

METHOD OF TREATING MEDULLOBLASTOMA WITH AN EZH2 INHIBITOR**RELATED APPLICATIONS**

[01] This application claims priority to, and the benefit of U.S. Provisional Application Nos. 62/238,074 filed October 6, 2015, and 62/299,312 filed February 24, 2016, the contents of each of which are incorporated herein by reference in their entireties.

FIELD OF THE DISCLOSURE

[02] The disclosure is directed to the fields of small molecule therapies, cancer, and methods of treating rare cancer types.

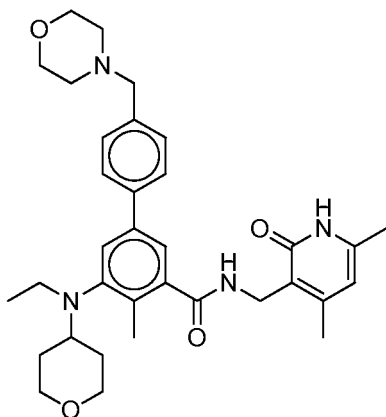
BACKGROUND

[03] There is a long-felt yet unmet need for effective treatments for certain cancers caused by genetic alterations or loss of function of subunits of the SWI/SNF chromatin remodeling complex that result in EZH2-dependent oncogenesis.

SUMMARY

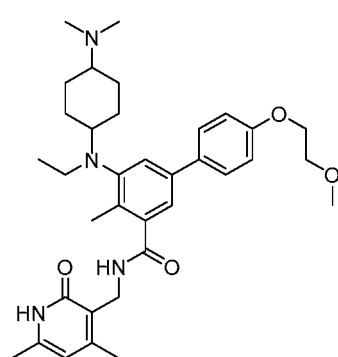
[04] The disclosure provides a method of treating a medulloblastoma in a subject in need thereof comprising administering to the subject a therapeutically-effective amount of an enhancer of a zeste homolog 2 (EZH2) inhibitor. Methods of treating medulloblastoma of the disclosure may comprise preventing and/or inhibiting proliferation of a medulloblastoma cell.

[05] In certain embodiments of the methods of the disclosure, the EZH2 inhibitor comprises

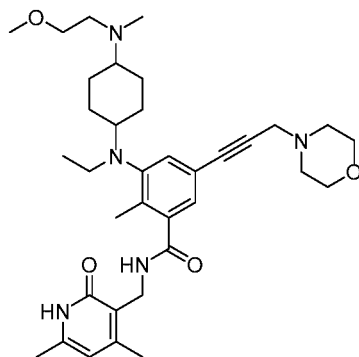


(Compound A or tazemetostat), or a pharmaceutically-acceptable salt thereof.

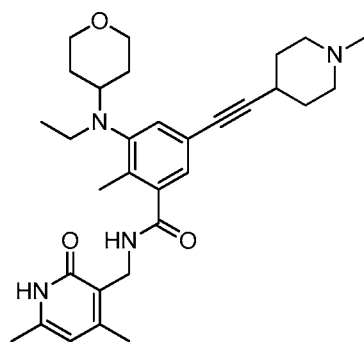
[06] In certain embodiments of the methods of the disclosure, the EZH2 inhibitor comprises



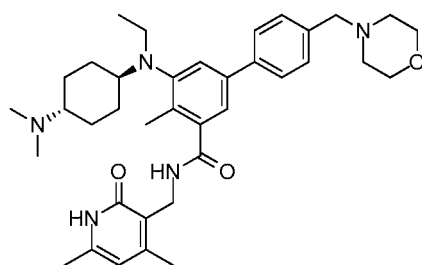
(A'),



(B),



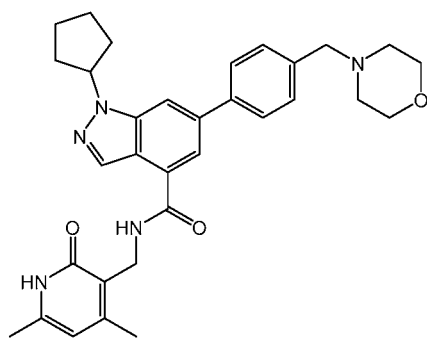
(C),



(D), a stereoisomer, a

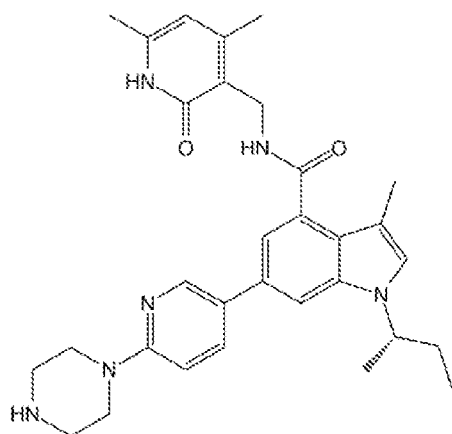
pharmaceutically acceptable salt and/or a solvate thereof.

[07] In certain embodiments of the methods of the disclosure, the EZH2 inhibitor comprises



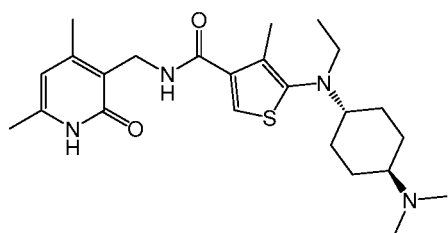
(E) or a pharmaceutically acceptable salt thereof.

[08] In certain embodiments of the methods of the disclosure, the EZH2 inhibitor comprises



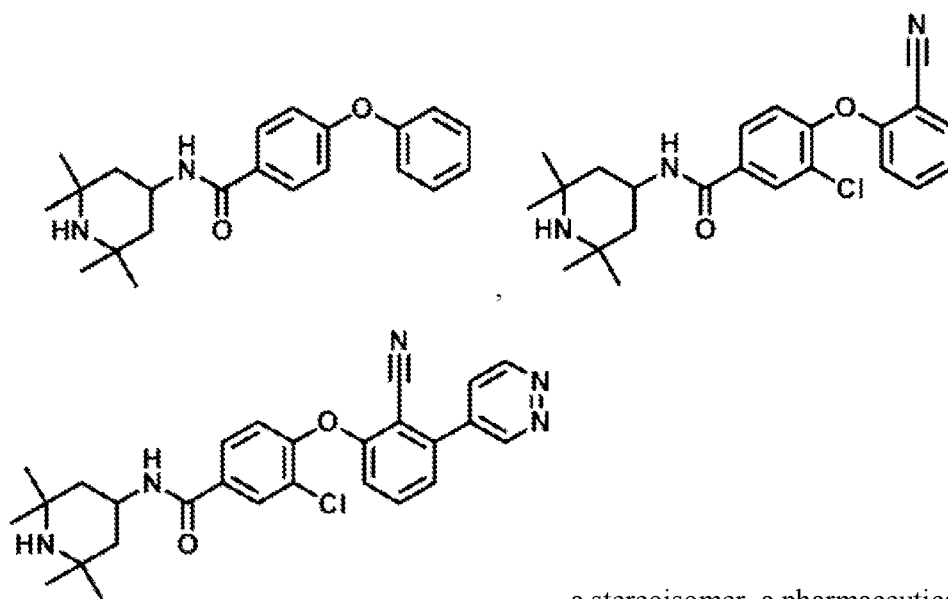
, a stereoisomer, a pharmaceutically acceptable salt and/or a solvate thereof.

[09] In certain embodiments of the methods of the disclosure, the EZH2 inhibitor comprises



, a stereoisomer, a pharmaceutically acceptable salt and/or a solvate thereof.

[010] In certain embodiments of the methods of the disclosure, the EZH2 inhibitor comprises



, a stereoisomer, a pharmaceutically acceptable salt and/or a solvate thereof.

[0111] EZH2 inhibitors of the disclosure may be administered orally. For example, the EZH2 inhibitor may be formulated as an oral tablet or suspension.

[012] EZH2 inhibitors of the disclosure may be formulated for administration to cerebral spinal fluid (CSF) by any route. Exemplary routes of administration to the CSF include, but are not limited to, an intraspinal, an intracranial, an intrathecal or an intranasal route.

[013] In certain embodiments of the methods of the disclosure, including, but not limited to, those embodiments wherein the EZH2 inhibitor is formulated as an oral tablet, EZH2 inhibitors of the disclosure may be administered at a dose of between 10 mg/kg/day and 1600 mg/kg/day. EZH2 inhibitors of the disclosure may be administered at a dose of about 100, 200, 400, 800, or 1600 mg. EZH2 inhibitors of the disclosure may be administered at a dose of about 800 mg. EZH2 inhibitors of the disclosure may be administered once or twice per day (BID). For example, EZH2 inhibitors of the disclosure may be administered at a dose of between 10 mg/kg/day and 1600 mg/kg/day BID. EZH2 inhibitors of the disclosure may be administered at a dose of 800 mg BID.

[014] In certain embodiments of the methods of the disclosure, including, but not limited to, those embodiments wherein the EZH2 inhibitor is formulated as an oral suspension and/or formulated to administration to the CSF by any route, EZH2 inhibitors of the disclosure may be administered at a dose of 50%, 60%, 70%, 80%, 90%, or any percentage in between of a value of an area under the curve (AUC) of a steady state plasma and/or CSF concentration (AUC_{ss}) of an EZH2 inhibitor, wherein the AUC_{ss} is determined following administration of the EZH2 inhibitor to an adult subject at a dose of between 10 mg/kg/day and 1600 mg/kg/day BID.

[015] In certain embodiments of the methods of the disclosure, including, but not limited to, those embodiments wherein the EZH2 inhibitor is formulated as an oral suspension and/or formulated to administration to the CSF by any route, EZH2 inhibitors of the disclosure may be administered at a dose of between 230 mg/m² and 600 mg/m², inclusive of the endpoints. EZH2 inhibitors of the disclosure may be administered at a dose of between 300 mg/m² and 600 mg/m². EZH2 inhibitors of the disclosure may be administered at a dose of between 230 mg/m² and 305 mg/m², inclusive of the endpoints. EZH2 inhibitors of the disclosure may be administered at a dose of 240 mg/m². EZH2 inhibitors of the disclosure may be administered at a dose of 300 mg/m². EZH2 inhibitors of the disclosure may be administered once or twice per day (BID). For example, EZH2 inhibitors of the disclosure may be administered at a dose of between 230 mg/m² and 600 mg/m² BID, inclusive of the endpoints.

[016] For example, an EZH2 inhibitor of the disclosure may be administered at a dose of about 60% of the area under the curve (AUC) at steady state (ACU_{ss}) following administration of 1600 mg twice a day to an adult subject. Accordingly, an EZH2 inhibitor of the disclosure administered at a dose of about 60% of the area under the curve (AUC) at steady state (ACU_{ss}) following administration of 1600 mg twice a day to an adult subject, is administered at a dose of about 600 mg/m^2 per day or at least 600 mg/m^2 per day. In certain aspects of this example, the subject treated with the EZH2 inhibitor is a pediatric subject.

[017] For example, an EZH2 inhibitor of the disclosure may be administered at a dose of about 80% of the area under the curve (AUC) at steady state (ACU_{ss}) following administration of 800 mg twice a day to an adult subject. Accordingly, an EZH2 inhibitor of the disclosure administered at a dose of about 80% of the area under the curve (AUC) at steady state (ACU_{ss}) following administration of 800 mg twice a day to an adult subject, is administered at a dose of about 390 mg/m^2 per day or at least 390 mg/m^2 per day. In certain aspects of this example, the subject treated with the EZH2 inhibitor is a pediatric subject.

[018] Subjects of the disclosure may be pediatric subjects. For example, a pediatric subject of the disclosure may be between 6 months and 21 years of age, inclusive of the endpoints. A pediatric subject of the disclosure may be between 1 year and 18 years of age, inclusive of the endpoints. A pediatric subject of the disclosure may be 10 years of age or less. A pediatric subject of the disclosure may be 5 years of age or less. A pediatric subject of the disclosure may be between 6 months and 1 year of age, inclusive of the endpoints.

[019] The disclosure provides a method of treating medulloblastoma in a subject in need thereof comprising administering to the subject a therapeutically-effective amount of tazemetostat, wherein the therapeutically effective amount is at least 300 mg/m^2 twice per day (BID), and wherein the subject is between 6 months and 21 years of age, inclusive of the endpoints.

BRIEF DESCRIPTION OF THE DRAWINGS

[020] Figures 1A and 1B are a series of Western blot analyses of cell lines with wild type (RD and SJCRH30) and mutant SNF5.

[021] Figures 2A-2E are a series of graphs establishing that SNF5 mutant cell lines A204 (C), G401 (D) and G402 (E) selectively respond to EZH2 compound (Compound D) compared to wild type cell lines RD (A) and SJCRH30 (B).

[022] Figures 3A-3D are a series of bar graphs showing that G401 SNF mutant cell line is responding to Compound D after 7 days in soft agar compared to wild type cells RD. A shows cell line RD (5,000 cells/well). B shows G401 cells (5,000 cells/well). C shows G401 cells in 2D growth. D shows G401 cells (10,000 cells/well).

[023] Figures 4A-4D are four graphs showing that G401 SNF5 mutant cell line is sensitive to Compound A *in vitro*. Wild type cell line SJCRH30 (A) and RD (C) and SNF5 mutant cell line G401 (B) and A204 (D) were pretreated for 7 days with indicated concentrations of Compound A and replated on day 0. Cell viability was determined by CellTiter-Glo® Luminescent Cell Viability Assay.

[024] Figures 5A-5E are a series of graphs showing durable regressions in G401 xenografts (malignant rhabdoid tumor model) with Compound A treatment. (A) Tumor regressions induced by Compound A at the indicated doses. (B) Tumor regressions induced by twice daily administration of Compound A at the indicated doses. Data represent the mean values $\pm$ SEM (n=8). Compound administration was stopped on day 28. (C) EZH2 target inhibition in G401 xenograft tumor tissue collected from a parallel cohort of mice on day 21. Each point shows the ratio of H3K27Me3 to total H3. Horizontal lines represent group mean values. BLLQ = below lower limit of quantification. (D, E) Immunohistochemical staining of tumor histone methylation of tumor samples from the vehicle treated (D) and Compound A treated (E) (at 125 mg/kg) mice.

[025] Figure 6 is a graph showing the locations of ATRX mutations identified in SCLC cell lines.

[026] Figure 7A is a graph showing that LNCAP prostate cancer cells display dose-dependent cell growth inhibition with Compound D treatment *in vitro*.

[027] Figure 7B is a graph showing IC₅₀ value of Compound D at day 11 and day 14 for WSU-DLCL2 and LNCAP cells.

[028] Figures 8A-8C are three graphs establishing that ATRX mutant SCLC lines NCI-H446 (A), SW1271 (B) and NCI-H841 (C) are responding to Compound D.

[029] Figures 9A-9C are three microscopy images showing that SCLC line NCI-H841 changes morphology after treatment with vehicle (A) or Compound D at concentration of 4.1E-02 μ M (B) or 3.3 μ M (C).

[030] Figures 10A-10C are a series of graphs showing effects of Compound A on cellular global histone methylation and cell viability. (A) Chemical structure of Compound A (or tazemetostat). (B) Concentration-dependent inhibition of cellular H3K27Me3 levels in

G401 and RD cells. (C) Selective inhibition of proliferation of *SMARCB1*-deleted G401 cells by Compound A in vitro (measured by ATP content). G401 (panels a and b) and RD cells (panels c and d) were re-plated at the original seeding densities on day 7. Each point represents the mean for each concentration (n=3).

[031] Figures 11A and 11B are a series of graphs showing biochemical mechanism of action studies. The IC₅₀ value of Compound A increases with increasing SAM concentration (A) and is minimally affected by increasing oligonucleosome concentration (B), indicating SAM-competitive and nucleosome-noncompetitive mechanism of action.

[032] Figures 12A and 12B are a series of panels demonstrating verification of SMARCB1 and EZH2 expression in cell lines and specificity of Compound A for inhibition of cellular histone methylation. (A) Cell lysates were analyzed by immunoblot with antibodies specific to SMARCB1, EZH2 and Actin (loading control). (B) Selective inhibition of cellular H3K27 methylation in G401 and RD cells. Cells were incubated with Compound A for 4 days, and acid-extracted histones were analyzed by immunoblot.

[033] Figures 13A and 13B are a series of bar graphs demonstrating that Compound A induces G₁ arrest and apoptosis in *SMARCB1*-deleted MRT cells. Cell cycle analysis (by flow cytometry) and determination of apoptosis (by TUNEL assay) in RD (panel A) or G401 cells (panel B) during incubation with either vehicle or 1 μ M Compound A for up to 14 days. G₁ arrest was observed as of day 7 and apoptosis was induced as of day 11. Data are represented as mean values $\pm$ SEM (n=2). The DMSO control values shown are the average $\pm$ SEM from each time point. Cells were split and re-plated on days 4, 7 and 11 at the original seeding density.

[034] Figures 14A-14C are a series of graphs showing that Compound A induces changes in expression of SMARCB1 regulated genes and cell morphology. (A) Basal expression of SMARCB1 regulated genes in G401 *SMARCB1*-deleted cells, relative to RD control cells (measured by qPCR, n=2). (B) G401 and RD cells were incubated with either DMSO or 1 μ M Compound A for 2, 4 and 7 days. Gene expression was determined by qPCR (n=2) and is expressed relative to the DMSO control of each time point. Panels a-j correspond to genes GLI1, PTCh1, DOCK4, CD133, PTPRK, BIN1, CDKN1A, CDKN2A, EZH2, and MYC, respectively. (C) G402 cells were incubated with either DMSO (left panel) or 1 μ M Compound A (right panel) for 14 days. Cells were split and re-plated to the original seeding density on day 7.

[035] Figures 15A-15D are series of graphs demonstrating body weights, tumor regressions and plasma levels in G401 xenograft bearing mice treated with Compound A. (A) Body weights were determined twice a week for animals treated with Compound A on a BID schedule for 28 days. Data are presented as mean values $\pm$ SEM (n=16 until day 21, n=8 from day 22 to 60). (B) Tumor regressions induced by twice daily (BID) administration of Compound A for 21 days at the indicated doses (mean values $\pm$ SEM, n=16). * $p < 0.05$, ** $p < 0.01$, repeated measures ANOVA, Dunnett's post-test vs. vehicle. (C) Tumor weights of 8 mice euthanized on day 21. **** $p < 0.0001$, Fisher's exact test. (D) Plasma was collected 5 min before and 3 h after dosing of Compound A on day 21, and compound levels were measured by LC-MS/MS. Animals were euthanized, and tumors were collected 3 h after dosing on day 21. Tumor homogenates were generated and subjected to LC-MS/MS analysis to determine Compound A concentrations. Note that tumor compound levels could not be determined from all animals especially in the higher dose groups because the xenografts were too small on day 21. Dots represent values for the individual animals; horizontal lines represent group mean values.

[036] Figures 16A-16C are a series of graphs showing that Compound A eradicates *SMARCB1*-deleted MRT xenografts in SCID mice. (A) Tumor regressions induced by twice daily (BID) administration of Compound A for 28 days at the indicated doses. Compound administration was stopped on day 28 and tumors were allowed to re-grow until they reached 2000 mm³ (data shown as mean values $\pm$ SEM, n=8). (B) EZH2 target inhibition in G401 xenograft tumor tissue collected from mice euthanized on day 21. Each point shows the ratio of H3K27Me3 to total H3, measured by ELISA. Horizontal lines represent group mean values; grey symbols are values outside of the ELISA standard curve. (C) Change in gene expression in G401 xenograft tumor tissue collected from mice treated with Compound A for 21 days. Panels a-d correspond to genes CD133, PTPRK, DOCK4, and GLI1, respectively. Data are presented as fold change compared to vehicle $\pm$ SEM (n=6, n=4 for 500 mg/kg group). * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$, vs. vehicle, Fisher's exact test.

[037] Figure 17 is a schematic diagram depicting epigenetic control of gene expression. Combinations of histone modifications encode information that governs coordinated activation or repression of genetic programs as well as developmental cell identity and fate decisions.

[038] Figure 18 is a graph showing that EZH2 is over expressed and associated with chromosome 7 amplification in medulloblastoma. Solid bars indicate a balanced chromosome 7 whereas hatched bars indicate a chromosome 7 gain.

[039] Figure 19 is a schematic diagram depicting control of histone lysine methylation by EZH2 and MLL.

[040] Figure 20A is a graph showing the probability of overall survival (OS) as a function of time since diagnosis (in months) with medulloblastoma. Histone lysine methylation is altered in medulloblastoma. H3K27me3 abundance is increased in medulloblastoma cells compared to control cells.

[041] Figure 20B is a graph showing the probability of overall survival (OS) as a function of time since diagnosis (in months) with medulloblastoma. Histone lysine methylation is altered in medulloblastoma. H3K27me3 abundance is increased in medulloblastoma cells compared to control cells.

[042] Figure 21A is a series of photographs and a graph showing the abundances of H3K4me3 and H3K27Me3 in medulloblastoma cells. The data demonstrate deregulation of the histone code in medulloblastoma.

[043] Figure 21B is a graph depicting the probability of overall survival as a function of time since diagnosis (in months) for medulloblastoma subjects having deregulated histone methylation at H3K4me3 and/or H3K27Me3.

[044] Figure 22A is a graph demonstrating that inhibition of EZH2 by a short-hairpin EZH2 (shEZH2) construct suppresses medulloblastoma cell growth (growth of the DAOY medulloblastoma cell line) compared to a negative-control construct.

[045] Figure 22B a series of photographs and a graph demonstrating that inhibition of EZH2 by a short-hairpin EZH2 (shEZH2) construct suppresses medulloblastoma cell growth (growth of the DAOY medulloblastoma cell line) compared to a negative-control construct and/or the empty pSIF vector control.

[046] Figure 23A is a schematic diagram depicting the mechanism by which INI1 loss creates an oncogenic dependency on EZH2 in tumors.

[047] Figure 23B is a graph showing the percent of tumor-free survival of INI1 deficient mice as a function of time (days) when EZH2 is knocked out. EZH2 knockout reverses oncogenesis induced by INI1 loss.

[048] Figure 24A is a series of photographs showing control or EZH2 inhibitor-treated (DNZep-treated) atypical teratoid rhabdoid tumors (ATRTs) at 1, 3, 5, and 7 days post-treatment. Inhibition of EZH2 suppresses ATRT cell self-renewal.

[049] Figure 24B is a graph quantifying the results of Figure 24A.

[050] Figure 24C is a graph quantifying the results of Figure 24A.

[051] Figure 24D is a series of photographs showing control or EZH2 inhibitor-treated (DNZep-treated) atypical teratoid rhabdoid tumors (ATRTs) at 3, 5, 8 and 10 days post-treatment. Inhibition of EZH2 suppresses ATRT cell self-renewal.

[052] Figure 24E is a graph quantifying the results of Figure 24D.

[053] Figure 25A is a pair of graphs showing a surviving fraction of untreated or DZNEP-treated ATRT cells (from a BT-16 ATRT cell line) exposed to 2Gy radiation. Inhibition of EZH2 radio-sensitizes ATRT.

[054] Figure 25B is a pair of graphs showing a surviving fraction of untreated or DZNEP-treated ATRT cells (from a UPN737 ATRT cell line, "737") exposed to 2Gy radiation. Inhibition of EZH2 radio-sensitizes ATRT.

[055] Figure 26A is a graph showing the concentration of medulloblastoma cells (total cells per milliliter) as a function of time (days) following treatment with GSK-126, a small molecule inhibitor of EZH2. Small molecule inhibitors of EZH2 decrease medulloblastoma cell growth.

[056] Figure 26B is a graph showing the concentration of medulloblastoma cells (total cells per milliliter) as a function of time (days) following treatment with UNC 1999, a small molecule inhibitor of EZH2. Small molecule inhibitors of EZH2 decrease medulloblastoma cell growth.

[057] Figure 26C is a graph showing the concentration of medulloblastoma cells (total cells per milliliter) as a function of time (days) following treatment with tazemetostat (EPZ 6438), a small molecule inhibitor of EZH2. Small molecule inhibitors of EZH2 decrease medulloblastoma cell growth.

[058] Figure 26D is a graph showing the concentration of medulloblastoma cells (total cells per milliliter) as a function of time (days) following treatment with GSK-126, UNC 1999, and tazemetostat (EPZ 6438). Tazemetostat has the greatest effect on medulloblastoma cell growth of the small molecule inhibitors tested.

[059] Figure 27 is a pair of schematic diagrams depicting the relative selectivity of tazemetostat for EZH2.

[060] Figure 28A is a schematic diagram depicting the process by which primary medulloblastoma cell growth is evaluated ex vivo.

[061] Figure 28B is a graph depicting the relative abundances (percent of cells) of untreated or tazemetostat (EPZ 6438)-treated primary medulloblastoma cells in various cell cycle stages (sub G₀/G₁, G₀/G₁, S, or G₂/M). A slice culture of medulloblastoma was freshly isolated from a 5 year old subject. The slice culture was treated with tazemetostat for 4 days before being disaggregated and analyzed by flow cytometry. Tazemetostat treatment decreases primary medulloblastoma cell growth ex vivo.

[062] Figure 28C is a graph depicting BrdU expression of the cells analyzed in Figure 28B. Tazemetostat treatment decreases primary medulloblastoma cell growth ex vivo.

[063] Figure 29A is a graph depicting percent survival of vehicle or tazemetostat (EPZ 6438)-treated ATRT cells in vivo as a function of time (days) post-treatment. Tazemetostat decreases ATRT in vivo.

[064] Figure 29B is a photograph of a Western blot showing the relative amounts of H2K27me3 and H3 in vehicle or tazemetostat (EPZ 6438)-treated ATRT cells from Figure 29A.

DETAILED DESCRIPTION

[065] The disclosure provides a method of treating a medulloblastoma in a subject in need thereof comprising administering to the subject a therapeutically-effective amount of an enhancer of a zeste homolog 2 (EZH2) inhibitor. Methods of treating medulloblastoma of the disclosure may comprise preventing and/or inhibiting proliferation of a medulloblastoma cell.

[066] The disclosure provides a method for treating or alleviating a symptom of a SWI/SNF-associated cancer in a subject by administering to a subject in need thereof a therapeutically effective amount of an EZH2 inhibitor. For example, the SWI/SNF-associated cancer is characterized by reduced expression and/or loss of function of the SWI/SNF complex or one or more components of the SWI/SNF complex. In a preferred embodiment, the cancer is medulloblastoma

[067] Medulloblastoma results from reduced expression and/or loss of function of the SWI/SNF complex or one or more components of the SWI/SNF complex, including, but not limited to, SNF5, ATRX, and ARID1A. For example, the loss of function is caused by a loss of function mutation resulting from a point mutation, a deletion, and/or an insertion.

[068] For example, the subject has a deletion of SNF5.

[069] For example, the subject has a mutation of ATRX selected from the group consisting of a substitution of asparagine (N) for the wild type residue lysine (K) at amino acid position 688 of SEQ ID NO: 5 (K688N), and a substitution of isoleucine (I) for the wild type residue methionine (M) at amino acid position 366 of SEQ ID NO: 5 (M366I).

[070] For example, subject has a mutation of ARID1A selected from the group consisting of a nonsense mutation for the wild type residue cysteine (C) at amino acid position 884 of SEQ ID NO: 11 (C884*), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 966 (E966K), a nonsense mutation for the wild type residue glutamine (Q) at amino acid position 1411 of SEQ ID NO: 11 (Q1411*), a frame shift mutation at the wild type residue phenylalanine (F) at amino acid position 1720 of SEQ ID NO: 11 (F1720fs), a frame shift mutation after the wild type residue glycine (G) at amino acid position 1847 of SEQ ID NO: 11 (G1847fs), a frame shift mutation at the wild type residue cysteine (C) at amino acid position 1874 of SEQ ID NO: 11 (C1874fs), a substitution of glutamic acid (E) for the wild type residue aspartic acid (D) at amino acid position 1957 (D1957E), a nonsense mutation for the wild type residue glutamine (Q) at amino acid position 1430 of SEQ ID NO: 11 (Q1430*), a frame shift mutation at the wild type residue arginine (R) at amino acid position 1721 of SEQ ID NO: 11 (R1721fs), a substitution of glutamic acid (E) for the wild type residue glycine (G) at amino acid position 1255 (G1255E), a frame shift mutation at the wild type residue glycine (G) at amino acid position 284 of SEQ ID NO: 11 (G284fs), a nonsense mutation for the wild type residue arginine (R) at amino acid position 1722 of SEQ ID NO: 11 (R1722*), a frame shift mutation at the wild type residue methionine (M) at amino acid position 274 of SEQ ID NO: 11 (M274fs), a frame shift mutation at the wild type residue glycine (G) at amino acid position 1847 of SEQ ID NO: 11 (G1847fs), a frame shift mutation at the wild type residue P at amino acid position 559 of SEQ ID NO: 11 (P559fs), a nonsense mutation for the wild type residue arginine (R) at amino acid position 1276 of SEQ ID NO: 11 (R1276*), a frame shift mutation at the wild type residue glutamine (Q) at amino acid position 2176 of SEQ ID NO: 11 (Q2176fs), a frame shift mutation at the wild type residue histidine (H) at amino acid position 203 of SEQ ID NO: 11 (H203fs), a frame shift mutation at the wild type residue alanine (A) at amino acid position 591 of SEQ ID NO: 11 (A591fs), a nonsense mutation for the wild type residue glutamine (Q) at amino acid position 1322 of SEQ ID NO: 11 (Q1322*), a nonsense mutation for the wild type residue serine (S) at amino acid position 2264 of SEQ ID NO: 11 (S2264*), a nonsense mutation for the wild type residue glutamine (Q) at amino acid position 586 of

SEQ ID NO: 11 (Q586*), a frame shift mutation at the wild type residue glutamine (Q) at amino acid position 548 of SEQ ID NO: 11 (Q548fs), and a frame shift mutation at the wild type residue asparagine (N) at amino acid position 756 of SEQ ID NO: 11 (N756fs).

[071] The disclosure also provides a method of treating or alleviating a symptom of a SWI/SNF-associated cancer in a subject in need thereof by (a) determining the expression level of at least one gene selected from the group consisting of neuronal differentiation genes, cell cycle inhibition genes and tumor suppressor genes in a sample obtained from the subject; (b) selecting the subject having a decreased expression level of at least one gene in step a; and (c) administering to the subject selected in step b an effective amount of an EZH2 inhibitor, thereby treating or alleviating a symptom of cancer in the subject. In a preferred embodiment, the cancer is medulloblastoma.

[072] The disclosure further provides a method of treating or alleviating a symptom of a SWI/SNF-associated cancer in a subject in need thereof by (a) determining the expression level of at least one gene selected from the group consisting of hedgehog pathway genes, myc pathway genes and histone methyltransferase genes in a sample obtained from the subject; (b) selecting the subject having an increased expression level of at least one gene in step a; and (c) administering to the subject selected in step b an effective amount of an EZH2 inhibitor, thereby treating or alleviating a symptom of cancer in the subject. In a preferred embodiment, the cancer is medulloblastoma.

[073] For example, the neuronal differentiation gene is CD133, DOCK4, or PTPRK.

[074] For example, the cell cycle inhibition gene is CKDN1A or CDKN2A.

[075] For example, the tumor suppressor gene is BIN1.

[076] For example, the hedgehog pathway gene is GLI1 or PTCH1.

[077] For example, the myc pathway gene is MYC.

[078] For example, the histone methyltransferase gene is EZH2.

[079] The disclosure also provides a method of inducing neuronal differentiation, cell cycle inhibition or tumor suppression by contacting a cell with an EZH2 inhibitor. The EZH2 inhibitor may be in an amount sufficient to increase expression of at least one gene selected from the group consisting of CD133, DOCK4, PTPRK, CKDN1A, CDKN2A and BIN1.

[080] The disclosure also provides a method of inhibiting hedgehog signaling by contacting a cell with an EZH2 inhibitor. The EZH2 inhibitor can be in an amount sufficient to reduce expression of GLI1 and/or PTCH1.

[081] The disclosure also provides a method of inducing gene expression by contacting a cell with an EZH2 inhibitor. The EZH2 inhibitor can be in an amount sufficient to induce neuronal differentiation, cell cycle inhibition and/or tumor suppression. For example, the gene can be CD133, DOCK4, PTPRK, CKDN1A, CKDN2A or BIN1.

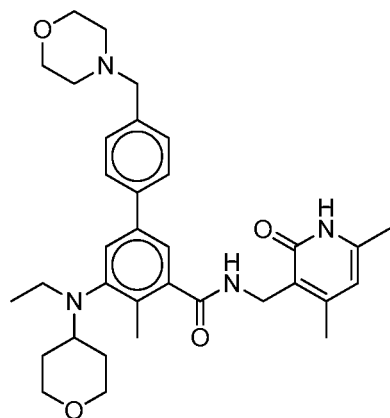
[082] The disclosure also provides a method of inhibiting gene expression by contacting a cell with an EZH2 inhibitor. The EZH2 inhibitor is in an amount sufficient to inhibit hedgehog signaling. For example, the gene can be GLI1 or PTCH1.

[083] For example, the cell may have loss of function of SNF5, ARID1A, ATRX, and/or a component of the SWI/SNF complex.

[084] For example, the loss of function is caused by a deletion of SNF5.

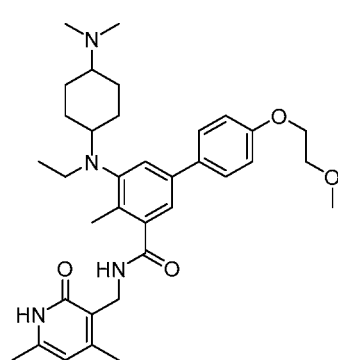
[085] For example, the cell is a cancer cell. Preferably, the cancer is medulloblastoma.

[086] For example, the EZH2 inhibitor comprises

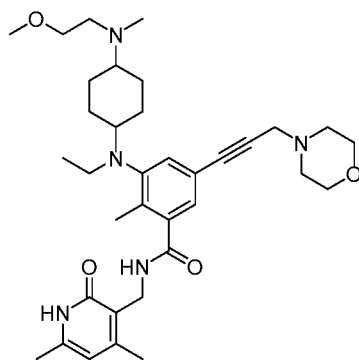


(tazemetostat), or a pharmaceutically-acceptable salt thereof.

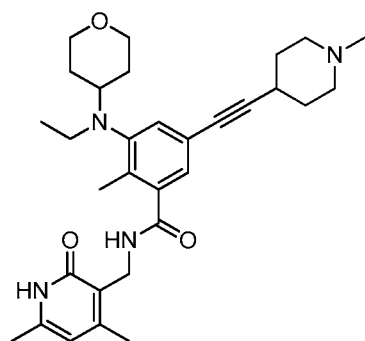
[087] For example, the EZH2 inhibitor comprises



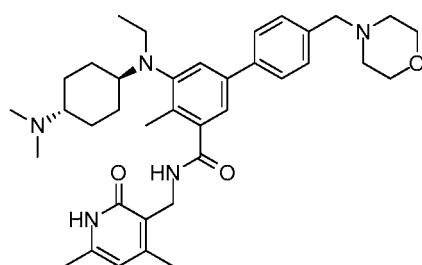
(A'),



(B),



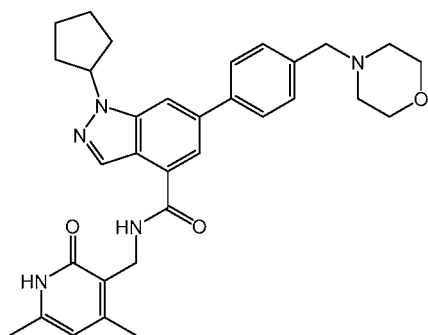
(C),



(D), a stereoisomer, a

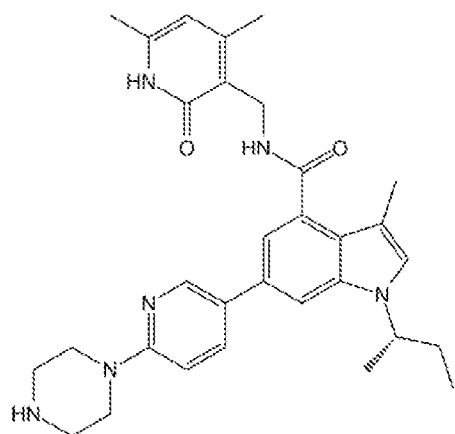
pharmaceutically acceptable salt and/or a solvate thereof.

[088] For example, the EZH2 inhibitor comprises



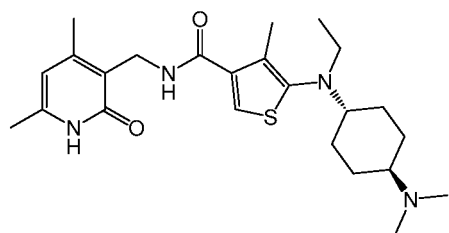
(E) or a pharmaceutically acceptable salt thereof.

[089] For example, the EZH2 inhibitor comprises



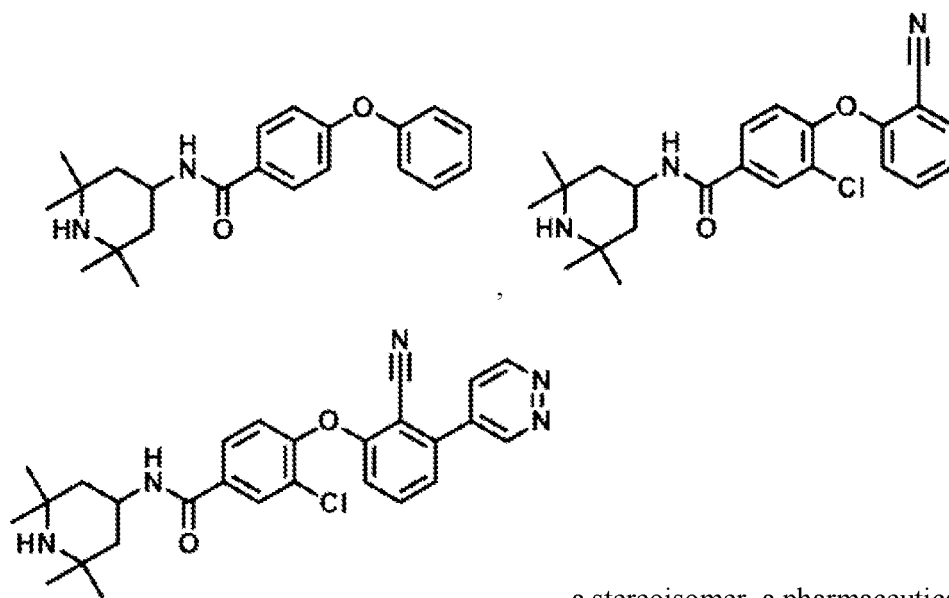
 , a stereoisomer, a pharmaceutically acceptable salt and/or a solvate thereof.

[090] For example, the EZH2 inhibitor comprises



and/or a solvate thereof.

[091] For example, the EZH2 inhibitor comprises



C1=CC=C(C=C1)C2=CC=CC=C2C3=CC=CC=C3C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9C10=CC=CC=C10C11=CC=CC=C11C12=CC=CC=C12C13=CC=CC=C13C14=CC=CC=C14C15=CC=CC=C15C16=CC=CC=C16C17=CC=CC=C17C18=CC=CC=C18C19=CC=CC=C19C20=CC=CC=C20C21=CC=CC=C21C22=CC=CC=C22C23=CC=CC=C23C24=CC=CC=C24C25=CC=CC=C25C26=CC=CC=C26C27=CC=CC=C27C28=CC=CC=C28C29=CC=CC=C29C30=CC=CC=C30C31=CC=CC=C31C32=CC=CC=C32C33=CC=CC=C33C34=CC=CC=C34C35=CC=CC=C35C36=CC=CC=C36C37=CC=CC=C37C38=CC=CC=C38C39=CC=CC=C39C40=CC=CC=C40C41=CC=CC=C41C42=CC=CC=C42C43=CC=CC=C43C44=CC=CC=C44C45=CC=CC=C45C46=CC=CC=C46C47=CC=CC=C47C48=CC=CC=C48C49=CC=CC=C49C50=CC=CC=C50C51=CC=CC=C51C52=CC=CC=C52C53=CC=CC=C53C54=CC=CC=C54C55=CC=CC=C55C56=CC=CC=C56C57=CC=CC=C57C58=CC=CC=C58C59=CC=CC=C59C60=CC=CC=C60C61=CC=CC=C61C62=CC=CC=C62C63=CC=CC=C63C64=CC=CC=C64C65=CC=CC=C65C66=CC=CC=C66C67=CC=CC=C67C68=CC=CC=C68C69=CC=CC=C69C70=CC=CC=C70C71=CC=CC=C71C72=CC=CC=C72C73=CC=CC=C73C74=CC=CC=C74C75=CC=CC=C75C76=CC=CC=C76C77=CC=CC=C77C78=CC=CC=C78C79=CC=CC=C79C80=CC=CC=C80C81=CC=CC=C81C82=CC=CC=C82C83=CC=CC=C83C84=CC=CC=C84C85=CC=CC=C85C86=CC=CC=C86C87=CC=CC=C87C88=CC=CC=C88C89=CC=CC=C89C90=CC=CC=C90C91=CC=CC=C91C92=CC=CC=C92C93=CC=CC=C93C94=CC=CC=C94C95=CC=CC=C95C96=CC=CC=C96C97=CC=CC=C97C98=CC=CC=C98C99=CC=CC=C99C100=CC=CC=C100C101=CC=CC=C101C102=CC=CC=C102C103=CC=CC=C103C104=CC=CC=C104C105=CC=CC=C105C106=CC=CC=C106C107=CC=CC=C107C108=CC=CC=C108C109=CC=CC=C109C110=CC=CC=C110C111=CC=CC=C111C112=CC=CC=C112C113=CC=CC=C113C114=CC=CC=C114C115=CC=CC=C115C116=CC=CC=C116C117=CC=CC=C117C118=CC=CC=C118C119=CC=CC=C119C120=CC=CC=C120C121=CC=CC=C121C122=CC=CC=C122C123=CC=CC=C123C124=CC=CC=C124C125=CC=CC=C125C126=CC=CC=C126C127=CC=CC=C127C128=CC=CC=C128C129=CC=CC=C129C130=CC=CC=C130C131=CC=CC=C131C132=CC=CC=C132C133=CC=CC=C133C134=CC=CC=C134C135=CC=CC=C135C136=CC=CC=C136C137=CC=CC=C137C138=CC=CC=C138C139=CC=CC=C139C140=CC=CC=C140C141=CC=CC=C141C142=CC=CC=C142C143=CC=CC=C143C144=CC=CC=C144C145=CC=CC=C145C146=CC=CC=C146C147=CC=CC=C147C148=CC=CC=C148C149=CC=CC=C149C150=CC=CC=C150C151=CC=CC=C151C152=CC=CC=C152C153=CC=CC=C153C154=CC=CC=C154C155=CC=CC=C155C156=CC=CC=C156C157=CC=CC=C157C158=CC=CC=C158C159=CC=CC=C159C160=CC=CC=C160C161=CC=CC=C161C162=CC=CC=C162C163=CC=CC=C163C164=CC=CC=C164C165=CC=CC=C165C166=CC=CC=C166C167=CC=CC=C167C168=CC=CC=C168C169=CC=CC=C169C170=CC=CC=C170C171=CC=CC=C171C172=CC=CC=C172C173=CC=CC=C173C174=CC=CC=C174C175=CC=CC=C175C176=CC=CC=C176C177=CC=CC=C177C178=CC=CC=C178C179=CC=CC=C179C180=CC=CC=C180C181=CC=CC=C181C182=CC=CC=C182C183=CC=CC=C183C184=CC=CC=C184C185=CC=CC=C185C186=CC=CC=C186C187=CC=CC=C187C188=CC=CC=C188C189=CC=CC=C189C190=CC=CC=C190C191=CC=CC=C191C192=CC=CC=C192C193=CC=CC=C193C194=CC=CC=C194C195=CC=CC=C195C196=CC=CC=C196C197=CC=CC=C197C198=CC=CC=C198C199=CC=CC=C199C200=CC=CC=C200C201=CC=CC=C201C202=CC=CC=C202C203=CC=CC=C203C204=CC=CC=C204C205=CC=CC=C205C206=CC=CC=C206C207=CC=CC=C207C208=CC=CC=C208C209=CC=CC=C209C210=CC=CC=C210C211=CC=CC=C211C212=CC=CC=C212C213=CC=CC=C213C214=CC=CC=C214C215=CC=CC=C215C216=CC=CC=C216C217=CC=CC=C217C218=CC=CC=C218C219=CC=CC=C219C220=CC=CC=C220C221=CC=CC=C221C222=CC=CC=C222C223=CC=CC=C223C224=CC=CC=C224C225=CC=CC=C225C226=CC=CC=C226C227=CC=CC=C227C228=CC=CC=C228C229=CC=CC=C229C230=CC=CC=C230C231=CC=CC=C231C232=CC=CC=C232C233=CC=CC=C233C234=CC=CC=C234C235=CC=CC=C235C236=CC=CC=C236C237=CC=CC=C237C238=CC=CC=C238C239=CC=CC=C239C240=CC=CC=C240C241=CC=CC=C241C242=CC=CC=C242C243=CC=CC=C243C244=CC=CC=C244C245=CC=CC=C245C246=CC=CC=C246C247=CC=CC=C247C248=CC=CC=C248C249=CC=CC=C249C250=CC=CC=C250C251=CC=CC=C251C252=CC=CC=C252C253=CC=CC=C253C254=CC=CC=C254C255=CC=CC=C255C256=CC=CC=C256C257=CC=CC=C257C258=CC=CC=C258C259=CC=CC=C259C260=CC=CC=C260C261=CC=CC=C261C262=CC=CC=C262C263=CC=CC=C263C264=CC=CC=C264C265=CC=CC=C265C266=CC=CC=C266C267=CC=CC=C267C268=CC=CC=C268C269=CC=CC=C269C270=CC=CC=C270C271=CC=CC=C271C272=CC=CC=C272C273=CC=CC=C273C274=CC=CC=C274C275=CC=CC=C275C276=CC=CC=C276C277=CC=CC=C277C278=CC=CC=C278C279=CC=CC=C279C280=CC=CC=C280C281=CC=CC=C281C282=CC=CC=C282C283=CC=CC=C283C284=CC=CC=C284C285=CC=CC=C285C286=CC=CC=C286C287=CC=CC=C287C288=CC=CC=C288C289=CC=CC=C289C290=CC=CC=C290C291=CC=CC=C291C292=CC=CC=C292C293=CC=CC=C293C294=CC=CC=C294C295=CC=CC=C295C296=CC=CC=C296C297=CC=CC=C297C298=CC=CC=C298C299=CC=CC=C299C300=CC=CC=C300C301=CC=CC=C301C302=CC=CC=C302C303=CC=CC=C303C304=CC=CC=C304C305=CC=CC=C305C306=CC=CC=C306C307=CC=CC=C307C308=CC=CC=C308C309=CC=CC=C309C310=CC=CC=C310C311=CC=CC=C311C312=CC=CC=C312C313=CC=CC=C313C314=CC=CC=C314C315=CC=CC=C315C316=CC=CC=C316C317=CC=CC=C317C318=CC=CC=C318C319=CC=CC=C319C320=CC=CC=C320C321=CC=CC=C321C322=CC=CC=C322C323=CC=CC=C323C324=CC=CC=C324C325=CC=CC=C325C326=CC=CC=C326C327=CC=CC=C327C328=CC=CC=C328C329=CC=CC=C329C330=CC=CC=C330C331=CC=CC=C331C332=CC=CC=C332C333=CC=CC=C333C334=CC=CC=C334C335=CC=CC=C335C336=CC=CC=C336C337=CC=CC=C337C338=CC=CC=C338C339=CC=CC=C339C340=CC=CC=C340C341=CC=CC=C341C342=CC=CC=C342C343=CC=CC=C343C344=CC=CC=C344C345=CC=CC=C345C346=CC=CC=C346C347=CC=CC=C347C348=CC=CC=C348C349=CC=CC=C349C350=CC=CC=C350C351=CC=CC=C351C352=CC=CC=C352C353=CC=CC=C353C354=CC=CC=C354C355=CC=CC=C355C356=CC=CC=C356C357=CC=CC=C357C358=CC=CC=C358C359=CC=CC=C3

[092] Human nucleic acid and amino acid sequence of components of the SWI/SNF complex have previously been described. *See, e.g.*, GenBank Accession Nos NP_003064.2, NM_003073.3, NP_001007469.1, and NM_001007468.1 for SNF5, GenBank Accession Nos NM_000489.3, NP_000480.2, NM_138270.2, and NP_612114.1 for ATRX, GenBank Accession Nos NP_006006.3, NM_006015.4, NP_624361.1, and NM_139135.2 for ARID1A, each of which is incorporated herein by reference in its entirety.

[093] Spectrum of hSNF5 somatic mutations in human has also been described in Sevenet *et al.*, Human Molecular Genetics, 8: 2359-2368, 1999, which is incorporated herein by reference in its entirety.

[094] A subject in need thereof may have reduced expression, haploinsufficiency, and/or loss of function of SNF5. For example, a subject can comprise a deletion of SNF5 in SNF5 polypeptide or a nucleic acid sequence encoding a SNF5 polypeptide.

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 isoform a (SMARCB1, also called SNF5) [Homo sapiens] (SEQ ID NO: 1)					
1	mmmmalsktf	gqkpvkfql	ddgefymigs	evgnylrmfr	gslykrypsl
61	kkivasshsk	ktkpnkdhg	ytatlatsvtl	lkaseveeil	dgndekykav
121	reqkakrnsq	wvptlpnssh	hldavpcstt	inrnmgrdk	krtfplcfdd
181	sqpevlvpir	ldmeidgqkl	rdaftwnmne	klmtpemfse	ilcddldlnp
241	irqqiesypt	dsiledqsdq	rviiklnihv	gnislvdqfe	wdmsekensp
301	lglggefvt	iaysirgqls	whqktyafse	nplptveiai	rntgdadqwc
361	mekkirdqdr	ntrrmrlan	tapaw		

Homo sapiens SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 (SMARCB1, also called SNF5), transcript variant 1, mRNA (SEQ ID NO: 2)						
1	aacgccagcg	cctgcgcaact	gagggcgggc	tggctgctcg	ctgcccgggc	ggcgcgggct
61	gaggagcccg	gctgaggcgc	cagtaaccgg	cccggctccg	atttcgcctt	ccggttcggg
121	tttccctcgg	cccagcacgc	cccggccccg	ccccagccct	cctgatccct	cgcagcccgg
181	ctccggccgc	ccgcctctgc	cgccgcaatg	atgatgatgg	cgctgagcaa	gaccttcggg
241	cagaagcccg	tgaagttcca	gctggaggag	gacggcgagt	tctacatgat	cggctccgag
301	gtgggaaact	acctccgtat	gttccgaggt	tctctgtaca	agagataccc	ctcactctgg
361	aggcgactag	ccactgtgga	agagaggaag	aaaatagttg	catcgtcaca	tggtaaaaaa
421	acaaaacct	acactaagga	tcacggatac	acgactctag	ccaccagtgt	gaccctgtta
481	aaagcctcgg	aagtgggaag	gattctggat	ggcaacgatg	agaagtacaa	ggctgtgtcc
541	atcagcacag	agccccccac	ctacctcagg	gaacagaagg	ccaagaggaa	cagccagtgg
601	gtacccaccc	tgcccaacag	ctccccacc	ttagatgccg	tgccatgctc	cacaaccatc
661	aacaggaacc	gcatgggccc	agacaagaag	agaaccttcc	ccctttgctt	tgatgaccat
721	gaccagctg	tgatccatga	gaacgcactc	cagcccaggg	tgctgggtccc	catccggctg
781	gacatggaga	tcgatgggca	gaagctgcga	gacgccttca	cctggaacat	gaatgagaag
841	ttgatgagcg	ctgagatgtt	ttcagaaatc	ctctgtgacg	atctggattt	gaaccgctg
901	acgtttgtgc	cagccatcgc	ctctgccatc	agacagcaga	tcgagtccta	ccccacggac
961	agcatcctgg	aggaccagtc	agaccagcgc	gtcatcatca	agctgaacat	ccatgtggga
1021	aacatttccc	tggtggacca	gtttgagtgg	gacatgtcag	agaaggagaa	ctcaccagag
1081	aagtttgccc	tgaagctgtg	ctcggagctg	gggttgggcg	gggagtttgt	caccaccatc
1141	gcatacagca	tccggggaca	gctgagctgg	catcagaaga	cctacgcctt	cagcgagaac
1201	cctctgccc	cagtggagat	tgccatccgg	aacacgggcg	atgcccagca	gtggtgccc
1261	ctgctggaga	ctctgacaga	cgctgagatg	gagaagaaga	tccgcgacca	ggacaggaac

1321	acgaggcgga	tgaggcgctct	tgccaacacg	gccccggcct	ggtaaccagc	ccatcagcac
1381	acggctccca	cggagcatct	cagaagattg	ggccgcctct	cctccatctt	ctggcaagga
1441	cagaggcgag	gggacagccc	agcgccatcc	tgaggatcgg	gtgggggtgg	agtgggggct
1501	tccagggtggc	ccttcccggc	acacattcca	tttgttgagc	cccagtcctg	ccccccaccc
1561	caccctccct	acccctcccc	agtctctggg	gtcaggaaga	aaccttattt	taggttgtgt
1621	tttgtttttg	tataggagcc	ccaggcaggg	ctagtaacag	tttttaataa	aaaggcaaca
1681	ggtcatgttc	aatttcttca	acaaaaaaaa	aaaaaaa		

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 isoform b [Homo sapiens] (SMARCB1, also called SNF5) (SEQ ID NO: 3)

1	mmmmalsktf	gqkpvkfql	ddgefymigs	evgnylrmfr	gslykrypsl	wrrlatveer
61	kkivasshdh	gyttlatsvt	llkaseveei	ldgndekyka	vsistepty	lreqkkrns
121	qwwptlpnss	hhldavpcst	tinrnmgrd	kkrtfplcfd	dhdpavihen	asqpevlvpi
181	rldmeidgqk	lrdaftwnmn	eklmtpemfs	eilcddldln	pltfvpaiaa	airqqiesyp
241	tdsiledqsd	qrviiklnih	vgnislvdqf	ewdmsekens	pekfalklcs	elglggefvt
301	tiaysirgql	swhqktyafs	enplptveia	irntgdadqw	cplletlttda	emekkirdqd
361	nrtrmrrla	ntapaw				

Homo sapiens SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 (SMARCB1, also called SNF5), transcript variant 2, mRNA (SEQ ID NO: 4)

1	aacgccagcg	cctgcgcact	gagggcgggc	tggtcgtcgt	ctgcggcggc	ggcgcgcgct
61	gaggagcccg	gctgaggcgc	cagtaaccgg	cccgggtccgc	atttcgcctt	ccggcttcgg
121	tttcctctcg	cccagcacgc	cccggccccg	cccagccct	cctgatccct	cgcagcccg
181	ctccggccgc	ccgcctctgc	cgccgcaatg	atgatgatgg	cgctgagcaa	gacctctggg
241	cagaagcccg	tgaagtcca	gctggaggac	gacggcgagt	tctacatgat	cggctccgag
301	gtgggaaact	acctccgtat	gttccgaggt	tctctgtaca	agagataccc	ctcactctgg
361	aggcgactag	ccactgtgga	agagaggaag	aaaatagttg	catcgtcaca	tgatcacgga
421	tacacgactc	tagccaccag	tgtgaccctg	ttaaaagcct	cggaaagtga	agagattctg
481	gatgggcaacg	atgagaagta	caaggctgtg	tccatcagca	cagagcccc	cacctacctc
541	agggaacaga	aggccaagag	gaacagccag	tgggtaccca	ccctgcccaa	cagctcccac
601	cacttagatg	ccgtgccatg	ctccacaacc	atcaacagga	accgcatggg	ccgagacaag
661	aagagaacct	tccccctttg	ctttgatgac	catgaccag	ctgtgatcca	tgagaacgca
721	tctcagcccg	aggtgctggt	ccccatccgg	ctggacatgg	agatcgatgg	gcagaagctg
781	cgagacgcct	tcacctggaa	catgaatgag	aagttgatga	cgctgagat	gttttcagaa
841	atcctctgtg	acgatctgga	tttgaaccgg	ctgacgtttg	tgccagccat	cgctctgcc
901	atcagacagc	agatcgagtc	ctaccccacg	gacagcatcc	tggaggacca	gtcagaccag
961	cgcgtcatca	tcaagctgaa	catccatgtg	ggaaacattt	ccctgggtgga	ccagtttgag
1021	tgggacatgt	cagagaagga	gaactcacca	gagaagtgtg	ccctgaagct	gtgctcggag
1081	ctgggggttg	gcgggggagtt	tgtaaccacc	atcgcataca	gcatccgggg	acagctgagc
1141	tggcatcaga	agacctacgc	cttcagcgag	aacctctctg	ccacagtggg	gattgccatc
1201	cggaaacacg	gcgatgcgga	ccagtgggtg	ccactgctgg	agactctgac	agacgtgag
1261	atggagaaga	agatccgcga	ccaggacagg	aacacgaggc	ggatgaggcg	tcttgccaac
1321	acggccccgg	cctggttaacc	agccccatcag	cacacggctc	ccacggagca	tctcagaaga
1381	ttggggccgc	tctcctccat	cttctggcaa	ggacagaggc	gaggggacag	cccagcgcca
1441	tcctgaggat	cgggtggggg	tggagtgggg	gcttccaggt	ggcccttccc	ggcacacatt
1501	ccatttggtg	agccccagtc	ctgcccccca	ccccaccctc	cctaccctct	ccagctctct
1561	ggggtcagga	agaaacctta	tttttaggttg	tgttttgttt	ttgtatagga	gcccaggcca
1621	gggctagtaa	cagtttttaa	ataaaaggca	acaggtcatg	ttcaatttct	tcaacaaaaa
1681	aaaaaaaaa					

[095] A subject in need thereof may have reduced expression, haploinsufficiency, and/or loss of function of ATRX. For example, a subject can comprise a mutation selected from the group consisting of a substitution of asparagine (N) for the wild type residue lysine (K) at amino acid position 688 of SEQ ID NO: 5 (K688N), and a substitution of isoleucine (I) for the wild type residue methionine (M) at amino acid position 366 of SEQ ID NO: 5 (M366I).

Homo sapiens alpha thalassemia/mental retardation syndrome X-linked (ATRX) isoform 1 (SEQ ID NO: 5)						
1	mtaepmsesk	lntlvqklhd	flahsseeese	etsspprlam	nqntdkisgs	gsnsdmmens
61	keegtsssek	skssgssrsk	rkpsivtkyv	esddeklpdd	etvnedasne	nsenditmqg
121	lpkgtvivqp	epvlnekdd	fkpgefrsrs	kmktenlkk	gedglhgivs	ctacgqqvnh
181	fqkdsiyrhp	slqvlicknc	fkyymsddis	rdsdgmdeqc	rwcaeggnli	ccdfchnafc
241	kkcilrnlgr	kelstimden	nqwycyichp	eplldlvtac	nsvfenleql	lqqnkkkikv
301	dseksnkvy	htsrfsppkt	ssncngeekk	lddscsgsvt	ysysalivpk	emikkakkli
361	ettanmnssy	vkflkqatdn	seissatklr	qlkafksvla	dikkahlale	edlnsefram
421	davnkeknk	ehkvidakfe	tkarkgekpc	alekkdisk	eaklsrkqvd	sehmhqnvp
481	eeqrtnkstg	gehksdrke	epqyepants	edldmdivsv	pssvpedife	nletamevqs
541	svdhqgdgss	gtegevevss	vklnisskdn	rggiksktta	kvtkelyvkl	tpvslsnspi
601	kgadcqevpq	dkdgykscgl	npklekcglg	qensdnehlv	enevslillee	sdlrrsprvk
661	ttplrrptet	npvtsnsdee	cnetvkekqk	lsvpvrkkdk	rnssdsaidn	pkpnklpksk
721	qsetvdqnsd	sdemlailke	vsrmshssss	dt dineihtn	hktlydlktq	agkddkgrk
781	rksstsgsdf	dtkkgksaks	siiskkkrrt	qsessnydse	lekeiksmk	igaarttkkr
841	ipntkdfdss	edekhskkgm	dnqghknlkt	sqegssddae	rkqeretfss	aegtvdkdt
901	imelrdrlpk	kqqasastdg	vdklsgkeqs	ftslevrkva	etkekskhk	tktckkvqdg
961	lsdiaekflk	kdqsdetsed	dkkqskkgte	ekkkpsdfkk	kvikmeqqye	sssdgteklp
1021	ereichfhp	gikqikngtt	dgeksskkir	dktskkkdel	sdyaekstgk	gdsdssedk
1081	kskngaygre	kkrcckllgk	srkrqdcsss	dtekysmked	gcnsddkrlk	rielrerrnl
1141	sskrntkeiq	sgssssdaee	ssednkkkkq	rtsskkkavi	vkekkrnsrl	tstkrkqadi
1201	tsssssdied	ddqnsigegs	sdeqkikpvt	enlvlsstg	fcqssgdeal	sksvpvtvdd
1261	ddddndpenr	iakkmllleei	kanlssdedg	ssddepeegk	krtgkqneen	pgdeeaqnq
1321	nsesdsdsee	skkpryrhrl	lrhklvtvsg	esgeekktkp	kehkevkggrn	rrkvssedse
1381	dsdfqesgvs	eevsesedeq	rprrtsakka	eleenqrsyk	qkkkrrrikv	qedsssenks
1441	nseeeeeeee	eeeeeeeeee	eeeedendds	kspgkgrkki	rkilkddklr	tetqnalkee
1501	eerrkriaer	erereklev	ieiedasptk	cpittklvld	edeetkeplv	qvhnmvikl
1561	kphqvqgvqf	mwdccesvk	ktkkspgsgc	ilahcmglgk	tlqvvsflht	vllcdkldfs
1621	talvvcpplt	alnwmnefek	wqeglkddk	levselatvk	rpqersymql	rwqedggvmi
1681	igyemyrnla	qgrnvksrkl	keifnkaldv	pgpdfvvcde	ghilkneasa	vskamnsirs
1741	rrriiltgtp	lqnnlieyhc	mvnfikenll	gsikefrnrf	inpiqngqca	dstmvdvrvm
1801	kkrahilyem	lagcvqrkdy	taltkflppk	heyvlavrmt	siqcklyqyy	ldhltgvgnn
1861	seggrgkaga	klfqdfqmls	riwthpwclq	ldyiskenkg	yfdedsmdf	iasdsdetsm
1921	slssddytkk	kkkgkkkgkd	sssgsgsdn	dvevikvwns	rsrgggegng	detgnnpsvs
1981	lkleeskats	ssnpsspapd	wykdfvtad	aevlehsgkm	vllfeilrma	eeigdkvlvf
2041	sqslisldli	edflelasre	ktedkdkpli	ykgegwlrn	idyyrldgst	taqsrkkwae
2101	efndetnvr	rlfiistkag	slginlvaan	rviifdaswn	psydiqsifr	vyrfgqtkpv
2161	yvyrfllaqgt	medkiydrqv	tkqslsfrvv	dqqqverhft	mneltelytf	epdllddpns
2221	ekkkkrdrtpm	lpkdtlael	lqihehivg	yhehdslldh	keeeelteee	rkaawaeyea
2281	ekkgltmrfn	iptgtnlppv	sfnsqtpyip	fnlgalsams	nqqledling	grekvveatn
2341	svtavriqpl	ediisavwke	nmnlseaqvq	alalsrqasq	eldvkrreai	yndvltkqqm
2401	liscvqrilm	nrllqqqynq	qqqqqmttyq	atlghlmpk	ppnlmnpns	yqqidmrgmy
2461	qpvaggmqpp	plqrapppmr	sknpgpsqgk	sm		

Homo sapiens alpha thalassemia/mental retardation syndrome X-linked (ATRX), transcript variant 1, mRNA (SEQ ID NO: 6)							
1	aattctcctg	cctgagcctc	ggcccaacaa	aatggcggcg	gcagcgggtg	cgctttgttt	
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421	gggaactagc	tcttcagaaa	aatccaagtc	ttcaggatcg	tcacgatcaa	agaggaaacc	
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961	cattctacgc	aaccttggtc	gaaaggagtt	gtccacaata	atggatgaaa	acaaccaatg	
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10321	atgtcattta	ataaagtgtg	caaaatgtgt	tgtgctcttt	attgtatttt	cacagctttg
10381	aaaatctgtg	cacatactgt	ttcatagaaa	atgtatagct	tttggtgtcc	tatataatgg
10441	tggttctttt	gcacatttag	ttattttaata	ttgagaggtc	acgaagtttg	gttattgaaat
10501	ctgttatata	ctaaattctg	taaagggaga	tctctcatct	caaaaagaat	ttacatacca
10561	ggaagtccat	gtgtgtttgt	gttagttttg	gatgtctttg	tgtaatccag	ccccattttc
10621	tgtttcccaa	cagctgtaac	actcatttta	agtcaagcag	ggctaccaac	ccacacttga

10681	tagaaaagct	gcttaccatt	cagaagcttc	cttattacct	ggcctccaaa	tgagctgaat
10741	atthttgtagc	cttcccttag	ctatgttcat	tttccctcca	ttatcataaa	atcagatcga
10801	tattttatgtg	ccccaaacaa	aactttaaga	gcagttacat	tctgtcccag	tagcccttgt
10861	ttccttttgag	agtagcatgt	tgtgaggcta	tagagactta	ttctaccagt	aaaacaggtc
10921	aatccttttta	catgtttatt	atactaaaaa	ttatgttcag	ggtattttact	actttatttc
10981	accagactca	gtctcaagtg	acttggtat	ctccaaatca	gatctaccct	tagagaataa
11041	acatthtttct	accgttattt	tttttcaagt	ctataatctg	agccagtcct	aaaggagtga
11101	tcaagtttca	gaaatgcttt	catcttcaca	acatthttata	tatactatta	tatggggtga
11161	ataaagttht	aaatccgaaa	tataaaaaaa	aaaaaaaaaa	aa	

**Homo sapiens alpha thalassemia/mental retardation syndrome X-linked (ATRX) isoform 2
(SEQ ID NO: 7)**

1	mtaepmsesk	lntlvqklhd	flahsseese	etsspprlam	nqntdkisgs	gsnsdmmens
61	keegtsssek	skssgssrsk	rkpsivtkyv	esddeklpdd	etvnedasne	nsenditmqs
121	lpkedglhgi	vsctacgqv	nhfqkdsiyr	hpslqvlick	ncfkyymsdd	isrdsdgmde
181	qcrwcaeggn	liccdfchna	fckkcilrnl	grkelstimd	ennqwycyic	hpeplldlvt
241	acnsvfenle	qllqqnkkki	kvdseksnk	yehtsrfsfk	ktssnncgee	kklddscsgs
301	vtysysaliv	pkemikkakk	liettanmns	syvklfkqat	dnseissatk	lrqlkafksv
361	ladikkahla	leedlnsefr	amdavnkekn	tkehkvidak	fetkarkgek	pcalekkdis
421	kseaklsrkq	vdsehmhqn	pteeqrtnks	tggehkksdr	keepqyepan	tsedldmdiv
481	svpsvpedi	fenletamev	qssvdhggdg	ssgteqeves	ssvklmissk	dnrggiksks
541	takvtekely	kltpvslsns	pikgadcqev	pqdkdgyksc	glnpklekcg	lgqensdneh
601	lvenevslll	eesdlrrspr	vkttplrrpt	etnpvtsnsd	eecnetvkek	qklsvprkkk
661	dkrnssdsai	dnpkpnklpk	skqsetvdqn	sdsdemlail	kevsrmshss	ssdtineih
721	tnhktlydlk	tqagkddkqk	rkrksstsgs	dfdtkkkksa	kssiiskkkk	qtqsessnyd
781	selekeiksm	skigaarttk	kripntkdfd	ssedekhskk	gmdnqghknl	qtsqegssdd
841	aerkqeretf	ssaegtvdkd	ttimelrdrl	pkkqqasast	dgvdklsgke	qsftslevrk
901	vaetkkskh	lktktckkvq	dglstdiaekf	lkdkqsdets	eddkkqskkg	teekkkpsdf
961	kkkvikmeqq	yesssdgtek	lpereichf	pkgikqikng	ttdegkkskk	irdktskkkd
1021	elsdyaekst	gkgdscdsse	dkkskngayg	rekkrckllg	kssrkrqdc	ssdtekysmk
1081	edgcnsddr	lkrielrerr	nlsskrntke	iqsgssssda	eessednkkk	kqrtsskkka
1141	vivkekkrns	lrtstkrkqa	ditssssdi	edddqnsige	gssdeqkikp	vtelnvlssh
1201	tgfcqssgde	alsksvpvtv	ddddddndpe	nriakmlle	eikanlssde	dgssddepee
1261	gkkrtgkqne	enpgdeeakn	qvnssedsds	eeskkpryrh	rllrhkltsv	dgesgeekkt
1321	kpkhekvekg	rnrrkvssed	sedsdqfges	vseevsesed	eqrprtrsak	kaeleenqrs
1381	ykqkkrrri	kvqedsssen	ksnseeeee	keeeeeeeee	eeeeeendend	dkspgkgrk
1441	kiriklkkdd	lrtetqnalk	eeeerrkria	erererekrl	evieiedasp	tkcpittklv
1501	ldedeetkep	lvqvhrnmvi	klkphqvdiv	qfmwdccces	vkktkkspgs	gcilahcmgl
1561	gkltqvvsfl	htvllcdkld	fstalvvcpl	ntalnwmnef	ekwqeglkdd	eklevselat
1621	vkqpqersym	lqrwqedggv	miigyemyrn	laqgrnvksr	klkeifnkak	vdpgpdfvvc
1681	deghilknea	savskamnsi	rsrrriiltg	tplqnnliey	hcmvnfiken	llgsikefrn
1741	rfinpiqngq	cadstmvdvr	vmkkrahily	emlagcvqrk	dylatlkflp	pkheyvlavr
1801	mtsiqcklyq	yyldhltgvg	nnseggrgka	gaklfqdfqm	lsriwtpwc	lqldyisken
1861	kgyfdegsmd	efiasdsdet	smslssddyt	kkkkkgkkkg	kdsssgsgs	dndvevikvw
1921	nsrsrgggeg	nvdetgnnps	vslkleeska	tsssnppspa	pdwykdfvtd	adaevlehsg
1981	kmvllfeilr	maeeigdkvl	vfsqslisld	liedflelas	rektdkdkp	liykggkwl
2041	rnidyryldg	sttaqsrkkw	aeefndetnv	rgrlfiistk	agslginlva	anrviiifdas
2101	wnpsydiqsi	frvyrfgqtk	pvyvyrfraq	gtmedkiydr	qvtkqslsfr	vvdqqqverh
2161	ftmneltey	tfepdllddp	nsekkkkrdt	pmlpkdtila	ellqihkehi	vgyhehdsll
2221	dhkeeeelte	eerkaawaey	eaekkgltmr	fniptgtlnp	pvsfnsqtpy	ipfnlgalsa
2281	msnqqledli	nqgrekvvea	tnsvtavriq	plediisavw	kenmnlseaq	vqalalsrqa
2341	sqeldvkrre	aiyndvltkq	qmliscvqri	lmnrllqqqy	nqqqqqqmty	qqatlghlmm
2401	pkppnlmnp	snyqqidmrq	myqpvaggmq	ppplqrappp	mrsknpgpsq	gksm

Homo sapiens alpha thalassemia/mental retardation syndrome X-linked (ATRX), transcript variant 2, mRNA (SEQ ID NO: 8)

1	aattctcctg	cctgagcctc	ggcccaacaa	aatggcggcg	gcagcgggtg	cgctttgttt
61	ccgcggctcc	tgccggcggtg	gcagtggtag	cggcctttga	gctgtgggga	ggttccagca
121	gcagctacag	tgacgactaa	gactccagtg	catttctatc	gtaaccgggc	gcgggggagc
181	gcagatcggc	gccagcaat	cacagaagcc	gacaaggcgt	tcaagcgaaa	acatgaccgc
241	tgagcccatg	agtgaagca	agttgaatac	attggtgcag	aagcttcatg	acttccttgc
301	acactcatca	gaagaatctg	aagaaacaag	ttctcctcca	cgacttgcaa	tgaatcaaaa
361	cacagataaa	atcagtgggt	ctggaagtaa	ctctgatatg	atggaaaaca	gcaagggaaga
421	gggaactagc	tcttcagaaa	aatccaagtc	ttcaggatcg	tcacgatcaa	agaggaaacc
481	ttcaattgta	acaaagtatg	tagaatcaga	tgatgaaaaa	cctttgggat	atgaaactgt
541	aaatgaagat	gcgtctaattg	aaaattcaga	aaatgatatt	actatgcaga	gcttgccaaa
601	agaagatggg	cttcatggga	ttgtgagctg	cactgcttgt	ggacaacagg	tcaatcattt
661	tcaaaaagat	tccattttata	gacacccttc	attgcaagtt	cttattttgta	agaattgctt
721	taagtattac	atgagtgatg	atattagccg	tgactcagat	ggaatggatg	aacaatgtag
781	gtggtgtgcg	gaagggtggaa	acttgatttg	ttgtgacttt	tgccataatg	ctttctgcaa
841	gaaatgcatt	ctacgcaacc	ttgggtcgaaa	ggagttgtcc	acaataatgg	atgaaaacaa
901	ccaatggtat	tgctacattt	gtcaccacaga	gcctttgttg	gacttgggtca	ctgcatgtaa
961	cagcgtat	gagaatttag	aacagttggt	gcagcaaaat	aagaagaaga	taaaagttga
1021	cagtgaanaag	agtaataaag	tatatgaaca	tacatccaga	ttttctccaa	agaagactag
1081	ttcaaatgtg	aatggagaag	aaaagaaatt	agatgattcc	tggtctggct	ctgtaacctta
1141	ctcttattcc	gcactaattg	tgcccaaaaga	gatgattaag	aaggcaaaaa	aactgattga
1201	gaccacagcc	aacatgaact	ccagttatgt	taaaattttta	aagcaggcaa	cagataattc
1261	agaaatcagt	tctgctacaa	aattacgtca	gcttaaggct	tttaagtctg	tggttgctga
1321	tattaagaag	gctcatcttg	cattggaaga	agacttaaat	tccgagtttc	gagcgtatgga
1381	tgctgtaaac	aaagagaaaa	ataccaaaga	gcataaaagtc	atagatgcta	agtttgaaac
1441	aaaagcacga	aaaggagaaa	aaccttgtgc	tttggaanaag	aaggatattt	caaagtcaga
1501	agctaaactt	tcaagaaaaa	aggtagatag	tgagcacatg	catcagaatg	ttccaacaga
1561	ggaacaaaga	acaaataaaa	gtaccggtgg	tgaacataag	aaactgtata	gaaaagaaga
1621	acctcaatat	gaacctgccca	acacttctga	agatttagac	atggatatgt	tgctgttcc
1681	ttcctcagtt	ccagaagaca	tttttgagaa	tcttgagact	gctatggaag	ttcagagttc
1741	agttgatcat	caaggggatg	gcagcagtg	aactgaacaa	gaagtggaga	gttcatctgt
1801	aaaattaaat	atttcttcaa	aagacaacag	aggaggtatt	aatcaaaaaa	ctacagctaa
1861	agtaacaaaa	gaattatatg	ttaaactcac	tcctgtttcc	ctttctaat	ccccatttaa
1921	aggtgctgat	tgctcaggaag	ttccacaaga	taaagatggc	tataaaaagt	gtggtctgaa
1981	ccccagttta	gagaaatgtg	gacttggaca	ggaaaacagt	gataatgagc	atttggttga
2041	aaatgaagtt	tcattacttt	tagaggaatc	tgatcttcga	agatccccac	gtgtaaagac
2101	tacacccttg	aggcgaccga	cagaaactaa	ccctgtaaca	tctaattcag	atgaagaatg
2161	taatgaaaca	gttaaggaga	aacaaaaact	atcagttcca	gtgagaaaaa	aggtaagcgc
2221	taattcttct	gacagtgcct	tagataatcc	taagccta	aaattgccaa	aatctaagca
2281	atcagagact	gtggatcaaa	attcagattc	tgatgaaatg	ctagcaatcc	tcaaagaggt
2341	gagcaggatg	agtcacagtt	cttcttcaga	tactgatatt	aatgaaattc	atacaaacca
2401	taagactttg	tatgatttaa	agactcaggc	ggggaaaagat	gataaaggaa	aaaggaaacg
2461	aaaaagttct	acatctggct	cagattttga	tactaaaaag	ggcaaatcag	ctaagagctc
2521	tataatttct	aaaaagaaac	gacaaaacca	gtctgagtct	tctaattatg	actcagaatt
2581	agaaaaagag	ataaagagca	tgagtataat	tggtgctgcc	agaaccacca	aaaaaagaat
2641	tccaaatata	aaagattttg	actcttctga	agatgagaaa	cacagcaaaa	aaggaaatgga
2701	taatcaagg	cacaaaaatt	tgaagacctc	acaagaagga	tcatctgatg	atgctgaaag
2761	aaaacaagag	agagagactt	tctcttcagc	agaaggcaca	gttgataaag	acacgaccat
2821	catggaatta	agagatcgac	ttcctaagaa	gcagcaagca	agtgcctcca	ctgatggtgt
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2941	aactaaagaa	aagagcaagc	atctcaaaac	caaaacatgt	aaaaaagtac	aggatggctt
3001	atctgatatt	gcagagaaat	tcctaaagaa	agaccagagc	gatgaaactt	ctgaagatga
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3121	agtaatttaa	atggaacaac	agtatgaatc	ttcatctgat	ggcactgaaa	agttacctga
3181	gcgagaagaa	atgtgtcatt	ttcctaagg	cataaaacaa	attaagaatg	gaaccaactga
3241	tggagaaaag	aaaagtaaaa	aaataagaga	taaaacttct	aaaaagaagg	atgaattatc
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3361	gagtaagaat	ggagcatatg	gtagagagaa	gaaaaggtgc	aagttgcttg	gaaagagttc
3421	aaggaagaga	caagattgtt	catcatctga	tactgagaaa	tattccatga	aagaagatgg

3481	ttgtaactct	tctgataaga	gactgaaaag	aatagaattg	agggaaagaa	gaaattttaag
3541	ttcaaagaga	aataactaag	aaatacaaa	tggctcatca	tcatctgatg	ctgaggaaag
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4561	gaagattctt	aaagatgata	aactgagaac	agaaacacaa	aatgctctta	aggaagagga
4621	agagagacga	aaacgtattg	ctgagaggga	gcgtgagcga	gaaaaattga	gagaggatga
4681	agaaattgaa	gatgcttcac	ccaccaagtg	tccaataaca	accaagttgg	ttttagatga
4741	agatgaagaa	accaaagaac	cttttagtgca	ggttcataga	aatatggtta	tcaaattgaa
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4921	tttcagggtg	gtaagttttc	ttcatacagt	tcttttgtgt	gacaaactgg	atttcagcac
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5161	aggctatgag	atgtatagaa	atcttgctca	aggaaggaa	gtgaagagtc	ggaaacttaa
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5701	tgaagggtgga	agaggaaagg	cagggtgcaa	gcttttccaa	gattttcaga	tgtaaagtag
5761	aatatggact	catccttggt	gtttgcagct	agactacatt	agcaaagaaa	ataagggtta
5821	ttttgatgaa	gacagtatgg	atgaatttat	agcctcagat	tctgatgaaa	cctccatgag
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6001	atctcgggga	ggtggtgaag	gaaatgtgga	tgaaacagga	aacaactcct	ctgtttcctt
6061	aaaactggaa	gaaagttaa	ctacttcttc	ttctaattcca	agcagcccag	ctccagactg
6121	gtacaaagat	tttgttacag	atgctgatgc	tgaggtttta	gagcattctg	ggaaaaagg
6181	acttctcttt	gaaattcttc	gaatggcaga	ggaaattggg	gataaagtcc	ttgttttcag
6241	ccagtccctc	atatctctgg	acttgattga	agattttctt	gaattagcta	gtaggagaa
6301	gacagaagat	aaagataaac	cccttattta	taaagggtgag	gggaagtggc	ttcgaacat
6361	tgactattac	cgtttagatg	gttccactac	tgacagtc	aggaagaagt	gggtgaaga
6421	atttaatatg	gaaactaatg	tgagaggacg	attatttatc	atttctacta	aagcaggatc
6481	tctaggaatt	aatctggtag	ctgctaactc	agtaattata	ttcgacgctt	cttggaaatc
6541	atcttatgac	atccagagta	tattcagagt	ttatcgcttt	ggacaaacta	agcctgttta
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6661	taagcagtc	ctgtcttttc	gagttgttga	tcagcagcag	gtggagcgtc	attttactat
6721	gaatgagctt	actgaacttt	atacttttga	gccagactta	ttagatgacc	ctaattcaga
6781	aaagaagaag	aagagggata	ctcccatgct	gccaaaggat	accatacttg	cagagctcct
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7081	tcaacagctg	gaggacctca	ttaatcaagg	aagagaaaaa	gttgtagaag	caacaaacag
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7201	catgaatctc	tcagaggccc	aagtacaggc	gttagcatta	agtagacaag	ccagccagga
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7561	caaaaatcca	ggaccttccc	aagggaaatc	aatgtgattt	tgactaaaaa	gcttaatgga
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7861	cataatagta	acaactccac	agatttcctc	tctaaatttt	tatgcctgct	tttagcaacc
7921	ataaaattgt	cataaaatta	ataaattttag	gaaagaataa	agattttatat	attcattctt
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8161	atctttgaca	cagaattgtg	tgcaatatcc	ttaaataacta	ctgctctaaa	agttggagaa
8221	gtcttgcagt	tatcttagca	ttgtataaac	agccttaagt	atagcctaag	aagagaattc
8281	ctttttcttc	tttagtcctt	ctgccatttt	ttattttcag	ttatatgtgc	tgaaataatt
8341	actggtaaaa	tttcaggggt	gtggattatc	ttccacacat	gaattttctc	tctcctggca
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8461	ggcagtggga	tgtggactta	gaaaatcaag	ttctagcatt	ttagtagggt	aacactgaag
8521	ttgtggttgt	taggttcaca	ccctgtttta	taaacacat	caaaatggca	gaaccattgc
8581	tgacttttag	ttcacatgag	gaatgtactt	ttaacaattc	ccagtactat	cagtattgtg
8641	aaataattcc	tctgaaagat	aagaatcact	ggcttctatg	cgcttctttt	ctctcatcat
8701	catgttcttt	tacccagtt	tccttacatt	tttttaaat	gtttcagagt	ttgttttttt
8761	tttagtttag	attgtgaggc	aattattaaa	tcaaaattaa	ttcatccaat	acccttttac
8821	tagaagtttt	actagaaaat	gtattacatt	ttattttttc	ttaatccagt	tctgcaaaaa
8881	tgacctataa	atatttcat	gtacaatttt	ggttacttga	attgttaaag	aaaacattgt
8941	ttttgactat	gggagtcaac	tcaacatggc	agaaccattt	ttgagatgat	gatacaacag
9001	gtagtgaaac	agcttaagaa	ttccaaaaaa	aaaaaaaaaa	aaaaaaaaaa	gaaaactggg
9061	tttgggcttt	gcttttagta	tcactggatt	agaatgagtt	taacattagc	taaaactgct
9121	ttgagtgtgt	tggaatgatt	agagattgcc	atttttatct	tggaagaact	agtggtaaaa
9181	catccaagag	cactaggatt	gtgatacaga	atttgtgagg	tttgggtgat	ccacgccctt
9241	ctccccact	ttcccatgat	gaaatatcac	taataaatcc	tgtatatatta	gatattatgc
9301	tagccatgta	atcagattta	tttaattggg	tggggcaggt	gtgtattttac	tttagaaaaa
9361	atgaaaaaga	caagatttat	gagaaatatt	tgaaggcagt	acactctggc	caactgttac
9421	cagttgggat	ttctacaagt	tcagaatatt	ttaaacctga	tttactagac	ctgggaattt
9481	tcaacatggg	ctaattattt	actcaaagac	atagatgtga	aaatttttag	caaccttcta
9541	aatctttttc	accatggatg	aaactataac	ttaaagaata	atacttagaa	gggttaattg
9601	gaaatcagag	tttgaaataa	aacttggacc	actttgtata	cactcttctc	acttgacatt
9661	ttagctatat	aatatgtact	ttgagtataa	catcaagctt	taacaaatat	ttaaagacaa
9721	aaaaatcacg	tcagtaaaat	actaaaaggc	tcatttttat	atttgtttta	gatgttttaa
9781	atagttgcaa	tggaataaaa	atgatgattt	aaaatgttgc	ttgtaataca	gttttgcttg
9841	ctaaattctc	cacattttgt	aacctgtttt	atttcttttg	gtgtaaagcg	tttttgctta
9901	gtattgtgat	attgtatatg	ttttgtccca	gttgatatag	aatgtttcag	tccatcatcc
9961	agctttggct	gctgaaatca	tacagctgtg	aagacttgcc	tttgtttctg	ttagactgct
10021	tttcagttct	gtattgagta	tcttaagtac	tgtagaaaag	atgtcacttc	ttcctttaag
10081	gctgttttgt	aatatatata	aggactggaa	ttgtgttttt	aaagaaaagc	attcaagtat
10141	gacaatatac	tatctgtgtt	ttcaccattc	aaagtgtgtg	ttagagtgtg	taactttaac
10201	tatttaaatg	catttaataa	agtgaacaaa	atgtgtgtgt	ctctttattg	tattttcaca
10261	gctttgaaaa	tctgtgcaca	tactgtttca	tagaaaaatg	atagcttttg	ttgtcctata
10321	taatgggtgg	tcttttgcac	attttagttat	ttaatattga	gaggtcacga	agtttggtta
10381	ttgaatctgt	tatatactaa	attctgtaaa	gggagatctc	tcattctcaa	aagaatttac
10441	ataccaggaa	gtccatgtgt	gtttgtgtta	gttttggtatg	tctttgtgta	atccagcccc
10501	atcttctgtt	tcccaacagc	tgtaacactc	attttaagtc	aagcagggct	accaaccac
10561	acttgataga	aaagctgctt	accattcaga	agcttcctta	ttacctggcc	tccaaatgag
10621	ctgaatattt	tgtagccttc	ccttagctat	gttcattttc	cctccattat	cataaaatca

10681	gatcgatatt	tatgtgcccc	aaacaaaact	ttaagagcag	ttacattctg	tcccagtagc
10741	ccttggtttcc	tttgagagta	gcatggttg	aggctataga	gacttattct	accagtaaaa
10801	caggtcaatc	cttttacatg	tttattatac	taaaaattat	gttcagggtg	tttactactt
10861	tatttcacca	gactcagtct	caagtgaact	ggctatctcc	aatcagatc	tacccttaga
10921	gaataaacat	ttttctaccg	ttatTTTTTT	tcaagtctat	aatctgagcc	agtcccaaag
10981	gagtgatcaa	gtttcagaaa	tgctttcatc	ttcacaacat	tttatatata	ctatttatg
11041	gggtgaataa	agtttttaaat	ccgaaatata	aaaaaaaaaa	aaaaaaaaaa	

[096] A subject in need thereof may have reduced expression, haploinsufficiency, and/or loss of function of ARID1A. For example, a subject may comprise a mutation selected from the group consisting of a nonsense mutation for the wild type residue cysteine (C) at amino acid position 884 of SEQ ID NO: 11 (C884*), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 966 (E966K), a nonsense mutation for the wild type residue glutamine (Q) at amino acid position 1411 of SEQ ID NO: 11 (Q1411*), a frame shift mutation at the wild type residue phenylalanine (F) at amino acid position 1720 of SEQ ID NO: 11 (F1720fs), a frame shift mutation after the wild type residue glycine (G) at amino acid position 1847 of SEQ ID NO: 11 (G1847fs), a frame shift mutation at the wild type residue cysteine (C) at amino acid position 1874 of SEQ ID NO: 11 (C1874fs), a substitution of glutamic acid (E) for the wild type residue aspartic acid (D) at amino acid position 1957 (D1957E), a nonsense mutation for the wild type residue glutamine (Q) at amino acid position 1430 of SEQ ID NO: 11 (Q1430*), a frame shift mutation at the wild type residue arginine (R) at amino acid position 1721 of SEQ ID NO: 11 (R1721fs), a substitution of glutamic acid (E) for the wild type residue glycine (G) at amino acid position 1255 (G1255E), a frame shift mutation at the wild type residue glycine (G) at amino acid position 284 of SEQ ID NO: 11 (G284fs), a nonsense mutation for the wild type residue arginine (R) at amino acid position 1722 of SEQ ID NO: 11 (R1722*), a frame shift mutation at the wild type residue methionine (M) at amino acid position 274 of SEQ ID NO: 11 (M274fs), a frame shift mutation at the wild type residue glycine (G) at amino acid position 1847 of SEQ ID NO: 11 (G1847fs), a frame shift mutation at the wild type residue P at amino acid position 559 of SEQ ID NO: 11 (P559fs), a nonsense mutation for the wild type residue arginine (R) at amino acid position 1276 of SEQ ID NO: 11 (R1276*), a frame shift mutation at the wild type residue glutamine (Q) at amino acid position 2176 of SEQ ID NO: 11 (Q2176fs), a frame shift mutation at the wild type residue histidine (H) at amino acid position 203 of SEQ ID NO: 11 (H203fs), a frame shift mutation at the wild type residue alanine (A) at amino acid position 591 of SEQ ID NO: 11 (A591fs), a nonsense mutation for the wild type residue glutamine (Q) at amino acid position 1322 of SEQ ID NO: 11

(Q1322*), a nonsense mutation for the wild type residue serine (S) at amino acid position 2264 of SEQ ID NO: 11 (S2264*), a nonsense mutation for the wild type residue glutamine (Q) at amino acid position 586 of SEQ ID NO: 11 (Q586*), a frame shift mutation at the wild type residue glutamine (Q) at amino acid position 548 of SEQ ID NO: 11 (Q548fs), and a frame shift mutation at the wild type residue asparagine (N) at amino acid position 756 of SEQ ID NO: 11 (N756fs). “*” used herein refers to a stop codon. “fs” used herein refers to a frame shift.

AT-rich interactive domain-containing protein 1A (ARID1A) isoform a [Homo sapiens] (SEQ ID NO: 9)						
1	maaqvapaaa	sslgnpppppp	pselkkaeeqq	qreeaggeaa	aaaaaergem	kaaagqeseg
61	pavggppqplg	kelqdgaesn	gggggggags	gggggaepdl	knsngnagpr	palnnnltep
121	pggggggssd	gvgapphsaa	aalpppaygf	gqpygrspsa	vaaaaaavfh	qqhggqqspg
181	laalqsgggg	glepyagpqq	nshdhgfphn	qynsyypnrs	aypppapaya	lssprggtpg
241	sgaaaaagsk	pppsssasas	sssssfaqqr	fgamggggps	aagggtppqt	atptlnqlt
301	spssargyqg	ypggdysggp	qdgagagkpa	dmasqcgwaa	aaaaaaaaas	ggaqqrshha
361	pmspgssggg	ggplartppp	sspmdqmgkm	rpqpyggtnp	ysqqqgpps	pqqghgypqg
421	pygsqtpqry	pmtmqgraqs	amgglsytqq	ippygqqggs	gygqqgqtpy	ynqqspbpqg
481	qpppysqppp	sqtphaqpsy	qqqpqsqppp	lqssqppysq	qpsqpphqq	papypsqqst
541	tqqhpqsqpp	ysqpqaqspy	qqqpqqqpap	stlsqqaayp	qpqsqqsqqt	aysqqrfrppp
601	qelsqdsfgs	qassapsmts	skgggedmnl	slqsrpsslp	dlsqsidldp	mgtegalisp
661	vstsgisssq	geqsnpaqsp	fsphstphlp	girgspspvp	gspasvaqsr	sgplspaavp
721	gnqmprrpps	qgsdsimhps	mnqssiaqdr	gymqrnpqmp	qyssppqgsa	lsprqpsggq
781	ihtgmgsyqq	nsmgsygpqg	gqygpqggyp	rqpnynalpn	anypsagmag	ginpmgaggg
841	mhgqpgippy	gtlppgrmsh	asmgnrpygp	nmanmppqvg	sgmcpppggm	nrktqetava
901	mhvaansiqn	rppgyppnmq	ggmmgtgppy	ggginsmagm	inpqgppysm	ggtmannsag
961	maaspepmgl	gdvkltpatk	mnnkadgtpk	teskskksss	stttnekitk	lyelggeper
1021	kmwvdrylaf	teekamgmtn	lpavgrkpdl	lyrlyvsvke	iggltqvnkn	kkwrelatnl
1081	nvgtsssaas	slkkqyiqcl	yafeckierg	edpppdifaa	adskksqpk	qppspagsgs
1141	mqgpqtppst	ssmaeggdl	kpptpastph	sqipplpgms	rsnsvigqda	fndgsdstfq
1201	knsmtppnpg	yqpsmaentsdm	mgrmsyepnk	dpygsmrkap	gsdpfmssgq	gpnggmddpy
1261	sraagpglgn	vamgprqhyp	yggpydrvrt	epgigpegnm	stgapqpnlm	psnpdsgmys
1321	psryppqqqq	qqqqrhdysg	nqfstqgtps	gspfpsqqt	myqqqqqnyk	rpmddgtygpp
1381	akrhegemys	vpystgqqqp	qqqqlppaqp	qpasqqqaaq	pspqqdvynq	ygnaypatat
1441	aaterppagg	pqnqfpfqfg	rdrvsappgt	naqqnmpqpm	mggpiqasae	vaqggtmwqg
1501	rndmtynyan	rqstgsapqg	payhgvnrt	emlhtdgran	hegswpshgt	rpppygpsap
1561	vppmtrppps	nyqpppsmqn	hipqvsspap	lprpmenrts	pskspflhsg	mkmqkagppv
1621	pashiapapv	qppmirrdit	fppgsveatq	pvlkqrrrlt	mkdigtpeaw	rvmmslksqgl
1681	laestwaldt	inillyddns	imtfnlsqpl	gllellveyf	rrclieifgi	lkeyevgdpq
1741	qrtlldpgrf	skvsspapme	ggeeelllg	pkleeeeeee	vvendeiaf	sgkdcpasen
1801	seekliskfd	klpvkivqkn	dpfvvdcsdk	lgrvqefdsq	llhwrigggd	ttehiqthfe
1861	sktellpsrp	hapcppapr	hvttaegtpg	ttdqegpppd	gppekritat	mddmlstrss
1921	tltedgakss	eaikesskfp	fgispaqshr	nikiledeph	skdetplctl	ldwqdsakr
1981	cvcvsntirs	lsfvpqndfe	mskhpgllli	lgklillhhk	hperkqaplt	yekeeeqdgq
2041	vscnkvevww	dclemlrent	lvtlanisqg	ldlspypesi	clpvldgllh	wavcpsaeaq
2101	dpfstlgnpna	vlspqrlvle	tlsklsiqdn	nvdllilatpp	fsrleklyst	mvrflsdrkn
2161	pvcremavvl	lanlaqgds	aaraiavqkg	signllgfle	dslaataqfqq	sqasllhmqn
2221	ppfeptsavdm	mrraaralla	lakvdenhse	ftlyesrll	isvsplmns	vsqvictvlf
2281	ligqs					

Homo sapiens AT rich interactive domain 1A (SWI-like) (ARID1A), transcript variant 1, mRNA (SEQ ID NO: 10)

1	cagaaagcgg	agagtcacag	cgggggccagg	ccctgggggag	cggagcctcc	accgcccccc
61	tcattcccag	gcaagggcct	gggggggaatg	agccgggaga	gccgggtccc	gagcctacag
121	agccgggagc	agctgagccg	ccggcgccctc	ggccggccgcc	gccgcctcct	cctcctccgc
181	cgccgccagc	ccggagcctg	agccggcgggg	gcggggggga	gaggagcgag	cgagcgcgag
241	cagcggagcc	ccgcgagggc	cgcccgggcg	ggtggggagg	gcagcccggg	ggactggggc
301	ccggggcggg	gtgggagggg	gggagaagac	gaagacaggg	ccgggtctct	ccgcggacga
361	gacagcgggg	atcatggccg	cgaggtcgcc	ccccgcggcc	gccagcagcc	tgggcaaccc
421	gccgccggcg	ccgccctcgg	agctgaagaa	agccgagcag	cagcagcggg	aggaggcggg
481	gggcgagggc	gcggcgggcg	cagcggccga	gcgcggggaa	atgaaggcag	ccgcggggca
541	ggaaaagcgag	ggccccggcg	tggggcgccg	gcagccgctg	ggaaaggagc	tgcaggacgg
601	ggccgagagc	aatgggggtg	gcggcgggcg	cggagccggc	agcggcgggc	ggccggcgcg
661	ggagccggac	ctgaagaact	cgaacgggaa	cgcgggccct	aggccccgcc	tgaacaataa
721	cctcacggag	ccgcccgggc	gcggcggtgg	cggcagcagc	gatgggggtg	gggcgcctcc
781	tactcagcc	gcggccgcct	tgcgcggccc	agcctacggc	tcggggcaac	cctacggccg
841	gagcccgtct	gccgtcgccg	ccgcgcgggc	cgccgtcttc	caccaacaac	atggcggaca
901	acaaagccct	ggcctggcag	cgctgcagag	cggcggcggc	gggggccttg	agccctacgc
961	ggggccccag	cagaactctc	acgaccacgg	cttccccaac	caccagtaca	actcctacta
1021	ccccaacccg	agcgccctacc	ccccgcggcg	cccgccctac	gcgctgagct	ccccgagagg
1081	tggcaactcc	ggctccggcg	cggcggcgcc	tgcgggctcc	aagccgcctc	cctcctccag
1141	cgctccggcc	tctctgctct	cttcgtcctt	cgctcagcag	cgcttcgggg	ccatgggggg
1201	aggcgggccc	tccgcggccg	gcgggggaac	tccccagccc	accgccaccc	ccaccctcaa
1261	ccaaactgct	acgtcgccca	gctcggcccc	gggtaccag	ggctacccc	ggggcgacta
1321	cagtggcggg	ccccaggacg	ggggcgccgg	caagggcccg	gcggacatgg	cctcgagctg
1381	ttggggggct	gcggcgggcg	cagctgcggc	ggcgggcgcc	tcgggagggg	cccaacaaag
1441	gagccaccac	gcgcccata	gccccgggag	cagcggcggc	ggggggcagc	cgctcgcccc
1501	gaccctcag	ccatccagtc	caatggatca	gatgggcaag	atgagacctc	agccatatgg
1561	cgggactaac	ccatactcgc	agcaaacagg	acctccgtca	ggaccgcagc	aaggacatgg
1621	gtaccacagg	cagccatacg	ggtcccagac	cccgcagcgg	taccgatga	ccatgcaggg
1681	ccgggcgcag	agtgccatgg	gcggcctctc	ttatacacag	cagattcctc	cttatggaca
1741	acaaggcccc	agcgggtatg	gtcaacaggg	ccagactcca	tattacaacc	agcaaagtcc
1801	tcaccctcag	cagcagcagc	caccctactc	ccagcaacca	ccgtcccaga	cccctcatgc
1861	ccaaccttcg	tatcagcagc	agccacagtc	tcaaccacca	cagctccagt	cctctcagcc
1921	tccatactcc	cagcagccat	ccagcctcc	acatcagcag	tccccggctc	cataccctcc
1981	ccagcagtcg	acgacacagc	agcaccctca	gagccagccc	ccctactcac	agccacaggc
2041	tcagtctcct	taccagcagc	agcaacctca	gcagccagca	ccctcgacgc	tctcccagca
2101	ggctgcgtat	cctcagcccc	agtctcagca	gtcccagcaa	actgcctatt	ccagcagcg
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2221	ctcaatgacc	tccagtaagg	gagggcaaga	agatatgaac	ctgagccttc	agtcaagacc
2281	ctccagcttg	cctgatctat	ctggttcaat	agatgacctc	cccatgggga	cagaaggagc
2341	tctgagtcct	ggagtgcgca	catcagggat	ttccagcagc	caaggagagc	agagtaatcc
2401	agctcagctc	cctttctctc	ctcatacctc	ccctcacctg	cctggcatcc	gaggcccttc
2461	cccgtccctc	gttggctctc	ccgccagtgt	tgctcagctc	cgctcaggac	cactctcgcc
2521	tgctgcagtg	ccaggcaacc	agatgccacc	tcggccaccc	agtggccagt	cggacagcat
2581	catgcacctc	tccatgaacc	aatcaagcat	tgcccaagat	cgagggtata	tgagagggaa
2641	ccccagatg	ccccagtaca	gttcccccca	gcccggctca	gccttatctc	cgcgtcagcc
2701	ttccggagga	cagatacaca	caggcatggg	ctcctaccag	cagaactcca	tggggagcta
2761	tgggtccccag	gggggtcagt	atggcccaca	aggtggctac	cccaggcagc	caaactataa
2821	tgcttggccc	aatgccaaact	acccagctgc	aggcatggct	ggaggcataa	accccatggg
2881	tgccggagggt	caaatgcatg	gacagcctgg	catcccacct	tatggcacac	tccctccagg
2941	gaggatgagt	cacgcctcca	tgggcaaccg	gccttatggc	cctaactatg	ccaatatgcc
3001	acctcaggtt	gggtcaggga	tgtgtccccc	accagggggc	atgaaccgga	aaacccaaga
3061	aactgctgtc	gccatgcatg	ttgctgcca	ctctatccaa	aacaggccgc	caggctaccc
3121	caatatgaat	caagggggca	tgatgggaac	tggacctcct	tatggacaag	ggattaatag
3181	tatggctggc	atgatcaaac	ctcagggacc	cccatattcc	atgggtggaa	ccatggccaa
3241	caattctgca	gggatggcag	ccagcccaga	gatgatgggc	cttggggatg	taaagttaac
3301	tccagccacc	aaaatgaaca	acaaggcaga	tgggacaccc	aagacagaat	ccaaatccaa
3361	gaaatccagt	tcttctacta	caaccaatga	gaagatcacc	aagttgtatg	agctgggtgg
3421	tgagcctgag	aggaagatgt	gggtggaccg	ttatctggcc	ttcactgagg	agaaggccat

3481	gggcatgaca	aatctgcctg	ctgtgggtag	gaaacctctg	gacctctatc	gcctctatgt
3541	gtctgtgaag	gagattgggtg	gattgactca	ggtcaacaag	aacaaaaaat	ggcggaact
3601	tgaaccaaac	ctcaatgtgg	gcacatcaag	cagtgtctgcc	agctccttga	aaaagcagta
3661	tatccagtgt	ctctatgcct	ttgaatgcaa	gattgaacgg	ggagaagacc	ctccccaga
3721	catcttttga	gctgctgatt	ccaagaagtc	ccagcccaag	atccagcctc	cctctcctgc
3781	gggatcagga	tctatgcagg	ggccccagac	tccccagtca	accagcagtt	ccatggcaga
3841	aggaggagac	ttaaagccac	caactccagc	atccacacca	cacagtca	tcccccat
3901	gccaggcatg	agcaggagca	attcagttgg	gatccaggat	gcctttaatg	atggaaagtga
3961	ctccacattc	cagaagcggg	attccatgac	tccaaaccct	gggtatcagc	ccagtatgaa
4021	tacctctgac	atgatggggc	gcatgtccta	tgagccaaat	aaggatcctt	atggcagcat
4081	gaggaaagct	ccaggagagt	atcccttcct	gtcctcaggg	cagggcccca	acggcgggat
4141	gggtgacccc	tacagtcgtg	ctgccggccc	tgggctagga	aatgtggcga	tgggaccacg
4201	acagcactat	ccctatggag	gtccttatga	cagagtgaag	acggagcctg	gaatagggcc
4261	tgagggaaac	atgagcactg	gggccccaca	gccgaatctc	atgccttcca	accagactc
4321	ggggatgtat	tctcctagcc	gctaccccc	gcagcagcag	cagcagcagc	agcaacgaca
4381	tgattcctat	ggcaatcagt	tctccaccca	aggcaccctt	tctggcgccc	tcttccccag
4441	ccagcagact	acaatgtatc	aacagcaaca	gcagaattac	aagcggccaa	tggatggcac
4501	atatggccct	cctgccaaag	ggcacgaagg	ggagatgtac	agcgtgccat	acagcactgg
4561	gcaggggcag	cctcagcagc	agcagttgcc	cccagcccag	ccccagcctg	ccagccagca
4621	acaagctgcc	cagccttccc	ctcagcaaga	tgtatacaac	cagtatggca	atgcctatcc
4681	tgccactgcc	acagctgcta	ctgagcgccg	accagcaggc	ggccccaga	accaatttcc
4741	attccagttt	ggccgagacc	gtgtctctgc	accccttggc	accaatgccc	agcaaaacat
4801	gccaccacaa	atgatgggag	gccccataca	ggcatcagct	gaggttgctc	agcaaggcac
4861	catgtggcag	gggcgtaatg	acatgaccta	taattatgcc	aacaggcaga	gcacgggctc
4921	tgccccccag	ggccccgcct	atcatggcgt	gaaccgaaca	gatgaaatgc	tgcacacaga
4981	tcagagggcc	aaccacgaag	gctcgtggcc	ttccccatgg	acacggcagc	ccccatattg
5041	tccctctgcc	cctgtgcccc	ccatgacaag	gccccctcca	tctaactacc	agccccacc
5101	aagcatgcag	aatcacattc	ctcaggtatc	cagccctgct	ccccgcccc	ggccaatgga
5161	gaaccgcacc	tctcctagca	agtctccatt	cctgcactct	gggatgaaaa	tgcagaaggc
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5281	gcgggatata	accttccacc	ctggctctgt	tgaagccaca	cagcctgtgt	tgaagcagag
5341	gaggcggtc	acaatgaaag	acattggaac	cccggaggca	tggcgggtaa	tgatgtccct
5401	caagtctgg	ctcctggcag	agagcacaat	ggcattagat	accatcaaca	tcctgtctga
5461	tgatgacaac	agcatcatga	ccttcaacct	cagtcagctc	ccagggttgc	tagagctcct
5521	tgtagaatat	ttccgacgat	gcctgattga	gatctttggc	attttaaagg	agtagaggt
5581	gggtgaccca	ggacagagaa	cgctactgga	tcctgggagg	ttcagcaagg	tgtctagtcc
5641	agctcccatg	gaggggtggg	aagaagaaga	agaacttcta	ggtcctaaac	tagaagagga
5701	agaagaagag	gaagtagttg	aaaatgatga	ggagatagcc	ttttcaggca	aggacaagcc
5761	agcttcagag	aatagtgagg	agaagctgat	cagtaagttt	gacaagcttc	cagtaaagat
5821	cgtacagaag	aatgatccat	ttgtgggtga	ctgctcagat	aagcttgggc	gtgtgcagga
5881	gtttgacagt	ggcctgctgc	actggcggat	tgggtggggg	gacaccactg	agcatatcca
5941	gacccacttc	gagagcaaga	cagagctgct	gccttcccgg	cctcacgcac	cctgcccacc
6001	agccccctcg	aagcatgtga	caacagcaga	gggtacacca	gggataacac	accaggagg
6061	gccccacact	gatggacctc	cagaaaaacg	gatcacagcc	actatggatg	acatgttgct
6121	tactcggtct	agcaccttga	ccgaggatgg	agctaagagt	tcagaggcca	tcaaggagag
6181	cagcaagttt	ccatttgcca	ttagcccagc	acagagccac	cggaaacatca	agatcctaga
6241	ggacgaaccc	cacagtaagg	atgagacccc	actgtgtacc	cttctggact	ggcaggattc
6301	tcttgccaag	cgctgcgtct	gtgtgtccaa	taccattcga	agcctgtcat	ttgtgccagg
6361	caatgacttt	gagatgtcca	aacacccagg	gctgctgctc	atcctgggca	agctgatcct
6421	gctgcaccac	aagcaccacg	aacggaagca	ggcaccacta	acttatgaaa	aggaggagga
6481	acaggaccac	ggggtgagct	gcaacaaagt	ggagtgggtg	tgggactgct	tggagatgct
6541	ccgggaaaac	accttggtta	cactcgccaa	catctcgggg	cagttggacc	tatctccata
6601	ccccgagagc	atttgccctg	ctgtcctgga	cggactcccta	cactgggcag	tttgcccttc
6661	agctgaagcc	caggacccct	tttccaccct	gggccccaat	gccgtccttt	ccccgcagag
6721	actggctctt	gaaaccctca	gcaaaactcag	catccaggac	aacaatgtgg	acctgattct
6781	ggccacaccc	cccttcagcc	gcctggagaa	gttgatagc	actatgggtg	gcttctcag
6841	tgaccgaaag	aaccgggtgt	gccgggagat	ggctgtggta	ctgctggcca	acctggctca
6901	gggggacagc	ctggcagctc	gtgccattgc	agtgcagaag	ggcagtatcg	gcaacctcct
6961	gggcttccta	gaggacagcc	ttgccgccac	acagttccag	cagagccagg	ccagcctcct
7021	ccacatgcag	aaccacccct	ttgagccaac	tagtgtggac	atgatgcggc	gggctgccc

7081	cgcgctgctt	gccttgccca	aggtggacga	gaaccactca	gagtttactc	tgtacgaatc
7141	acggctgttg	gacatctcgg	tatcacccgtt	gatgaactca	ttggtttcac	aagtcatttg
7201	tgatgtactg	tttttgattg	gccagtcag	acagccgtgg	gacacctccc	ccccccgtgt
7261	gtgtgtgcgt	gtgtggagaa	cttagaaact	gactgttgcc	ctttatttat	gcaaaaccac
7321	ctcagaatcc	agtttaccct	gtgctgtcca	gcttctccct	tgggaaaaag	tctctcctgt
7381	ttctctctcc	tccttccacc	ccccctccct	ccatcacctc	acgcctttct	gttccttgct
7441	ctcaccttac	ccccctcagg	accctacccc	accctctttg	aaaagacaaa	gctctgccta
7501	catagaagac	tttttttatt	ttaaccaaaag	ttactgttgt	ttacagttag	tttggggaaa
7561	aaaaataaaa	taaaaatggc	tttcccagtc	cttgcacaa	cgggatgcca	catttcataa
7621	ctgtttttta	tggtaaaaaa	aaaaaaaaaa	aatacaaaaa	aaaattctga	aggacaaaaa
7681	aggtgactgc	tgaactgtgt	gtggttttatt	gttgatcatt	cacaatcttg	caggagccaa
7741	gaagttcgca	gttgtgaaca	gaccctgttc	actggagagg	cctgtgcagt	agagtgtaga
7801	ccctttcatg	tactgtactg	tacacctgat	actgtaaca	tactgtaata	ataatgtctc
7861	acatggaaac	agaaaacgct	gggtcagcag	caagctgtag	tttttaaaaa	tgtttttagt
7921	taaacgttga	ggagaaaaaa	aaaaaaggct	tttcccccaa	agtatcatgt	gtgaacctac
7981	aacaccctga	cctctttctc	tcctccttga	ttgtatgaat	aaccttgata	tcacctctta
8041	gaactgggtt	taacctttag	ctgcagcggc	tacgctgcca	cgtgtgtata	tatatgacgt
8101	tgtacattgc	acataccctt	ggatccccac	agtttggtcc	tcctcccagc	tacctcttta
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8281	gtctcagcag	ccaatcaact	tatagtttat	ttttttctgg	gtttttgttt	tgttttgttt
8341	tctttctaatt	cgagggtgtga	aaaagttcta	ggttcagttg	aagttctgat	gaagaaacac
8401	aattgagatt	ttttcagtga	taaaatctgc	atatttgtat	ttcaacaatg	tagctaaaaac
8461	ttgatgtaaa	ttcctccttt	ttttcctttt	ttggcttaaat	gaatatcatt	tattcagtat
8521	gaaatccttta	tactatatgt	tccacgtgtt	aagaataaat	gtacattaaa	tcttggtgaag
8581	actttt					

AT-rich interactive domain-containing protein 1A (ARID1A) isoform b (SEQ ID NO: 11)

1	maaqvapaaa	sslgnpptppp	pselkkaeqq	qreeaggeaa	aaaaaergem	kaaagqeseg
61	pavppqpplg	kelqdgaesn	gggggggags	gggpgaepdl	knsngnagpr	palnnnltep
121	pggggggssd	gvgapphsaa	aalpppaygf	gppygrpsa	vaaaaaavfh	qhqggqspg
181	laalqsgggg	glepyagpqq	nshdhgfpnh	qynsyypnrs	aypppapaya	lssprggtpg
241	sgaaaaagsk	pppssasas	sssssfagqr	fgamgggpps	aagggtppqt	atptlnqlt
301	spssargyqg	ypggdysggp	qdgagkgpa	dmasqwgaa	aaaaaaaaas	ggaqqrshha
361	pmspgssggg	gqplartpqp	sspmqmgkm	rpqpyggtnt	ysqqqgppsg	pkqghgypgq
421	pygsqtppry	pmtmqgrags	amgglsytqq	ippyqgqgps	gygqqgqtpy	ynqqsphppq
481	qpppysqppp	sqtphaqpsy	qqqpqsqppq	lqssqppysq	qpsqpphqq	papypsqst
541	tqhqpsqppp	ysqpqaqspy	qqqpqqpap	stlsqqaayp	qpqsqqsqqt	aysqqrfrpp
601	qelsqdsfgs	qassapsmts	skgggedmnl	slqsrpsslp	dlsgsiddlp	mgtegalisp
661	vstsgissssq	geqsnpaasp	fsphtsphlp	girgspspv	gspasvaqsr	sgplspaavp
721	gnqmprrpps	gqsdsimhps	mnqssiaqdr	gymqrnpqmp	qyssppqgsa	lsprqpsggq
781	ihtgmgsyqq	nsmgsygpqg	qyypqggyp	rqpnynalpn	anypsagmag	ginpmgaggq
841	mhgqpgippy	gtlppgrmsh	asmgnrpygp	nmanmppqv	sgmcpptggm	nrktqetava
901	mhvaansiqn	rppgyppnmq	ggmngtgppp	ggginsmagm	inppqppysm	ggtmannsag
961	maaspermgl	gdvkltpatk	mnnkadgtpk	teskskssss	stttnekitk	lyelgggeper
1021	kmwvdrylaf	teekamgmtn	lpavgrkpld	lyrlyvsvke	iggltqvnkn	kkwrelatnl
1081	nvgtsssaas	slkkqyiqcl	yafeckierg	edpppdifaa	adskksqpk	qppspagsgs
1141	mqqpqtppst	ssmaeggdl	kpptpastph	sqipplpgms	rsnsvgiqda	fndgsdstfq
1201	krnsmtpppg	yqpsmntsdm	mgrmsyepnk	dpygsmrkap	gsdpfmssgq	gpnggmgdpy
1261	sraagpglgn	vamgprqhyp	ygpydrvrt	epgigpegnm	stgapqpnlm	psnpdsgmys
1321	psryppqqqq	qqqqrhdsyg	nqfstqgtps	gspfpsqqt	myqqqqqvss	paplprpmen
1381	rtspksqfll	hsgmkmqkag	ppvpashiap	apvqppmirr	ditfppgsve	atqpvlkqrr
1441	rltmkdigt	eawrvmslk	sgllaestwa	ldtinillyd	dnsimtfnl	qlpgllellv
1501	eyfrrcliei	fgilkeyevg	dpgqrtlldp	grfskvsspa	pmeggeeeee	llgpkleeee
1561	eeevvendee	iafsgkdka	senseeklis	kfdklpvkiv	qkndpfvvd	sdklgrvqef
1621	dsgllhwrig	ggdttehiqt	hfesktellp	srphapcpa	prkhvttae	tpgttdqegp
1681	ppdgppekri	tatmdmlst	rsstltedga	ksseaikess	kfpfgispaq	shrnkiled
1741	ephskdetpl	ctllwdqds	akrcvcvsnt	irslsfvpgn	dfemskhpgl	llilgklill
1801	hhkhperkqa	pltyekeeeq	dqgvscnkve	wwwdclemlr	entlvltani	sgqldlspyp

1861	esiclpvldg	llhwavcpsa	eaqdpfstlg	pnavlspqrl	vletlsklsl	qdnndvlila
1921	tppfsrlekl	ystmvrflsd	rknvpcrema	vvllanlaqg	dslaaraiav	qkgsignllg
1981	fledslaataq	fqqsqasllh	mqnppfepts	vdmrrraara	llalakvden	hseftlyesr
2041	lldisvsplm	nslvsqvied	vlfligqs			

Homo sapiens AT rich interactive domain 1A (SWI-like) (ARID1A), transcript variant 2, mRNA (SEQ ID NO: 12)

1	cagaaagcgg	agagtcacag	cgggggccagg	ccctggggag	cggagcctcc	accgcccccc
61	tcattcccag	gcaagggcct	ggggggaatg	agccgggaga	gccgggtccc	gagcctacag
121	agccgggagc	agctgagccg	ccggcgccctc	ggccgcccgc	gccgcctcct	cctcctccgc
181	cgccgccagc	ccggagcctg	agccggcgagg	gcggggggga	gaggagcgag	cgagcgcag
241	cagcggagcc	ccgcgaggcc	cgcccgggag	ggtggggagg	gcagcccggg	ggactggggc
301	ccggggcggg	gtgggagggg	gggagaagac	gaagacaggg	ccgggtctct	ccgcggacga
361	gacagcgggg	atcatggccg	cgcaggtcgc	ccccgccgcc	gccagcagcc	tgggcaaccc
421	gccgcccgcg	ccgcccctcg	agctgaagaa	agccgagcag	cagcagcggg	aggaggcggg
481	gggcgagggc	gcggcggcgg	cagcggccga	gcgcggggaa	atgaaggcag	ccgcccggga
541	ggaaagcgag	ggccccgcgg	tggggccgcc	gcagccgctg	ggaaaggagc	tgaggagcgg
601	ggccgagagc	aatgggggtg	gcggcgccgg	cggagccggc	agcggcgccg	ggcccggcgc
661	ggagccggac	ctgaagaact	cgaacgggaa	cgcgggccct	aggcccgcgc	tgaacaataa
721	cctcacggag	ccgcccggcg	gcggcgggtg	cggcagcagc	gatgggggtg	gggcgcctcc
781	tactcagcc	gcggccgcct	tgcgcgcctc	agcctacggc	ttcgggcaac	cctacggccg
841	gagcccgctc	gccgtcgccg	ccgcgcgggc	cgccgtcttc	caccaacaac	atggcggaca
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961	ggggccccag	cagaactctc	acgaccacgg	cttccccaac	caccagtaca	actcctacta
1021	ccccaaaccg	agcgcctacc	ccccgcccgc	cccggcctac	gcgctgagct	ccccgagagg
1081	tggaactccg	ggctccggcg	cggcggcgcc	tgccggctcc	aagccgcctc	cctcctccag
1141	cgccctccgc	tctcgtcgt	cttcgtcctt	cgctcagcag	cgcttcgggg	cgtatggggg
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1501	gacccctcag	ccatccagtc	caatggatca	gatgggcaag	atgagacctc	agccatatgg
1561	cgggactaac	ccatactcgc	agcaacaggg	acctccgtca	ggaccgcagc	aaggacatgg
1621	gtacccaggg	cagccatacg	ggtcccagac	cccgcagcgg	taccgcaggg	tactgcaggg
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1741	acaaggcccc	agcgggtatg	gtcaacaggg	ccagactcca	tattacaacc	agcaaaagtc
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1921	tccatactcc	cagcagccat	cccagcctcc	acatcagcag	tccccggctc	cataccctc
1981	ccagcagtcg	acgacacagc	agcaacccca	gagccagccc	ccctactcac	agccacaggc
2041	tcagtctcct	taccagcagc	agcaacctca	gcagccagca	ccctcgacgc	tctcccagca
2101	ggctgcgtat	cctcagcccc	agtctcagca	gtcccagcaa	actgcctatt	cccagcagcg
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2281	ctccagcttg	cctgatctat	ctgggtcaat	agatgacctc	cccatgggga	cagaaggagc
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2401	agctcagtc	cctttctctc	ctcatacctc	ccctcacctg	cctggcatcc	gaggcccttc
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2641	ccccagatg	ccccagtaca	gttcccccca	gcccggctca	gccttatctc	cgctcagcc
2701	ttccggagga	cagatacaca	caggcatggg	ctcctaccag	cagaacctca	tggggagcta
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3181	tatggctggc	atgatcaacc	ctcagggacc	cccatattcc	atgggtggaa	ccatggccaa
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3301	tccagccacc	aaaatgaaca	acaaggcaga	tgggacaccc	aagacagaat	ccaatccaa
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4261	tgagggaaac	atgagcactg	gggccccaca	gccgaatctc	atgccttcca	accagactc
4321	ggggatgtat	tctcctagcc	gctaccccc	gcagcagcag	cagcagcagc	agcaacgaca
4381	tgattcctat	ggcaatcagt	tctccaccca	aggcaccctt	tctggcagcc	ccttccccag
4441	ccagcagact	acaatgtatc	aacagcaaca	gcaggtatcc	agccctgtct	ccctgccccg
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4621	catgattcgg	cgggatatca	ccttcccacc	tggctctgtt	gaagccacac	agcctgtgtt
4681	gaagcagagg	aggcggctca	caatgaaaga	cattggaacc	ccggaggcat	ggcgggtaat
4741	gatgtccctc	aagtctggct	tcttggcaga	gagcacatgg	gcattagata	ccatcaacat
4801	cctgctgtat	gatgacaaca	gcatcatgac	cttcaacctc	agtcagctcc	cagggttgct
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5881	ggagatgctc	cgggaaaaca	ccttggttac	actcgccaac	atctcggggc	agttggacct
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6001	ttgcccttca	gctgaagccc	aggacccctt	ttccaccctg	ggccccaatg	ccgtcctttc
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6121	cctgattctg	gccacacccc	ccttcagccg	cctggagaag	ttgtatagca	ttgtggtgcg
6181	cttccctcag	gaccgaaaga	acccgggtgtg	ccgggagatg	gctgtggtac	tgtggcccaa
6241	cctggctcag	ggggacagcc	tggcagctcg	tgccattgca	gtgcagaagg	gcagtatcgg
6301	caacctcctg	ggcttcctag	aggacagcct	tgccgcccaca	cagttccagc	agagccaggc
6361	cagcctcctc	cacatgcaga	acccacccctt	tgagccaact	agtgtggaca	tgatgcggcg
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6481	gtacgaatca	cggctgttgg	acatctcggt	atcacccgtt	atgaactcat	tggtttcaca
6541	agtcatttgt	gatgtactgt	ttttgattgg	ccagtcatga	cagccgtggg	acacctcccc
6601	cccccggtg	tgtgtgcgtg	tgtggagaac	ttagaaactg	actgttgccc	tttatttatg

6661	caaaaccacc	tcagaatcca	gtttaccctg	tgctgtccag	cttctccctt	gggaaaaagt
6721	ctctcctggt	tctctctcct	ccttccacct	cccctccctc	catcacctca	cgcctttctg
6781	ttccttggtc	tcaccttact	cccctcagga	ccctacccca	ccctccttga	aaagacaaag
6841	ctctgcctac	atagaagact	ttttttatgt	taaccaaagt	tactgttggt	tacagtgagt
6901	ttggggaaaa	aaaataaaat	aaaaatggct	ttcccagtc	ttgcatcaac	gggatgccac
6961	atttcataac	tgtttttaat	ggtaaaaaaa	aaaaaaaaaa	atacaaaaaa	aaattctgaa
7021	ggacaaaaaa	ggtgactgct	gaactgtgtg	tggtttattg	ttgtacattc	acaatcttgc
7081	aggagccaag	aagttcgag	ttgtgaacag	accctgttca	ctggagaggc	ctgtgcagta
7141	gagtgtagac	cctttcatgt	actgtactgt	acacctgata	ctgtaaacad	actgtaataa
7201	taatgtctca	catggaaaca	gaaaacgctg	ggtcagcagc	aagctgtagt	ttttaaaaat
7261	gttttttagtt	aaacgttgag	gagaaaaaaa	aaaaaggctt	ttcccccaaa	gtatcatgtg
7321	tgaacctaca	acaccctgac	ctctttctct	cctccttgat	tgtatgaata	accctgagat
7381	cacctcttag	aactggtttt	aaccttttagc	tgcagcggct	acgctgccac	gtgtgtatat
7441	atatgacgtt	gtacattgca	catacccttg	gatccccaca	gtttggtcct	cctcccagct
7501	acccctttat	agtatgacga	gttaacaagt	tggtgacctg	cacaaagcga	gacacagcta
7561	tttaattctc	tgccagatat	cgccccctct	ggtgcgatgc	tgtacaggtc	tctgtaaaaa
7621	gtccttgctg	tctcagcagc	caatcaactt	atagtttatt	tttttctggg	tttttggttt
7681	gttttggttt	ctttctaata	gaggtgtgaa	aaagtcttag	gttcagttga	agttctgatg
7741	aagaaacaca	attgagattt	tttcagtgat	aaaatctgca	tatttgattt	tcaacaatgt
7801	agctaaaact	tgatgtaaat	tcctcctttt	tttccttttt	tggcttaaat	aatatcatgt
7861	attcagtatg	aaatctttat	actatatgtt	ccacgtgtta	agaataaatg	tacattaaat
7921	cttggttaaga	cttt				

[097] The term “inducing neuronal differentiation” used herein refers to causing a cell to develop into a cell

[098] According to the methods of the disclosure, a “normal” cell may be used as a basis of comparison for one or more characteristics of a cancer cell, including expression and/or function of SNF5, ATRX, and/or ARID1A. As used herein, a “normal cell” is a cell that cannot be classified as part of a “cell proliferative disorder”. A normal cell lacks unregulated or abnormal growth, or both, that can lead to the development of an unwanted condition or disease. Preferably, a normal cell expresses a comparable amount of EZH2 as a cancer cell. Preferably a normal cell contains a wild type sequence for a SNF5, ATRX, and/or ARID1A gene, expresses a SNF5, ATRX, and/or ARID1A transcript without mutations, and expresses a SNF5, ATRX, and/or ARID1A protein without mutations that retains all functions a normal activity levels.

[099] As used herein, “contacting a cell” refers to a condition in which a compound or other composition of matter is in direct contact with a cell, or is close enough to induce a desired biological effect in a cell.

[0100] As used herein, “treating” or “treat” describes the management and care of a subject for the purpose of combating a disease, condition, or disorder and includes the administration of an EZH2 inhibitor of the disclosure, or a pharmaceutically acceptable salt,

prodrug, metabolite, polymorph or solvate thereof, to alleviate the symptoms or complications of cancer or to eliminate the cancer.

[0101] As used herein, the term "alleviate" is meant to describe a process by which the severity of a sign or symptom of cancer is decreased. Importantly, a sign or symptom can be alleviated without being eliminated. In a preferred embodiment, the administration of pharmaceutical compositions of the disclosure leads to the elimination of a sign or symptom, however, elimination is not required. Effective dosages are expected to decrease the severity of a sign or symptom. For instance, a sign or symptom of a disorder such as cancer, which can occur in multiple locations, is alleviated if the severity of the cancer is decreased within at least one of multiple locations.

[0102] As used herein, the term "severity" is meant to describe the potential of cancer to transform from a precancerous, or benign, state into a malignant state. Alternatively, or in addition, severity is meant to describe a cancer stage, for example, according to the TNM system (accepted by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC)) or by other art-recognized methods. Cancer stage refers to the extent or severity of the cancer, based on factors such as the location of the primary tumor, tumor size, number of tumors, and lymph node involvement (spread of cancer into lymph nodes). Alternatively, or in addition, severity is meant to describe the tumor grade by art-recognized methods (see, National Cancer Institute, www.cancer.gov). Tumor grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread. Many factors are considered when determining tumor grade, including the structure and growth pattern of the cells. The specific factors used to determine tumor grade vary with each type of cancer. Severity also describes a histologic grade, also called differentiation, which refers to how much the tumor cells resemble normal cells of the same tissue type (see, National Cancer Institute, www.cancer.gov). Furthermore, severity describes a nuclear grade, which refers to the size and shape of the nucleus in tumor cells and the percentage of tumor cells that are dividing (see, National Cancer Institute, www.cancer.gov).

[0103] In another aspect of the disclosure, severity describes the degree to which a tumor has secreted growth factors, degraded the extracellular matrix, become vascularized, lost adhesion to juxtaposed tissues, or metastasized. Moreover, severity describes the number of locations to which a primary tumor has metastasized. Finally, severity includes the difficulty of treating tumors of varying types and locations. For example, inoperable tumors, those

cancers which have greater access to multiple body systems (hematological and immunological tumors), and those which are the most resistant to traditional treatments are considered most severe. In these situations, prolonging the life expectancy of the subject and/or reducing pain, decreasing the proportion of cancerous cells or restricting cells to one system, and improving cancer stage/tumor grade/histological grade/nuclear grade are considered alleviating a sign or symptom of the cancer.

[0104] As used herein the term "symptom" is defined as an indication of disease, illness, injury, or that something is not right in the body. Symptoms are felt or noticed by the individual experiencing the symptom, but may not easily be noticed by others. Others are defined as non-health-care professionals.

[0105] As used herein the term "sign" is also defined as an indication that something is not right in the body. But signs are defined as things that can be seen by a doctor, nurse, or other health care professional.

[0106] Cancer is a group of diseases that may cause almost any sign or symptom. The signs and symptoms will depend on where the cancer is, the size of the cancer, and how much it affects the nearby organs or structures. If a cancer spreads (metastasizes), then symptoms may appear in different parts of the body.

[0107] As a cancer grows, it begins to push on nearby organs, blood vessels, and nerves. This pressure creates some of the signs and symptoms of cancer. Cancers may form in places where it does not cause any symptoms until the cancer has grown quite large.

[0108] Cancer may also cause symptoms such as fever, fatigue, or weight loss. This may be because cancer cells use up much of the body's energy supply or release substances that change the body's metabolism. Or the cancer may cause the immune system to react in ways that produce these symptoms. While the signs and symptoms listed above are the more common ones seen with cancer, there are many others that are less common and are not listed here. However, all art-recognized signs and symptoms of cancer are contemplated and encompassed by the disclosure.

[0109] Treating cancer may result in a reduction in size of a tumor. A reduction in size of a tumor may also be referred to as "tumor regression". Preferably, after treatment according to the methods of the disclosure, tumor size is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor size is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater;

and most preferably, reduced by greater than 75% or greater. Size of a tumor may be measured by any reproducible means of measurement. The size of a tumor may be measured as a diameter of the tumor.

[0110] Treating cancer may result in a reduction in tumor volume. Preferably, after treatment according to the methods of the disclosure, tumor volume is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor volume is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Tumor volume may be measured by any reproducible means of measurement.

[0111] Treating cancer may result in a decrease in number of tumors. Preferably, after treatment, tumor number is reduced by 5% or greater relative to number prior to treatment; more preferably, tumor number is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. Number of tumors may be measured by any reproducible means of measurement. The number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0112] Treating cancer may result in a decrease in number of metastatic lesions in other tissues or organs distant from the primary tumor site. Preferably, after treatment according to the methods of the disclosure, the number of metastatic lesions is reduced by 5% or greater relative to number prior to treatment; more preferably, the number of metastatic lesions is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. The number of metastatic lesions may be measured by any reproducible means of measurement. The number of metastatic lesions may be measured by counting metastatic lesions visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0113] An effective amount of an EZH2 inhibitor of the disclosure, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, is not significantly cytotoxic to normal cells. For example, a therapeutically effective amount of an EZH2

inhibitor of the disclosure is not significantly cytotoxic to normal cells if administration of the EZH2 inhibitor of the disclosure in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells. A therapeutically effective amount of an EZH2 inhibitor of the disclosure does not significantly affect the viability of normal cells if administration of the compound in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells.

[0114] Contacting a cell with an EZH2 inhibitor of the disclosure, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can inhibit EZH2 activity selectively in cancer cells. Administering to a subject in need thereof an EZH2 inhibitor of the disclosure, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can inhibit EZH2 activity selectively in cancer cells.

Medulloblastoma

[0115] Medulloblastoma is a fast-growing, aggressive, high-grade brain tumor. Regardless of the subtype, medulloblastoma always occurs in the cerebellum of the brain, and more specifically, within the posterior fossa of the cerebellum. The cerebellum controls balance and other complex motor functions.

[0116] Medulloblastoma rarely spreads beyond the central nervous system (CNS) (i.e., the brain and spinal cord); however, metastatic medulloblastoma may spread to the bones and bone marrow. Medulloblastoma cells arise from immature cells in the cerebellum that frequently divide under normal conditions to produce and replace cells of the cerebellum.

[0117] Medulloblastoma is relatively rare, accounting for less than 2% of all primary brain tumors and 18% of all pediatric brain tumors. More than 70% of all pediatric medulloblastomas are diagnosed in children under age 10. Medulloblastoma can occur in adults, and when found, occur most often in adults aged 20-44. Medulloblastoma occurs more frequently in males than females.

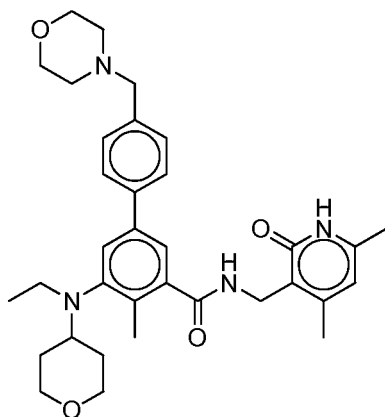
[0118] Subtypes of medulloblastoma include, but are not limited to, classic medulloblastoma, desmoplastic nodular medulloblastoma, large-cell or anaplastic medulloblastoma, medulloblastoma with neuroblastic or neuronal differentiation, medulloblastoma with glial differentiation, medulloblastoma and melanotic medulloblastoma. As used in this disclosure, the term “medulloblastoma” may include all subtypes of this cancer. Medulloblastoma may also be referred to as cerebellar primitive neuroectodermal tumor (PNET).

[0119] Symptoms of medulloblastoma include, but are not limited to, behavioral changes, changes in appetite, and symptoms of increased pressure on the brain (e.g., headache, nausea, vomiting, and drowsiness, as well as problems with coordination (e.g. clumsiness, problems with handwriting, and visual problems)). Unusual eye movements may also occur. If the cancer has spread to the spinal cord, symptoms may include back pain, trouble walking, and/or problems controlling bladder and bowel functions.

[0120] Medulloblastoma is often treated with surgery as a first line therapy in combination with or followed by radiation therapy and/or chemotherapy. Subjects of the disclosure in need of treatment with an EZH2 inhibitor, and, preferably, treatment with Tazemetostat, may be treated with an EZH2 inhibitor in combination with surgery, radiation, and/or chemotherapy. Subjects of the disclosure in need of treatment with an EZH2 inhibitor, and, preferably, treatment with Tazemetostat, may have undergone surgery, radiation, or a course of chemotherapy prior to treatment with an EZH2 inhibitor of the disclosure. Subjects of the disclosure in need of treatment with an EZH2 inhibitor, and, preferably, treatment with Tazemetostat, may have undergone surgery, radiation, or a course of chemotherapy prior to treatment with an EZH2 inhibitor of the disclosure and may have experienced no benefit from the surgery, radiation, and/or chemotherapy. EZH2 inhibitors of the disclosure, including, but not limited to, tazemetostat, may be used as a first line therapy prior to recommending or performing surgery, radiation, and/or chemotherapy to the subject.

EZH2 Inhibitors

[0121] EZH2 inhibitors of the disclosure comprise tazemetostat (EPZ-6438 or Compound A):



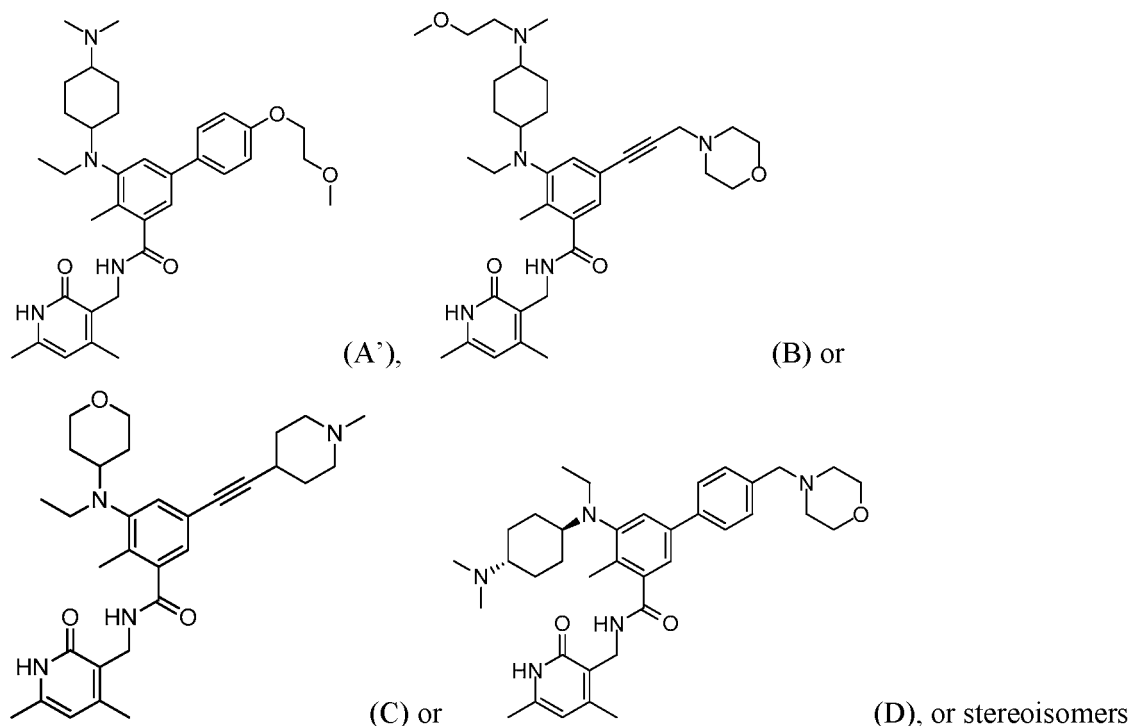
or a pharmaceutically acceptable salt thereof.

[0122] Tazemetostat is also described in US Patent Nos. 8,410,088, 8,765,732, and 9,090,562 (the contents of which are each incorporated herein in their entireties).

[0123] Tazemetostat or a pharmaceutically acceptable salt thereof, as described herein, is potent in targeting both WT and mutant EZH2. Tazemetostat is orally bioavailable and has high selectivity to EZH2 compared with other histone methyltransferases (i.e. >20,000 fold selectivity by K_i). Importantly, tazemetostat has targeted methyl mark inhibition that results in the killing of genetically defined cancer cells *in vitro*. Animal models have also shown sustained *in vivo* efficacy following inhibition of the target methyl mark. Clinical trial results described herein also demonstrate the safety and efficacy of tazemetostat.

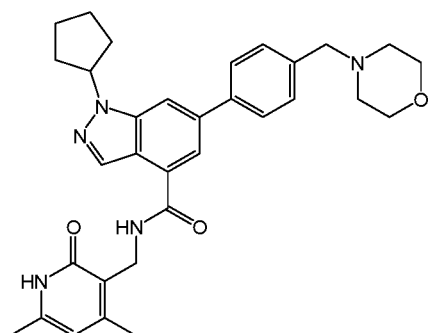
[0124] In one embodiment, tazemetostat or a pharmaceutically acceptable salt thereof is administered to the subject at a dose of approximately 100 mg to approximately 3200 mg daily, such as about 100 mg BID to about 1600 mg BID (e.g., 100 mg BID, 200 mg BID, 400 mg BID, 800 mg BID, or 1600 mg BID), for treating a NHL. On one embodiment the dose is 800 mg BID.

[0125] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of:



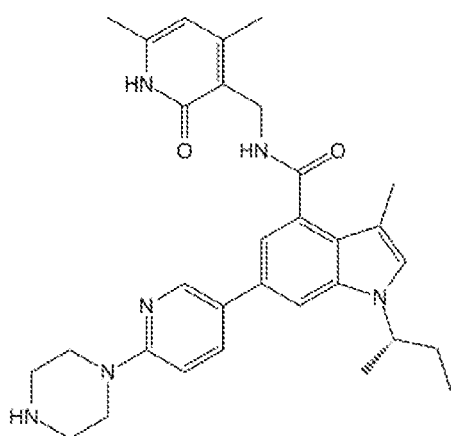
thereof or pharmaceutically acceptable salts and solvates thereof.

[0126] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of Compound E:



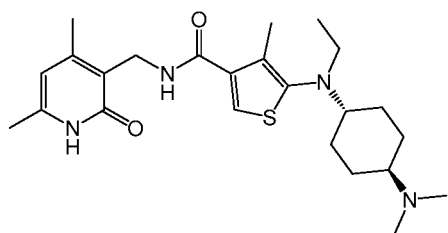
(E) or pharmaceutically acceptable salts thereof.

[0127] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of GSK-126, having the following formula:



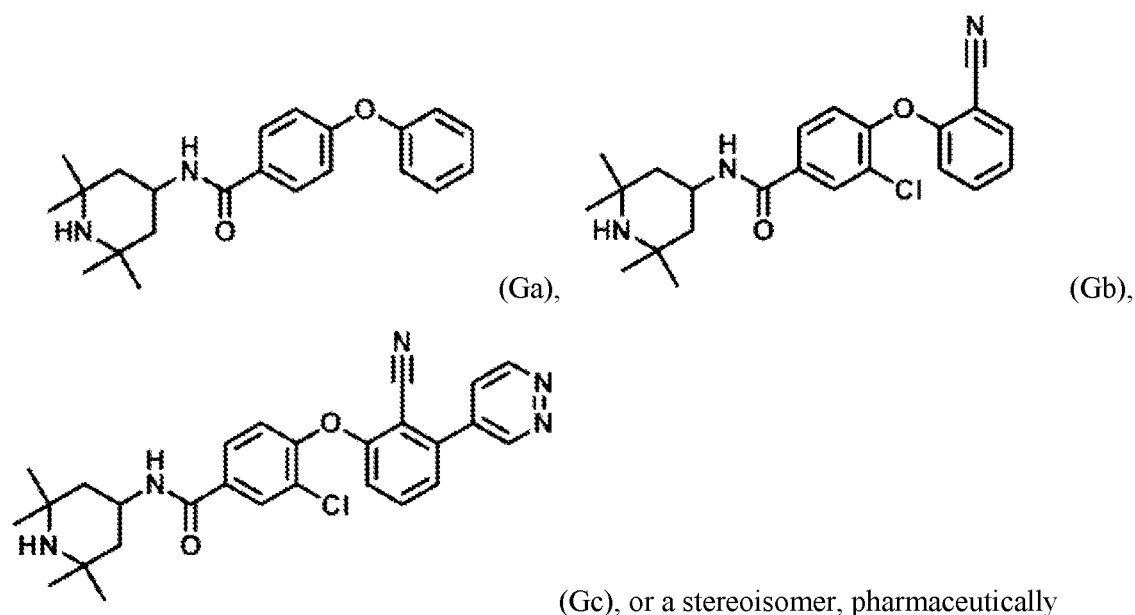
, stereoisomers thereof, or pharmaceutically acceptable salts or solvates thereof.

[0128] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of Compound F:



(F), or stereoisomers thereof or pharmaceutically acceptable salts and solvates thereof.

[0129] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of any one of Compounds Ga-Gc:



acceptable salt or solvate thereof.

[0130] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of CPI-1205 or GSK343.

[0131] Additional suitable EZH2 inhibitors will be apparent to those skilled in the art. In some embodiments of the strategies, treatment modalities, methods, combinations, and compositions provided herein, the EZH2 inhibitor is an EZH2 inhibitor described in US 8,536,179 (describing GSK-126 among other compounds and corresponding to WO 2011/140324), the entire contents of each of which are incorporated herein by reference.

[0132] In some embodiments of the strategies, treatment modalities, methods, combinations, and compositions provided herein, the EZH2 inhibitor is an EZH2 inhibitor described in PCT/US2014/015706, published as WO 2014/124418, in PCT/US2013/025639, published as WO 2013/120104, and in US 14/839,273, published as US 2015/0368229, the entire contents of each of which are incorporated herein by reference.

[0133] In one embodiment, the compound disclosed herein is the compound itself, i.e., the free base or “naked” molecule. In another embodiment, the compound is a salt thereof, e.g., a mono-HCl or tri-HCl salt, mono-HBr or tri-HBr salt of the naked molecule.

[0134] Compounds disclosed herein that contain nitrogens can be converted to N-oxides by treatment with an oxidizing agent (e.g., 3-chloroperoxybenzoic acid (*m*CPBA) and/or hydrogen peroxides) to afford other compounds suitable for any methods disclosed herein. Thus, all shown and claimed nitrogen-containing compounds are considered, when allowed by valency and structure, to include both the compound as shown and its N-oxide derivative

(which can be designated as $N \rightarrow O$ or N^+-O^-). Furthermore, in other instances, the nitrogens in the compounds disclosed herein can be converted to N-hydroxy or N-alkoxy compounds. For example, N-hydroxy compounds can be prepared by oxidation of the parent amine by an oxidizing agent such as *m*-CPBA. All shown and claimed nitrogen-containing compounds are also considered, when allowed by valency and structure, to cover both the compound as shown and its N-hydroxy (*i.e.*, N-OH) and N-alkoxy (*i.e.*, N-OR, wherein R is substituted or unsubstituted C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, 3-14-membered carbocycle or 3-14-membered heterocycle) derivatives.

[0135] “Isomerism” means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space.

Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.”

Stereoisomers that are not mirror images of one another are termed “diastereoisomers,” and stereoisomers that are non-superimposable mirror images of each other are termed

“enantiomers” or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a “racemic mixture.”

[0136] A carbon atom bonded to four nonidentical substituents is termed a “chiral center.”

[0137] “Chiral isomer” means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed “diastereomeric mixture.” When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0138] “Geometric isomer” means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes *cis* and *trans*, or *Z* and *E*, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[0139] It is to be understood that the compounds disclosed herein may be depicted as different chiral isomers or geometric isomers. It should also be understood that when

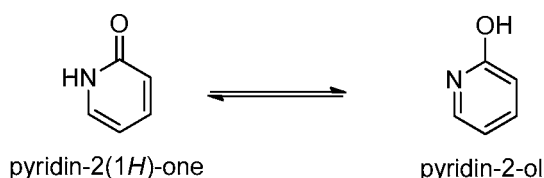
compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the disclosure, and the naming of the compounds does not exclude any isomeric forms.

[0140] Furthermore, the structures and other compounds discussed in this disclosure include all atropic isomers thereof. “Atropic isomers” are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[0141] “Tautomer” is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerizations is called tautomerism.

[0142] Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0143] Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (*e.g.*, in nucleobases such as guanine, thymine and cytosine), imine-enamine and enamine-enamine. An example of keto-enol equilibria is between pyridin-2(1H)-ones and the corresponding pyridin-2-ols, as shown below.



[0144] It is to be understood that the compounds disclosed herein may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the disclosure, and the naming of the compounds does not exclude any tautomer form.

[0145] The compounds disclosed herein include the compounds themselves, as well as their salts and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on an aryl- or heteroaryl-substituted benzene compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (e.g., trifluoroacetate). The term “pharmaceutically acceptable anion” refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on an aryl- or heteroaryl-substituted benzene compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The aryl- or heteroaryl-substituted benzene compounds also include those salts containing quaternary nitrogen atoms. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ration other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

[0146] Additionally, the compounds disclosed herein, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0147] “Solvate” means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

[0148] As used herein, the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the

replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0149] As defined herein, the term “derivative” refers to compounds that have a common core structure, and are substituted with various groups as described herein. For example, all of the compounds represented by Formula (I) are aryl- or heteroaryl-substituted benzene compounds, and have Formula (I) as a common core.

[0150] The term “bioisostere” refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulfonimides, tetrazoles, sulfonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0151] The present disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include C-13 and C-14.

Pharmaceutical Formulations

[0152] The present disclosure also provides pharmaceutical compositions comprising at least one EZH2 inhibitor described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0153] A “pharmaceutical composition” is a formulation containing the EZH2 inhibitors of the present disclosure in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are

contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers or propellants that are required.

[0154] As used herein, the phrase “pharmaceutically acceptable” refers to those compounds, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0155] “Pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the disclosure includes both one and more than one such excipient.

[0156] A pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0157] A compound or pharmaceutical composition of the disclosure can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, for treatment of cancers, a compound of the disclosure may be injected directly

into tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not as high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, cancer, precancer, and the like) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0158] The term “therapeutically effective amount”, as used herein, refers to an amount of an EZH2 inhibitor, composition, or pharmaceutical composition thereof effective to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician. In a preferred aspect, the disease or condition to be treated is cancer, including but not limited to, medulloblastoma.

[0159] For any EZH2 inhibitor of the disclosure, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0160] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions

may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0161] The pharmaceutical compositions containing an EZH2 inhibitor of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0162] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0163] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic

dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0164] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0165] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0166] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0167] The active compounds (*i.e.* EZH2 inhibitors of the disclosure) can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters,

and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0168] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0169] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer. An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. For example, regression of a tumor in a patient may be measured with reference to the diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Regression is also indicated by failure of tumors to reoccur after treatment has stopped. As used herein, the term “dosage effective manner” refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[0170] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0171] The compounds of the present disclosure are capable of further forming salts. All of these forms are also contemplated within the scope of the claimed disclosure.

[0172] As used herein, “pharmaceutically acceptable salts” refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making

acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0173] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0174] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0175] The EZH2 inhibitors of the present disclosure can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.*, a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.*, an acetate, propionate or other ester.

[0176] The EZH2 inhibitors of the present disclosure can also be prepared as prodrugs, for example, pharmaceutically acceptable prodrugs. The terms “pro-drug” and “prodrug” are used interchangeably herein and refer to any compound which releases an active parent drug *in vivo*. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, etc.), the compounds of the present disclosure can be delivered in prodrug form. Thus, the present disclosure is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. “Prodrugs” are intended to include any covalently bonded carriers that release an active parent drug of the present disclosure *in vivo* when such prodrug is administered to a subject. Prodrugs in the present disclosure are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present disclosure wherein a hydroxy, amino, sulfhydryl, carboxy or carbonyl group is bonded to any group that may be cleaved *in vivo* to form a free hydroxyl, free amino, free sulfhydryl, free carboxy or free carbonyl group, respectively.

[0177] Examples of prodrugs include, but are not limited to, esters (*e.g.*, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives) and carbamates (*e.g.*, N,N-dimethylaminocarbonyl) of hydroxy functional groups, esters (*e.g.*, ethyl esters, morpholinoethanol esters) of carboxyl functional groups, N-acyl derivatives (*e.g.*, N-acetyl) N-Mannich bases, Schiff bases and enaminones of amino functional groups, oximes, acetals, ketals and enol esters of ketone and aldehyde functional groups in compounds of the disclosure, and the like, See Bundegaard, H., *Design of Prodrugs*, p1-92, Elsevier, New York-Oxford (1985).

[0178] The EZH2 inhibitors, or pharmaceutically acceptable salts, esters or prodrugs thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0179] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily

skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[0180] The dosage regimen can be daily administration (*e.g.* every 24 hours) of a compound of the present disclosure. The dosage regimen can be daily administration for consecutive days, for example, at least two, at least three, at least four, at least five, at least six or at least seven consecutive days. Dosing can be more than one time daily, for example, twice, three times or four times daily (per a 24 hour period). The dosing regimen can be a daily administration followed by at least one day, at least two days, at least three days, at least four days, at least five days, or at least six days, without administration.

[0181] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0182] All percentages and ratios used herein, unless otherwise indicated, are by weight.

[0183] Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

EXAMPLES

[0184] In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the disclosure in any manner.

Example 1: Tazemetostat decreases medulloblastoma cell growth.

[0185] Medulloblastoma cells are treated with either a negative control (DMSO) or varying concentrations of tazemetostat (EPZ 6438): 0.5 μ M, 2 μ M and 6 μ M. The total cells per milliliter of culture were counted each day for 10 days. While each tazemetostat treatment demonstrated a significant decrease on medulloblastoma cell growth compared to wild type (Figure 26C), the effect was concentration dependent.

[0186] When compared to the efficacy of other small molecule EZH2 inhibitors, including GSK-126 and UNC 1999, Tazemetostat demonstrated a superior ability to decrease medulloblastoma cell growth (Figure 26D).

Example 2: Tazemetostat decreases medulloblastoma cell growth in an ex vivo slice culture.

[0187] A 5 year old patient having medulloblastoma underwent surgery to remove a slice of tumor tissue for testing. The medulloblastoma slice was cultured ex vivo on tissue supporting inserts (Figure 28A). Portions of the slice culture were untreated, treated with a lower concentration of tazemetostat (500 nM) or a higher concentration of tazemetostat (2 μ M) for 4 days. Following the treatment period, the cells of the slice culture were treated with BrdU for 4 hours prior to disaggregation and sorting by flow cytometry.

[0188] Figure 28B provides the results of the treatment by depicting the percent of cells in each of four cell cycle stages (sub G0/G1, G0/G1, S or G2/M) following each one of the treatment conditions. The data demonstrate that, compared to the untreated control, an increased proportion of medulloblastoma cells treated with tazemetostat are in the G0/G1 stage and a decreased proportion of medulloblastoma cells treated with tazemetostat are in the G2/M stage. The data indicate that treatment with tazemetostat inhibits proliferation/growth of medulloblastoma cells by interfering with cell division.

[0189] Figure 28C confirms the results of Figure 28B showing that the number of cells synthesizing DNA is significantly decreased in the tazemetostat-treated cells as evidenced by decreased incorporation of BrdU.

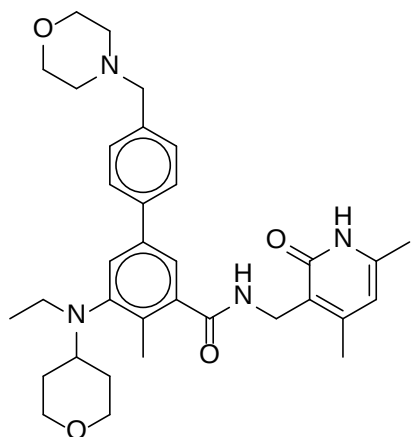
[0151] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow. Where names of cell lines or genes are used, abbreviations and names conform to the nomenclature of the American Type Culture Collection (ATCC) or the National Center for Biotechnology Information (NCBI), unless otherwise noted or evident from the context.

[0152] The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

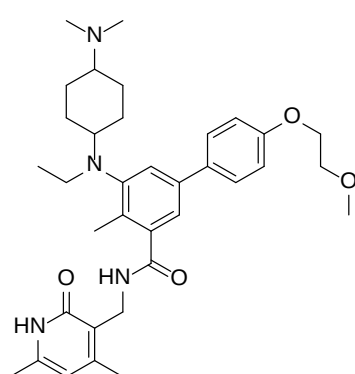
CLAIMS

What is claimed is:

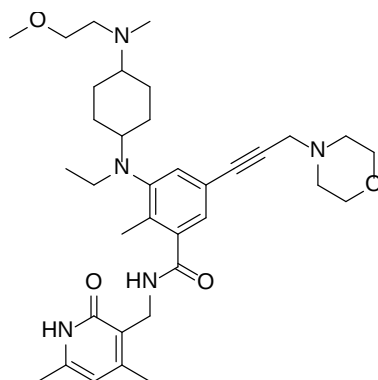
1. Use of a therapeutically-effective amount of an enhancer of a zeste homolog 2 (EZH2) inhibitor in the manufacture of a medicament for the treatment of a medulloblastoma in a subject in need thereof; optionally wherein the EZH2 inhibitor comprises



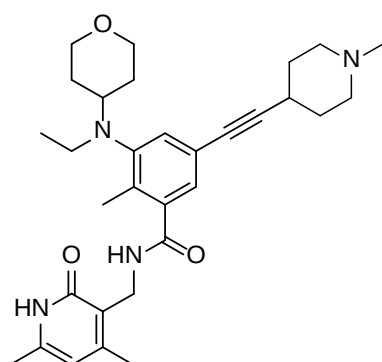
(tazemetostat), or a pharmaceutically-acceptable salt thereof; or



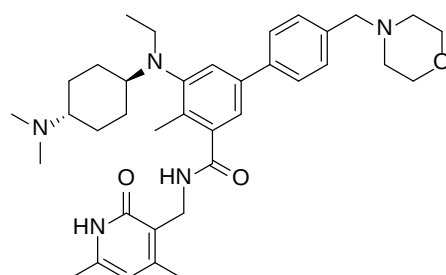
(A'),



(B),

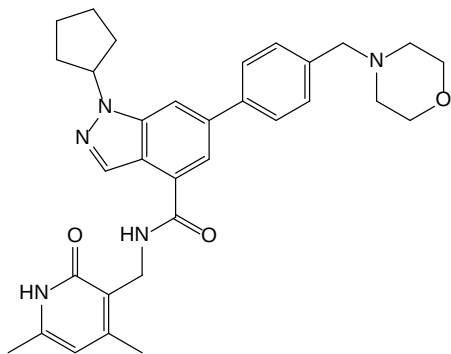


(C),

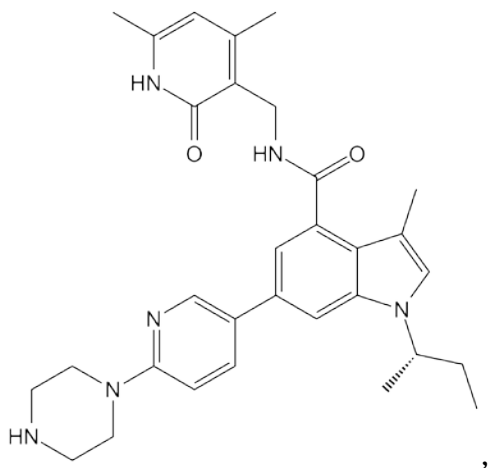


(D),

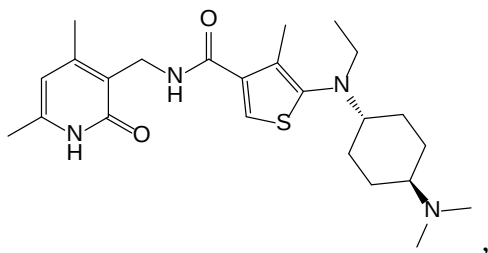
a stereoisomer, a pharmaceutically acceptable salt and/or a solvate thereof; or



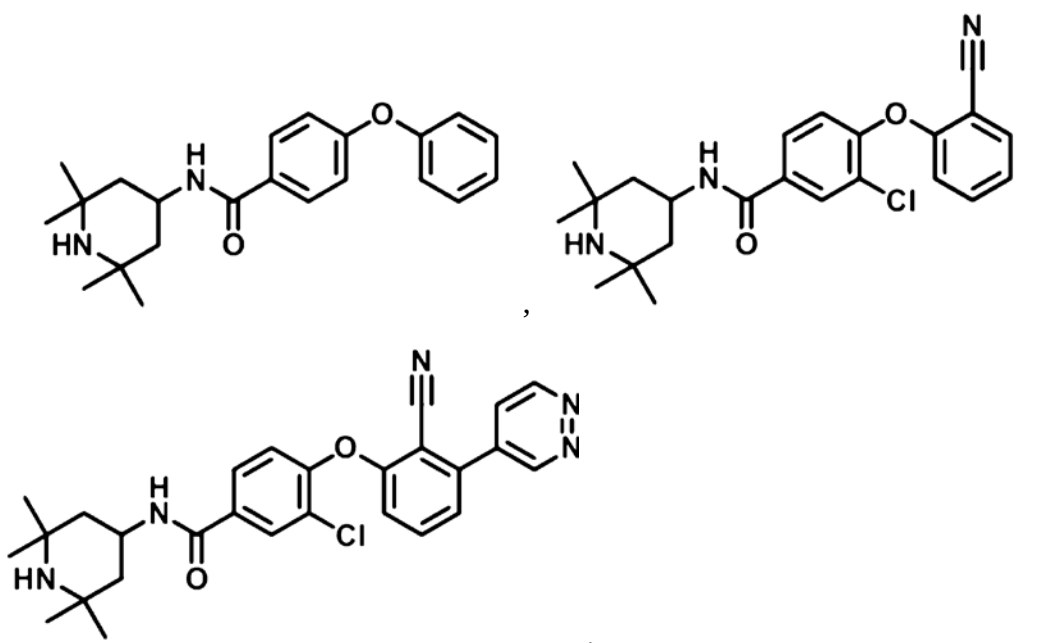
(E) or a pharmaceutically acceptable salt thereof; or



a stereoisomer, a pharmaceutically acceptable salt and/or a solvate thereof; or



a stereoisomer, a pharmaceutically acceptable salt and/or a solvate thereof; or



a stereoisomer, a pharmaceutically acceptable salt and/or a solvate thereof.

2. The use of any one of the foregoing claims, wherein the EZH2 inhibitor is to be administered orally.
3. The use of any one of the foregoing claims, wherein the EZH2 inhibitor is formulated as an oral tablet.
4. The use of any one of the foregoing claims, wherein the EZH2 inhibitor is to be administered at a dose of between 10 mg/kg/day and 1600 mg/kg/day; preferably wherein the EZH2 inhibitor is to be administered at a dose of about 100, 200, 400, 800, or 1600 mg; more preferably wherein the EZH2 inhibitor is to be administered at a dose of about 800 mg.
5. The use of any one of claims 1-2, wherein the EZH2 inhibitor is formulated as an oral suspension.
6. The use of any one of claims 1-2, wherein the EZH2 inhibitor is formulated for administration to cerebral spinal fluid (CSF); preferably wherein the EZH2 inhibitor is to be administered to cerebral spinal fluid by an intraspinal, an intracranial, an intrathecal or an intranasal route.
7. The use of any one of claims 5-6, wherein the EZH2 inhibitor is to be administered at a dose of between 230 mg/m² and 600 mg/m² twice per day (BID), inclusive of the endpoints; preferably wherein the EZH2 inhibitor is to be administered at a dose of between 230 mg/m² and 305 mg/m² twice per day (BID), inclusive of the endpoints.
8. The use of any one of claims 5-6, wherein the EZH2 inhibitor is to be administered at a dose of 240 mg/m² twice per day (BID); or wherein the EZH2 inhibitor is to be administered at a dose of 300 mg/m² twice per day (BID); or wherein the EZH2 inhibitor is to be administered at a dose of between 300 mg/m² and 600mg/m² twice per day (BID).
9. The use of any one of claims 5-6, wherein the EZH2 inhibitor is to be administered at a dose of about 60% of the area under the curve (AUC) at steady state (ACU_{ss}) following administration of 1600 mg twice a day to an adult subject.

10. The use of claim 5 or 9, wherein the EZH2 inhibitor is to be administered at a dose of about 600 mg/m² per day; or wherein the EZH2 inhibitor is to be administered at a dose of at least 600 mg/m² per day.
11. The use of any one of claims 5-6, wherein the EZH2 inhibitor is to be administered at a dose of about 80% of the area under the curve (AUC) at steady state (ACU_{ss}) following administration of 800 mg twice a day to an adult subject.
12. The use of claim 5 or 11, wherein the EZH2 inhibitor is to be administered at a dose of about 390 mg/m² twice per day (BID); or wherein the EZH2 inhibitor is to be administered at a dose of at least 390 mg/m² twice per day (BID).
13. The use of any one of the foregoing claims, wherein the EZH2 inhibitor is to be administered twice per day (BID); and/or wherein the EZH2 inhibitor is to be administered to a pediatric subject; preferably wherein the subject is between 6 months and 21 years of age, inclusive of the endpoints; preferably wherein the subject is between 1 year and 18 years of age, inclusive of the endpoints; preferably wherein the subject is 10 years of age or less; preferably wherein the subject is 5 years of age or less.
14. The use of any one of the foregoing claims, wherein the treatment comprises preventing and/or inhibiting proliferation of a medulloblastoma cell.
15. Use of a therapeutically-effective amount of tazemetostat in the manufacture of a medicament for the treatment of medulloblastoma in a subject in need thereof,
wherein the therapeutically effective amount is at least 300 mg/m² twice per day (BID), and
wherein the subject is between 6 months and 21 years of age, inclusive of the endpoints.