = 0.06
NANOG ES cell targets: P = 0.01 P = 0.4
SOX2 ES cell targets: P = 10-4 P = 1
B
TPD52L2
MRPL12
NUCKS1
GEMIN5
Fold change expression
siNTC
siCDK8 -1
siCDK8 -2
C
Average CDK8 expression
P = 0.002
Tumours sorted by all MYC ES targets: P = 0.2
fold change
HT-29 CDK8-induced MYC ES targets
Human colon tumors
D
Normal human colon
Human colon tumors
Metastatic human colon tumors
CDK8
MYC
MYC-pS62
MYC-pT58
ACTIN
Protein levels (relative to normal avg)
CDK8
MYC
MYC-pS62 / pT58 ratio
Pearson to CDK8:
0.8 (P = 10-6)
0.4 (P = 0.02)
E
Avg expression HT-29 CDK8-induced MYC ES targets
P = 0.02
= Poorly differentiated
Tumors sorted by all MYC ES targets: P = 0.3
Human colon tumors
F
Avg expression HT-29 CDK8-induced MYC ES targets
Human colon tumors
Time to recur (months)
P = 0.02
Average time to recur (months)
Tumors sorted by all MYC ES targets: P = 0.1

Figure 6

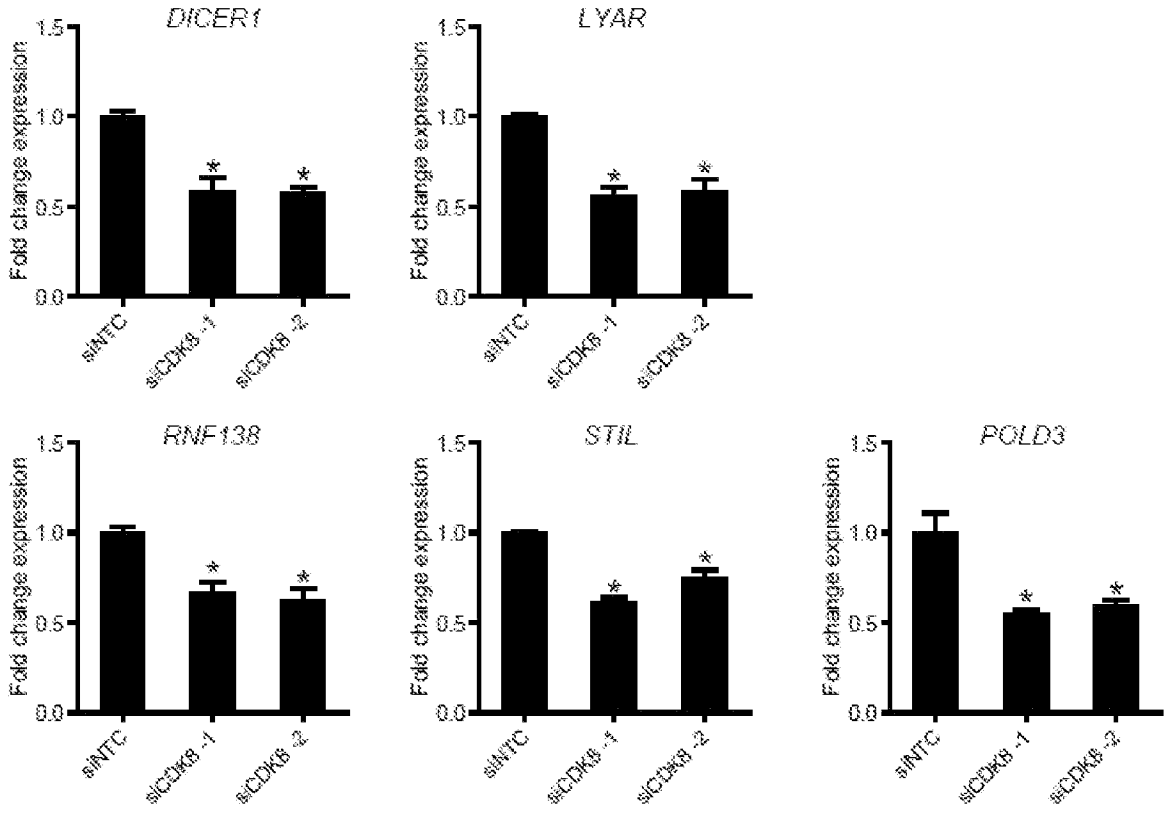

DICER1
LYAR
RNF138
STIL
POLD3
Fold change expression
1.5
1.0
0.5
0.0
*
siNTC
siCDK8 -1
siCDK8 -2

Figure 7

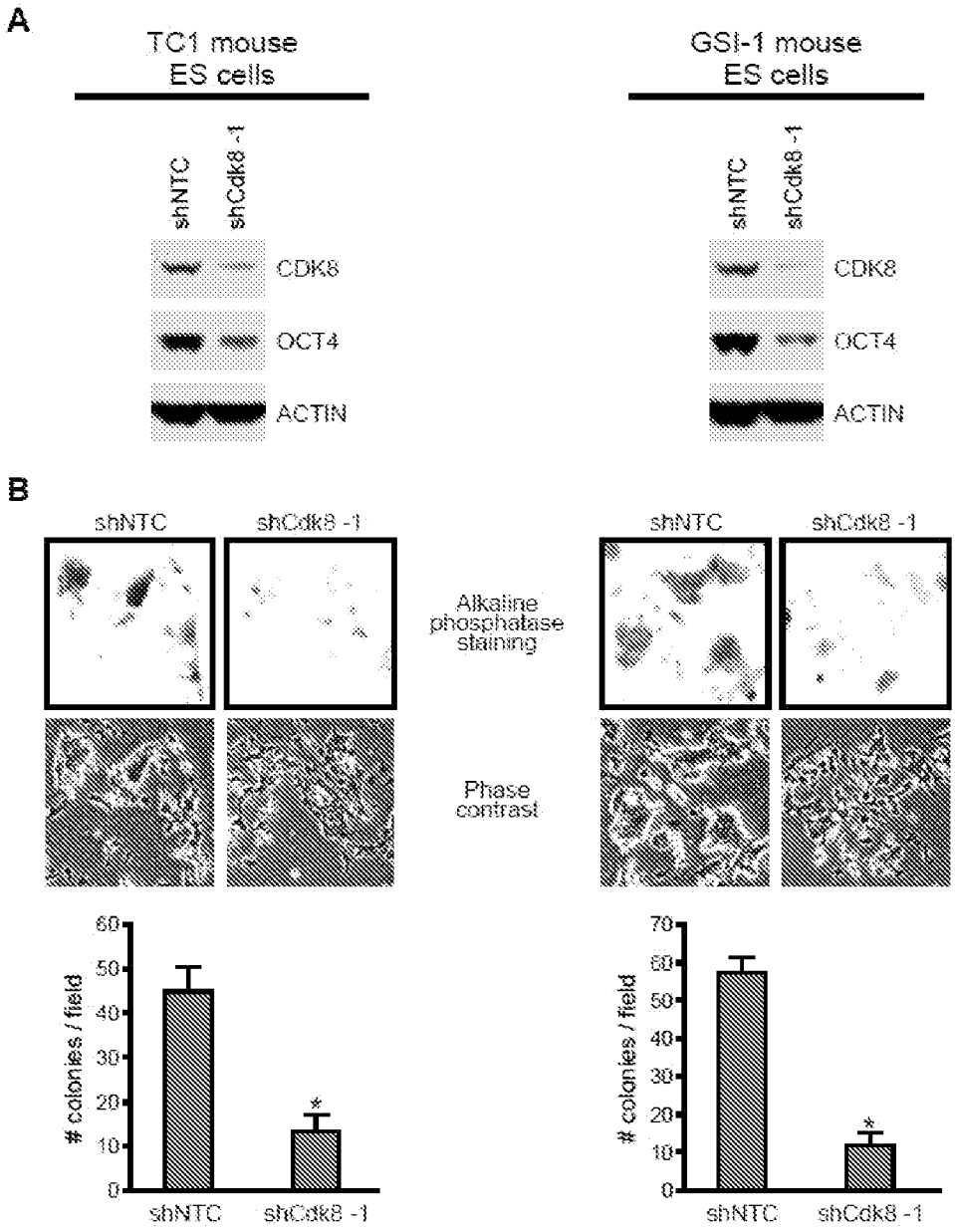

A
TC1 mouse ES cells
GSI-1 mouse ES cells
shNTC
shCdk8 -1
CDK8
OCT4
ACTIN
B
shNTC
shCdk8 -1
Alkaline phosphatase staining
Phase contrast
colonies / field
shNTC
shCdk8 -1

Figure 8

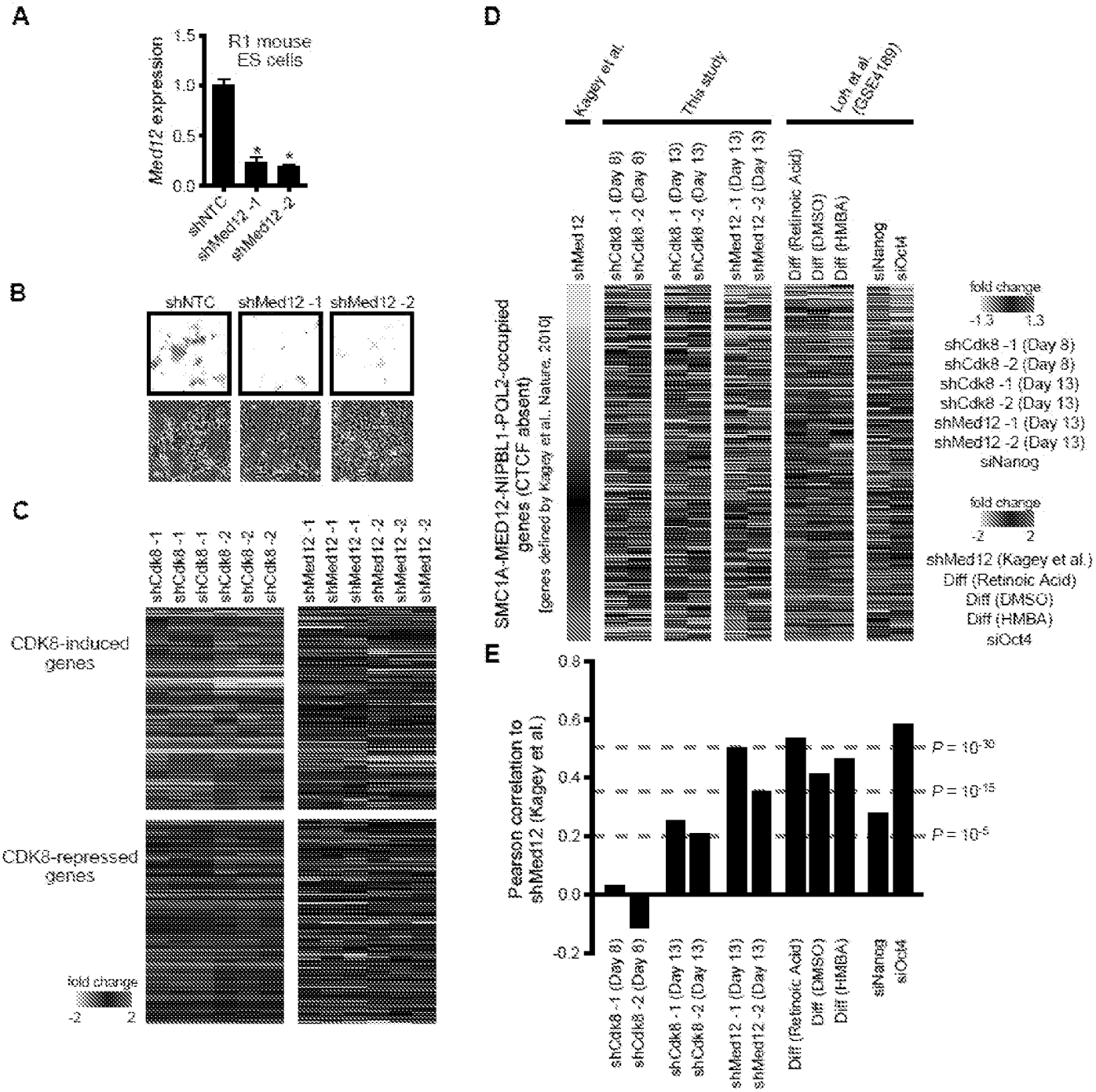

A
R1 mouse ES cells
Med12 expression
1.5
1.0
0.5
0.0
shNTC
shMed12 -1
shMed12 -2
B
shNTC
shMed12 -1
shMed12 -2
C
shCdk8 -1
shCdk8 -1
shCdk8 -1
shCdk8 -2
shCdk8 -2
shCdk8 -2
shMed12 -1
shMed12 -1
shMed12 -1
shMed12 -2
shMed12 -2
shMed12 -2
CDK8-induced genes
CDK8-repressed genes
fold change
-2
2
D
Kagey et al.
This study
Loh et al. (GSE41189)
shMed12
shCdk8 -1 (Day 8)
shCdk8 -2 (Day 8)
shCdk8 -1 (Day 13)
shCdk8 -2 (Day 13)
shMed12 -1 (Day 13)
shMed12 -2 (Day 13)
Diff (Retinoic Acid)
Diff (DMSO)
Diff (HMBA)
siNanog
siOct4
SMC1A-MED12-NIPBL1-POL2-occupied genes (CTCF absent)
(genes defined by Kagey et al., Nature, 2010)
fold change
-1.3
1.3
shCdk8 -1 (Day 8)
shCdk8 -2 (Day 8)
shCdk8 -1 (Day 13)
shCdk8 -2 (Day 13)
shMed12 -1 (Day 13)
shMed12 -2 (Day 13)
siNanog
fold change
-2
2
shMed12 (Kagey et al.)
Diff (Retinoic Acid)
Diff (DMSO)
Diff (HMBA)
siOct4
E
Pearson correlation to shMed12 (Kagey et al.)
1.0
0.8
0.4
0.2
0.0
-0.2
P = 10-30
P = 10-15
P = 10-5
shCdk8 -1 (Day 8)
shCdk8 -2 (Day 8)
shCdk8 -1 (Day 13)
shCdk8 -2 (Day 13)
shMed12 -1 (Day 13)
shMed12 -2 (Day 13)
Diff (Retinoic Acid)
Diff (DMSO)
Diff (HMBA)
siNanog
siOct4

Figure 9

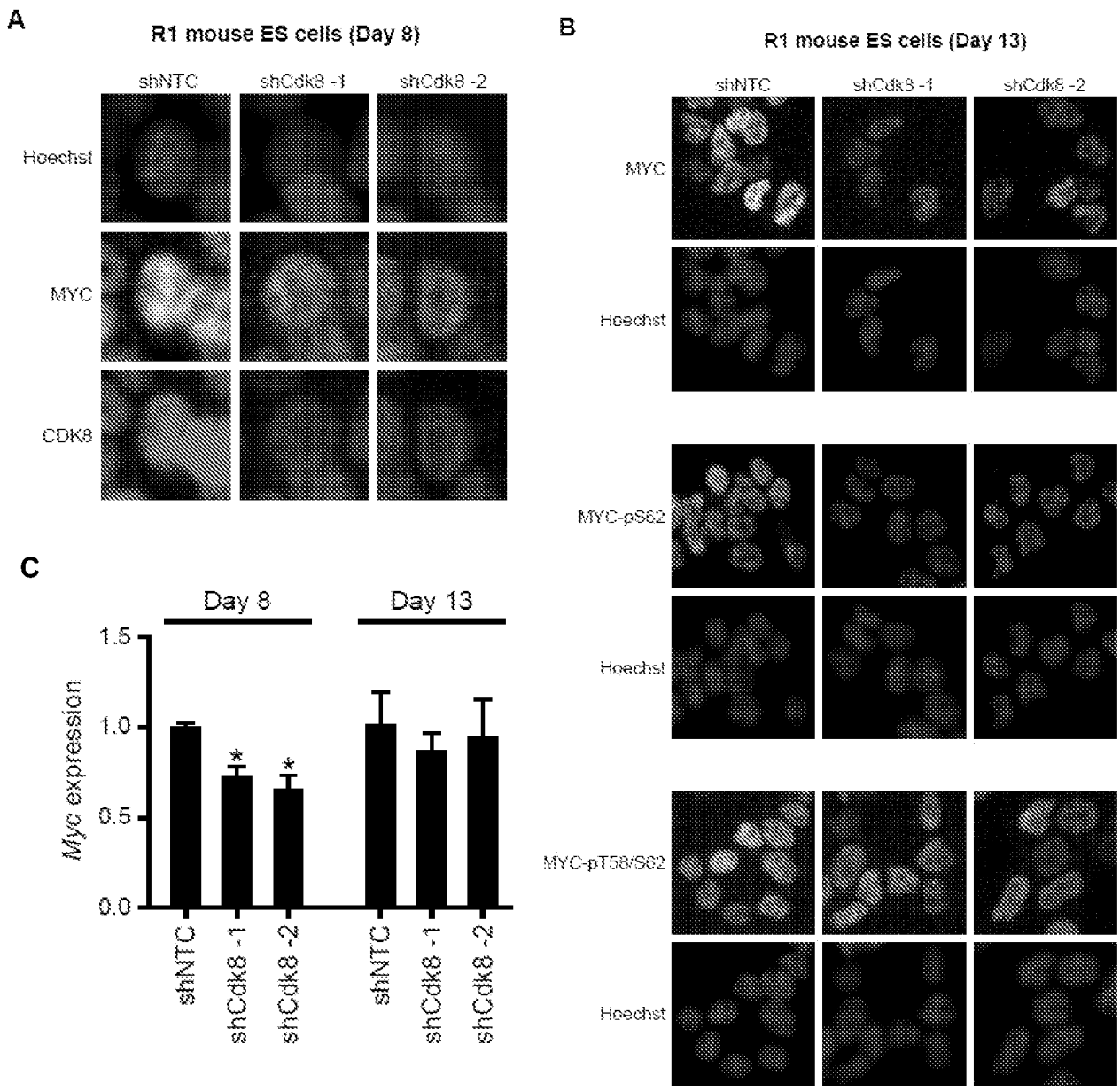

A
R1 mouse ES cells (Day 8)
shNTC
shCdk8 -1
shCdk8 -2
Hoechst
MYC
CDK8
B
R1 mouse ES cells (Day 13)
shNTC
shCdk8 -1
shCdk8 -2
MYC
Hoechst
MYC-pS62
Hoechst
MYC-pT58/S62
Hoechst
C
Day 8
Day 13
Myc expression
1.5
1.0
0.5
0.0
*
*
shNTC
shCdk8 -1
shCdk8 -2
shNTC
shCdk8 -1
shCdk8 -2

Figure 10

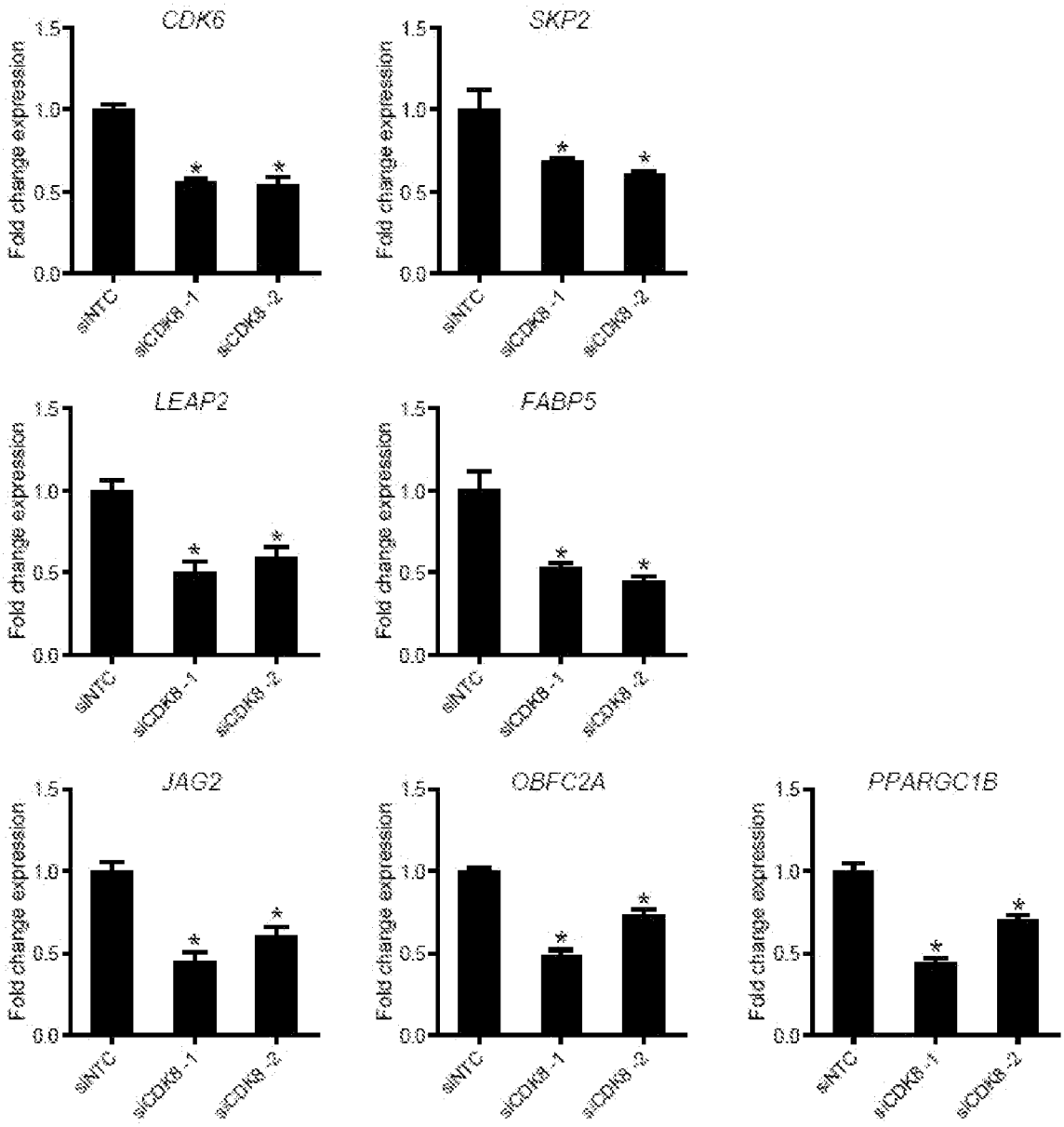
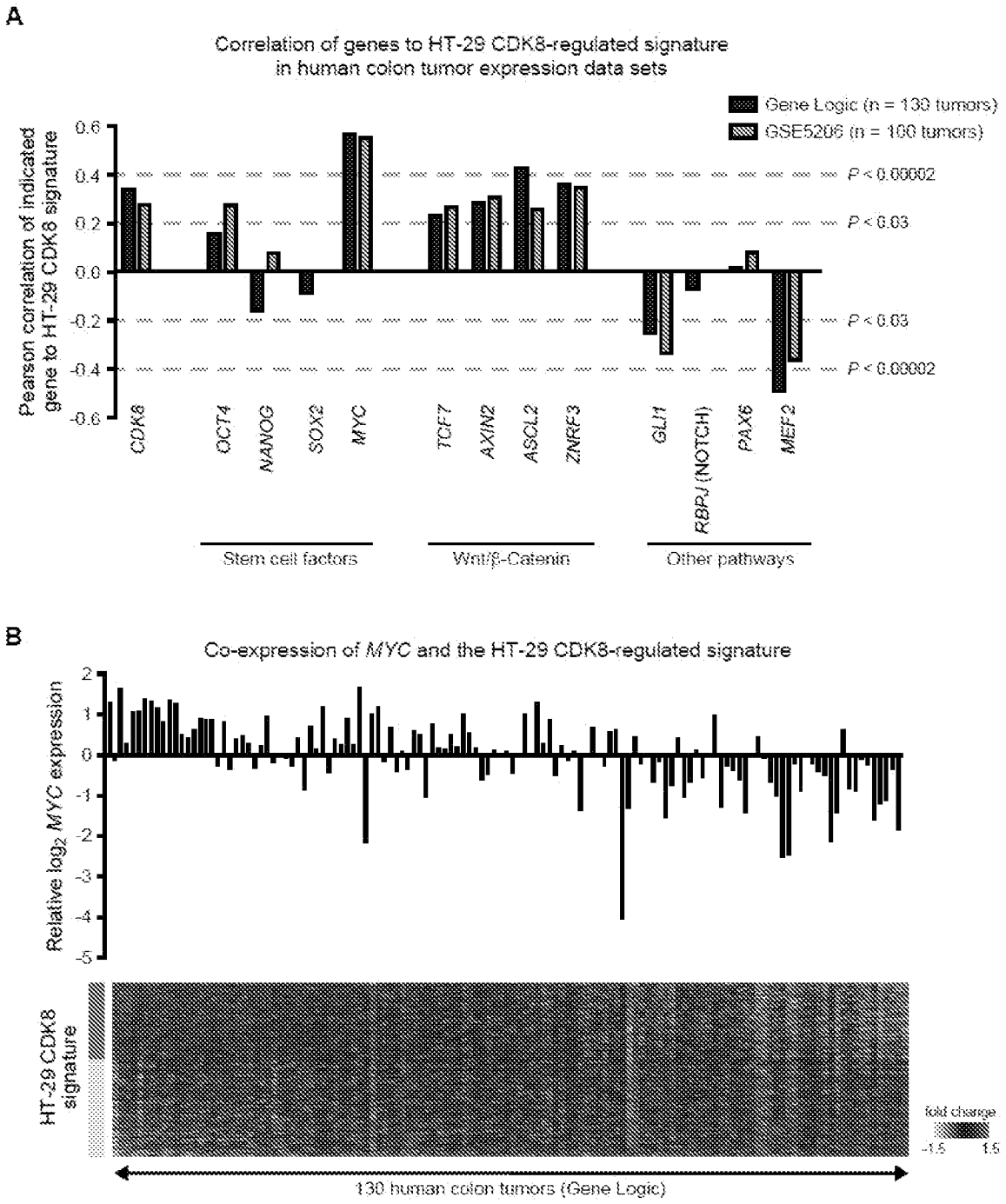

CDK6
SKP2
LEAP2
FABP5
JAG2
OBFC2A
PPARGC1B
Fold change expression
1.5
1.0
0.5
0.0
*
siNTC
siCDK8 -1
siCDK8 -2

Figure 11


A
Correlation of genes to HT-29 CDK8-regulated signature
in human colon tumor expression data sets
Gene Logic (n = 130 tumors)
GSE5206 (n = 100 tumors)
Pearson correlation of indicated gene to HT-29 CDK8 signature
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
P < 0.00002
P < 0.03
P < 0.03
P < 0.00002
CDK8
OCT4
NANOG
SOX2
MYC
TCF7
AXIN2
ASCL2
ZNRF3
GLI1
RBPJ (NOTCH)
PAX6
MEF2
Stem cell factors
Wnt/β-Catenin
Other pathways
B
Co-expression of MYC and the HT-29 CDK8-regulated signature
Relative log2 MYC expression
2
1
0
-1
-2
-3
-4
-5
HT-29 CDK8 signature
fold change
-1.5
1.5
130 human colon tumors (Gene Logic)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/025729

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C12Q 1/68 (2006.01) ***A61P 35/00*** (2006.01) ***G01N 33/68*** (2006.01)
A61K 31/7105 (2006.01) ***G01N 33/574*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI, EPODOC, MEDLINE, HCAPLUS, EMBASE, BIOSIS, BIOTECHABS: CDK8, antagonist, sorafenib, cancer, differentiation and like terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ADLER, A. S. et al., 'CDK8 maintains tumor dedifferentiation and embryonic stem cell pluripotency', Cancer Research, available online 16 February 2012, Vol. 72, No. 8, pages 2129-2139 See the whole document, particularly the abstract, page 2130 right column third paragraph to page 2131 right column first paragraph, page 2135 left column third paragraph to page 2137 left column second paragraph, page 2137 final paragraph, Figures 1-2 and Supplementary Tables 1-2	1-34
X	HE, S.-B., 'Effects of cyclin-dependent kinase 8 specific siRNA on the proliferation and apoptosis of colon cancer cells', Journal of Experimental & Clinical Cancer Research, 2011, Vol. 30, No. 109, pages 1-9 See the whole document, particularly the abstract, Figures 4 and 6-7 and the final paragraphs of the discussion and conclusions sections	8-34

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

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"O" document referring to an oral disclosure, use, exhibition or other means
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 May 2012	24 May 2012
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **JONATHAN KONRAD** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6283 2601

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/023525 A2 (DHARMACON, INC.) 19 February 2009 See Examples 4-5 and Table 6 on page 121	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/025729

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
WO 2009023525	US 2011263675

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX